Worldwide country situation analysis:
response to antimicrobial resistance

April 2015
## Contents

Acronyms and abbreviations

1. Country strategies to control antimicrobial resistance

2. WHO African Region

3. WHO Region of the Americas

4. WHO Eastern Mediterranean Region

5. WHO European Region

6. WHO South-East Asia Region

7. WHO Western Pacific Region

8. Conclusions

Annex 1

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acronyms and abbreviations</td>
<td>v</td>
</tr>
<tr>
<td>1. Country strategies to control antimicrobial resistance</td>
<td>1</td>
</tr>
<tr>
<td>2. WHO African Region</td>
<td>13</td>
</tr>
<tr>
<td>3. WHO Region of the Americas</td>
<td>17</td>
</tr>
<tr>
<td>4. WHO Eastern Mediterranean Region</td>
<td>21</td>
</tr>
<tr>
<td>5. WHO European Region</td>
<td>25</td>
</tr>
<tr>
<td>6. WHO South-East Asia Region</td>
<td>29</td>
</tr>
<tr>
<td>7. WHO Western Pacific Region</td>
<td>33</td>
</tr>
<tr>
<td>8. Conclusions</td>
<td>37</td>
</tr>
<tr>
<td>Annex 1</td>
<td>41</td>
</tr>
</tbody>
</table>
Acknowledgements

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### Acronyms and abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AMR</td>
<td>antimicrobial resistance</td>
</tr>
<tr>
<td>CAESAR</td>
<td>Central Asian and Eastern European Surveillance of Antimicrobial Resistance network</td>
</tr>
<tr>
<td>EARS-Net</td>
<td>European Antimicrobial Resistance Surveillance Network</td>
</tr>
<tr>
<td>IPC</td>
<td>infection prevention and control</td>
</tr>
<tr>
<td>MDR</td>
<td>multidrug-resistant</td>
</tr>
<tr>
<td>PAHO</td>
<td>Pan American Health Organization</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>WePARS</td>
<td>Western Pacific Antimicrobial Resistance Surveillance</td>
</tr>
</tbody>
</table>
1. Country strategies to control antimicrobial resistance

Global overview

Antimicrobial resistance has been detected in all parts of the world; it is one of the greatest challenges to global public health today, and the problem is increasing. Although antimicrobial resistance is a natural phenomenon, it is being propagated by misuse of antimicrobial medicines, inadequate or inexistent programmes for infection prevention and control (IPC), poor-quality medicines, weak laboratory capacity, inadequate surveillance and insufficient regulation of the use of antimicrobial medicines.

A strong, collaborative approach will be required to combat antimicrobial resistance, involving countries in all regions and actors in many sectors. Over a 2-year period, from 2013 to 2014, WHO undertook an initial "country situation analysis" in order to determine the extent to which effective practices and structures to address antimicrobial resistance were already in place and where gaps remained. The survey was conducted in countries in each of the six WHO regions.

A multi-stage analytical tool was developed to assess the situation at the national level. The tool was based on existing WHO assessment tools and reflected the elements contained in the policy package to address antimicrobial resistance that was issued on World Health Day 2011. Country authorities were asked to complete a questionnaire on their existing strategies, systems and activities. The questionnaires were completed either by the authorities themselves through self-assessment or at an interview with a WHO officer on the occasion of a country visit.

This report presents the overall findings of the survey. It provides an analysis, by region and globally, of the initiatives under way to address antimicrobial resistance and identifies areas in which more work is needed. The survey focused on the building blocks that are considered prerequisites to combat antimicrobial resistance: a comprehensive national plan, laboratory capacity to undertake surveillance for resistant microorganisms, access to safe, effective antimicrobial medicines, control of the misuse of these medicines, awareness and understanding among the general public and effective infection prevention and control programmes. Since the survey was conducted, some countries have made further advances and additional initiatives have been launched. No reference therefore is made to individual countries, and the results reflect the situation at the time the questionnaires were completed.

Comprehensive national plans, based on a multisectoral approach and with sustainable financing, are regarded as one of the main ways to fight antimicrobial resistance globally (WHO, 2011); however, few countries reported having such a plan. Some countries did report that a national focal point for antimicrobial resistance had been identified and had a national coordination mechanism in place. Others had introduced national strategies and policies to address antimicrobial resistance.

A national surveillance mechanism and the necessary laboratory capacity are essential to detect, analyse and track resistant microorganisms. Surveillance can reveal the presence of patterns of resistant microorganisms and identify trends and outbreaks. In many regions, however, poor laboratory capacity, infrastructure and data management prevented effective surveillance. Although laboratory capacity varied by country in all regions, at least one country in each of the six regions had a national reference laboratory capable of testing for antibiotic sensitivity and subject to external quality assessment. The same countries also reported monitoring of antimicrobial resistance in humans.
Regions in which there are many high-income countries, such as the European and the Western Pacific regions, reported higher rates of access to high-quality medicines than other regions.

The survey also revealed that the sale of antimicrobial medicines without prescription was widespread in many countries. Furthermore, many countries lacked standard treatment guidelines for health care. Thus, the potential for overuse of antimicrobial medicines by the public and by the medical profession was common in countries in all regions. Few countries reported a system for monitoring the use of antimicrobial medicines. Thus, tracking prescribing patterns and over-the-counter sales remains a significant challenge.

Public awareness of antimicrobial resistance was low in all regions. Even in some countries in which national public awareness campaigns had been conducted, there was still widespread belief that antibiotics are effective against viral infections. More education and collaborative awareness-raising campaigns in sectors such as health care, politics and the media may therefore be required.

Programmes to prevent and control the spread of antimicrobial-resistant infections are also essential. Without effective hygiene and sanitation measures, infections can spread rapidly through health care facilities and between countries and regions by travel and trade. Half of the countries in the European, South-East Asia and Western Pacific regions that responded to the survey reported having a national IPC programme in place; fewer had comparable programmes in all tertiary hospitals. IPC thus tended to be inadequate.

Overall, the findings of this survey reveal that much is under way and indicate that countries are committed to addressing this complex problem. Some countries already have a number of activities in place, while others are embarking on the work and face challenges. This initial country situation analysis provides an overview and can serve as a reference against which countries and WHO can monitor progress in implementing actions to address the challenge of antimicrobial resistance in coming years.

### 1.1 Introduction

Antimicrobial resistance is recognized as one of the principal threats to public health throughout the world: its impact is felt all areas of health, and it affects the whole of society. Although antimicrobial resistance is a natural phenomenon, it is exacerbated by the misuse of antimicrobial medicines, poor or non-existent IPC programmes, poor-quality medicines, weak laboratory capacity, inadequate surveillance and poor regulation or enforcement of regulations to assure access to high-quality antimicrobial medicines and their appropriate use.

On 7 April 2011, on the occasion of World Health Day, WHO introduced a policy package to combat antimicrobial resistance, which lists critical actions by all stakeholders to stimulate change.

Although widely recognized as an urgent problem by many international organizations and ministries of health, not all countries have a response plan to tackle antimicrobial resistance. Some regions face other, more pressing problems, and many low- to middle-income countries do not have the resources to implement response mechanisms. A “country situation analysis” was subsequently conducted in countries in each of the six WHO regions to assess current practices and to determine the structures that were in place to control antimicrobial resistance. The results of that analysis are summarized in this report.

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At the Sixty-seventh World Health Assembly, in May 2014, Member States approved a resolution, WHA67.25, requesting WHO to draft a global action plan on antimicrobial resistance. The draft plan will be reviewed at the Sixty-eighth World Health Assembly2. It is based on input received during broad multisectoral consultations with countries, international organizations, nongovernmental organizations and other stakeholders and sets out five strategic objectives: to improve awareness and understanding of antimicrobial resistance, to gain knowledge through surveillance and research, to reduce the incidence of infection, to optimize the use of antimicrobial medicines and to ensure sustainable investment in countering antimicrobial resistance.

1.2 Data collection methods

WHO is represented throughout the world, divided into six regions: the African Region, the Region of the Americas, the Eastern Mediterranean Region, the European Region, the South-East Asia Region and the Western Pacific Region (Figure 1.1). The survey was conducted in countries in all WHO regions.

A multi-stage rapid assessment analytical tool was devised to assess the situation in countries. The tool was based on existing WHO assessment tools and reflected the elements contained in the policy package to address antimicrobial resistance that was issued on World Health Day 2011, which built on previous recommendations (WHO global strategy for containment of antimicrobial resistance, 2001) and resolution WHA51.17. It listed the following activities for combatting antimicrobial resistance:

- Adhere to a comprehensive, financed national plan with accountability and civil society engagement.
- Strengthen surveillance and laboratory capacity.
- Ensure uninterrupted access to essential medicines of assured quality.
- Regulate and promote rational use of medicines, and ensure proper patient care.
- Enhance infection prevention and control.
- Foster innovation, research and new tools.

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The questionnaire was pilot-tested in 2012, and a simplified version was distributed to countries for completion between 2013 and 2014. Authorities in each country were invited to complete the questionnaire themselves or with WHO staff from the regional or country office and to return it to the regional office. The data were compiled, and the results were recorded as simple frequencies. Blank responses were recorded as “unknown”.

The questionnaire addressed the use of antimicrobial medicines in both human and animal health; however, this report is limited to the findings in humans. In due course, a further survey will be conducted, in collaboration with the Organisation for Animal Health and the Food and Agriculture Organization of the United Nations, on issues related to antimicrobial resistance and animal health.

Table 1.1 gives the numbers of Member States in each region from which information was received. A total of 133 of the 194 WHO Member States provided information.

<table>
<thead>
<tr>
<th>WHO region</th>
<th>No. of Member States</th>
<th>Total no. of Member States in region</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>African Region</td>
<td>8</td>
<td>47</td>
<td>17</td>
</tr>
<tr>
<td>Region of the Americas</td>
<td>26</td>
<td>35</td>
<td>74</td>
</tr>
<tr>
<td>Eastern Mediterranean Region</td>
<td>13</td>
<td>21</td>
<td>62</td>
</tr>
<tr>
<td>European Region</td>
<td>49</td>
<td>53</td>
<td>92</td>
</tr>
<tr>
<td>South-East Asia Region</td>
<td>11</td>
<td>11</td>
<td>100</td>
</tr>
<tr>
<td>Western Pacific Region</td>
<td>26</td>
<td>27</td>
<td>96</td>
</tr>
</tbody>
</table>

For each region, all data were analysed on the basis of the number of countries from which information was received.

The aim of this report is to provide an overview of the extent to which effective practices and structures designed to address antimicrobial resistance are in place and where gaps remain. Some of the data are more than 1 year old; it is likely that improvements have been made since the original assessment, which will be reflected in future reports.

In view of the difference in the proportions of countries in each region that responded, the results should be interpreted with caution, particularly in making any comparisons between countries or regions.
1.3 National plans and other strategies

A financed national plan with multisectoral input is essential for addressing antimicrobial resistance, and the draft global action plan urges all countries to have such a plan. Figure 1.2 shows that the South-East Asia Region had the highest proportion of countries with such plans (45%); the European Region followed closely, with 43%. Further work is therefore needed, including among countries that have strong health care systems.

Other national mechanisms, such as a national focal point and a central coordination mechanism, were generally more common than plans (Figure 1.2). Many countries reported having a national policy or strategy, but few had published a progress report within the previous 5 years.

Figure 1.2 – Percentages of Member States that had a national plan for antimicrobial resistance, a coordinating mechanism, a focal point, a policy or a strategy and had prepared a report in the previous 5 years, by region (Note: numbers above the bars represent the numbers of participating Member States that answered “yes”)

AFR, WHO African Region; AMER, WHO Region for the Americas; EMR, WHO Eastern Mediterranean Region; EUR, WHO European Region; SEAR, WHO South-East Asia Region; WPR, WHO Western Pacific Region
1.4 Surveillance and laboratory capacity

Well-equipped laboratories with well-trained staff that report regularly to functioning surveillance systems allow the detection and tracking of antimicrobial-resistant microorganisms and prompt notification to the relevant authorities when an outbreak occurs. Data from surveillance also allow policy-makers to introduce evidence-based standards and regulations and health care managers to make decisions on appropriate care.

Antimicrobial resistance among rapidly growing bacteria and Mycobacterium tuberculosis was monitored in all regions, over 60% of respondents in each region reporting this type of surveillance (Figure 1.3). Regional networks support surveillance in many countries; however, none includes all the countries in its respective region.

Figure 1.3 – Percentages of Member States that had conducted surveillance for antimicrobial resistance in bacteria in general and in the causative agents of tuberculosis, malaria, influenza and HIV infection, all regions (Note: numbers above the bars represent the numbers of participating Member States that answered “yes”)

Typically, countries cited a lack of laboratories with sufficient competent technical staff, weak infrastructure, poor data management and lack of standards as impediments to effective laboratory surveillance. Figure 1.4 shows that the highest percentage of countries with national reference laboratories in which organisms are tested for antibiotic sensitivity (96%) was in the Region of the Americas. National reference laboratories existed in 69–82% of countries in the European, South-East Asia and Western Pacific regions. National reference laboratories are often responsible for implementing national external quality assessment schemes, to ensure that the same testing standards and methods are used throughout the country. Although at least one country in each region reported having a national reference laboratory, many did not participate in external quality assessment schemes to ensure that the data on antimicrobial resistance that were collected were of reliable quality (Figure 1.4).
WoRld Wide countR y situAtion AnAlysis: Response to AntiMicR obiAl Resist Ance

Figure 1.4 – Percentages of Member States in which laboratory sensitivity was tested and which participated in external quality assessment, all regions
(Note: numbers above the bars represent the numbers of Member States that answered “yes”)

NRL, national reference laboratory; EQA, external quality assessment
AFR, WHO African Region; AMER, WHO Region for the Americas; EMR, WHO Eastern Mediterranean Region; EUR, WHO European Region; SEAR, WHO South-East Asia Region; WPR, WHO Western Pacific Region

With the exception of two regions in which most countries reported on antimicrobial resistance surveillance, national reports on this topic were infrequent (Figure 1.5).

Figure 1.5 – Percentages of Member States in which reports on surveillance for antimicrobial resistance had been prepared in the past 5 years, all regions
(Note: numbers above the bars represent the numbers of Member States that answered “yes”)

AFR, WHO African Region; AMER, WHO Region for the Americas; EMR, WHO Eastern Mediterranean Region; EUR, WHO European Region; SEAR, WHO South-East Asia Region; WPR, WHO Western Pacific Region
1.5 Access to quality-assured antimicrobial medicines

Ready access to quality-assured antimicrobial medicines is important for preventing the appearance of new antimicrobial-resistant microorganisms. Poor-quality medicines may not contain the correct amount of active ingredient, resulting in sub-optimal dosing. This can be overcome with strong national regulations on medicine production and by strengthening the ability of authorities to regulate the industry.

Counterfeit medicines have been reported to be a problem in many regions (WHO, 2006, 2010; Ndihokubwayo et al., 2013; WHO Regional Office for the Eastern Mediterranean, 2013). The situation stems from weak regulatory systems and inability to enforce laws. The wide availability of medicines for direct sale to patients—for example, on the Internet—remained a problem for all regions. Figure 1.6 shows the percentages of countries in each region that reported having a national regulatory authority, national quality standards and capacity within the regulatory authority to enforce the standards. In the regions in which there were problems of low-quality and/or counterfeit medicines, few countries had a national regulatory authority, national standards or the capacity to enforce them.

The majority of countries participating in the survey had a list of essential medicines (Figure 1.7), which are those that “satisfy the priority health care needs of the population” (WHO, 2003). Comparison of Figures 1.6 and 1.7 would indicate, however, that having such a list does not necessarily result in access to high-quality essential medicines.

![Graph showing percentages of Member States with a regulatory authority, quality standards, and the capacity to enforce the standards, all regions](image-url)
1.6 Use of antimicrobial medicines

Both overuse and misuse of antimicrobial medicines accelerate the emergence of resistant microorganisms. Misuse can be due to:

- poor prescribing practice, including prescribing antimicrobial medicines when not required, incorrect choice of medicine, or at an incorrect dosage;
- self-medication in countries in which antimicrobial medicines are freely available;
- failure to finish a course of antimicrobial medicines or taking them for too long;
- lack of regulations or standards for health care workers (WHO, 2011); and
- misuse and overuse in animal husbandry and agriculture.

Table 1.2 shows that antimicrobial medicines were generally freely available in all countries and regions. Furthermore, regulations on the sale of prescription-only medicines could not be widely enforced in several regions, and many countries had no guidelines for proper prescribing practice. Poor awareness of antimicrobial resistance represents a major area for urgent national and regional action (see section 1.7).

Monitoring of the use of antimicrobial medicines was infrequent in most regions; the highest proportion of countries that monitored such use was in the European Region. Monitoring use enables national authorities to identify unmet needs in order to improve prescribing practice, for example through standard treatment guidelines, public awareness campaigns and education and training for health care workers (WHO, 2011). Even knowledgeable personnel may lack up-to-date information on prescribing antimicrobial medicines in line with current standard treatment recommendations.
Table 1.2 – Practices related to use of antimicrobial medicines, all WHO regions

<table>
<thead>
<tr>
<th>WHO region (percentage: no. of positive responses/ no. of Member States)</th>
<th>African</th>
<th>Americas</th>
<th>Eastern Mediterranean</th>
<th>European</th>
<th>South-East Asia</th>
<th>Western Pacific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial medicines are available without a prescription.</td>
<td>17</td>
<td>51</td>
<td>43</td>
<td>43</td>
<td>64</td>
<td>52</td>
</tr>
<tr>
<td>Restriction of prescription-only medicines can be enforced.</td>
<td>11</td>
<td>31</td>
<td>33</td>
<td>55</td>
<td>82</td>
<td>85</td>
</tr>
<tr>
<td>Standard treatment guidelines could be drawn up.</td>
<td>11</td>
<td>40</td>
<td>33</td>
<td>43</td>
<td>100</td>
<td>59</td>
</tr>
<tr>
<td>Use of antimicrobial medicines was monitored in the previous 5 years.</td>
<td>6</td>
<td>17</td>
<td>19</td>
<td>66</td>
<td>9</td>
<td>52</td>
</tr>
</tbody>
</table>

1.7 Public awareness

At the time of the survey, public awareness appeared to be low in all regions (Figure 1.8). This situation is alarming, particularly in countries where antimicrobial medicines are readily available without a prescription (see section 1.6). In the analysis of the level of awareness about antimicrobial resistance in health care, politics, the media and academia, academics were generally more aware of the problem than others, including health care workers. The general lack of awareness in these sectors would indicate that antimicrobial resistance is likely to spread further. Without sufficient awareness, the appropriate regulations and standards will not be legislated, and other sectors will lack the information needed to implement them effectively.

Figure 1.8 – Percentages of Member States that had conducted a public information campaign about use of antimicrobial medicines in the previous 2 years, by region
(Note: numbers above the bars represent the numbers of Member States that answered “yes”)

AFR, WHO African Region; AMER, WHO Region for the Americas; EMR, WHO Eastern Mediterranean Region; EUR, WHO European Region; SEAR, WHO South-East Asia Region; WPR, WHO Western Pacific Region
1.8 Infection prevention and control programmes

Resistant microorganisms can spread rapidly across countries, regions and the world, facilitated by global trade, travel and tourism. Poor infection control in any setting can greatly increase the spread of drug-resistant infections, especially during outbreaks of disease. IPC programmes are thus essential to curb the movement of antimicrobial-resistant organisms, starting with good basic hygiene, which limits the spread of all infections, including those that are resistant to antimicrobial medicines.

Figure 1.9 shows that relatively few countries had a national IPC programme. At least half the Member States in the European, South-East Asia and Western Pacific regions reported having such a programme; fewer stated that all tertiary hospitals in the country had one.

Figure 1.9 – Percentages of Member States that had an infection prevention and control (IPC) programme and in which all tertiary hospitals had such a programme, all regions
(Note: numbers above the bars represent the numbers of Member States that answered “yes”)

AFR, WHO African Region; AMER, WHO Region for the Americas; EMR, WHO Eastern Mediterranean Region; EUR, WHO European Region; SEAR, WHO South-East Asia Region; WPR, WHO Western Pacific Region
2. WHO African Region

Regional facts

Number of Member States: 47
Number of Member States for which information was available for the analysis: 8 (17%)
Regional population: 805 million
Life expectancy in the Region: average: 58 years; range: 51–62 years

Regional overview

The WHO African Region comprises 47 Member States. As information was available for only eight (17%), the data are incomplete and perhaps misleading with regard to some aspects of antimicrobial resistance. All those that participated in the survey are low- or middle-income countries. The results suggest, however, that antimicrobial resistance is a growing problem in the Region.

Only one of the eight countries reported having a national plan, while this is considered crucial for addressing antimicrobial resistance on a national scale. Few countries had a national coordinating mechanism, national focal point, policy or strategy or had issued a progress report, although some countries were preparing plans or strategies.

Awareness of antimicrobial resistance was generally low among the public and in sectors including politics and health care. Education and training could be key activities.

Although surveillance of resistance in bacteria (including M. tuberculosis) was reported by six of the eight countries that participated, some noted the importance of increasing laboratory capacity and surveillance for controlling antimicrobial resistance. Many laboratories that perform surveillance were not coordinated nationally, limiting their effectiveness. The Regional Office recently published guidelines to help countries establish laboratory-based surveillance (WHO Regional Office for Africa, 2013). Field epidemiology and laboratory training programmes established in Africa (e.g. Ghana AMR Project, 2014) have helped to increase laboratory capacity.

The countries had little capacity for IPC, and programmes were not common in tertiary hospitals.

Counterfeit and poor-quality medicines, including antimicrobial medicines, are a general problem in the Region, further contributing to the spread of antimicrobial resistance.

2.1 Introduction

The WHO African Region comprises most of the African continent, although some countries are included in the Eastern Mediterranean Region. All eight countries that participated are lower- or middle-income countries. As the response was limited (17%), the data in this section are less complete than for other regions and may misrepresent the situation. The Region recognizes, however, that antimicrobial resistance is a growing problem. In 1998, Member States endorsed the Integrated Disease Surveillance Response strategy, which helps strengthen public laboratory networks, and thus antimicrobial resistance surveillance, and, in 2013, the Regional Office
published guidelines for establishing laboratory-based surveillance (WHO Regional Office for Africa, 2013).

For this country situation analysis, all eight countries that responded reported that malaria and tuberculosis (TB) were their greatest public health challenges. Multidrug- and extensively drug-resistant (MDR and XDR) TB are problems in many countries (Ndihokubwayo et al., 2013). Cholera and meningitis were also reported to be important concerns.

### 2.2 National plans and other strategies

Only one of the countries that responded reported having a national plan (Figure 2.1), whereas having a comprehensive, funded national plan is one of the best ways to control antimicrobial resistance. In addition, few countries reported having a national coordinating mechanism (two countries), a national focal point (two countries), policies or strategies (two countries) or having made a progress report (one country). Two countries reported, however, that they were aware of the problem and were preparing guidelines or policies. Two other countries recognized the need for national coordination, and one has established a global antibiotic resistance partnership as a first step. At the Sixty-seventh World Health Assembly, in May 2014, Ghana urged all countries that do not yet have a national plan to develop one through a multisectoral approach (Ghana AMR Project, 2014).

![Figure 2.1](image_url)

**Figure 2.1** – Percentages of Member States that had a national antimicrobial resistance plan, coordinating mechanism, focal point, policy or strategy and had prepared a report in the previous 5 years, WHO African Region. (Note: numbers above the bars represent the numbers of responses)
2.3 Surveillance and laboratory capacity

Standardized diagnostics are critical for tracking antimicrobial resistance, and the field epidemiology and laboratory training programmes established in Africa are helping to strengthen the capacity of health care professionals in laboratory management, including antimicrobial resistance (Ghana AMR Project, 2014). Six of the eight responding countries undertook some bacterial surveillance (Figure 2.2); however, in many, it was not coordinated at national level, reducing its effectiveness. As MDR-TB is present in a number of countries, surveillance for resistance in this disease is reasonably frequent.

![Figure 2.2 - Percentages of Member States that had conducted surveillance for antimicrobial resistance in bacteria in general and in the causative agents of tuberculosis, malaria, influenza and HIV infection, WHO African Region (Note: numbers above the bars represent the numbers of responses)](image)

Six of the eight countries had a national reference laboratory and undertook testing for sensitivity to antibiotics. Some countries reported that building laboratory capacity is essential for tackling antimicrobial resistance. Only one of the countries that responded had prepared a report on surveillance of antimicrobial resistance in humans within the past 5 years.

2.4 Access to quality-assured antimicrobial medicines

Seven of the eight countries that responded had a national regulatory authority, and five had quality standards. Seven countries reported that they could enforce standards. Many of the countries had fragmented supplies of good-quality medicines, and many face the problem of counterfeit antimicrobial medicines (Ndihokubwayo et al., 2013). Although some of the countries that participated thus had the capacity to ensure good-quality medicines, the situation may be different in the Region as a whole.

Seven of the responding countries had an essential medicines list.
2.5 Use of antimicrobial medicines

Table 2.1 shows a high potential for misuse of antimicrobial medicines in the countries of the African Region that responded. All the countries reported that these drugs are available without a prescription, which represents a significant problem, especially when combined with the overall poor awareness of antimicrobial resistance (see section 2.6). Furthermore, the countries reported limited ability to enforce any existing regulations for use of these drugs in human medicine, and there was little monitoring of antimicrobial resistance.

Table 2.1 – Monitoring of use of antimicrobial medicines, WHO African Region

<table>
<thead>
<tr>
<th></th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Unknown (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial medicines are available without a prescription.</td>
<td>17</td>
<td>0</td>
<td>83</td>
</tr>
<tr>
<td>Restriction of prescription-only medicines can be enforced.</td>
<td>11</td>
<td>4</td>
<td>85</td>
</tr>
<tr>
<td>Standard treatment guidelines could be drawn up.</td>
<td>11</td>
<td>4</td>
<td>85</td>
</tr>
<tr>
<td>Use of antimicrobial medicines was monitored in the previous 5 years.</td>
<td>6</td>
<td>6</td>
<td>88</td>
</tr>
</tbody>
</table>

2.6 Public awareness

The data indicated little public awareness of the proper use of antimicrobial medicines. Only two of the countries that responded had conducted a public awareness campaign in the previous 2 years. Some reported that education of both the public and health care workers would be essential to tackle antimicrobial resistance in their country, and many reported poor awareness in the important sectors of politics, health care, pharmaceuticals, the mass media and academia.

2.7 Infection prevention and control programmes

Four of the eight countries that responded had national IPC programmes (Figure 2.5), but none reported that all their tertiary hospitals had such a programme. These programmes are important for preventing the spread of infectious diseases, including those caused by antimicrobial-resistant microorganisms.
3. **WHO Region of the Americas**

Regional facts

- Number of Member States: 35
- Number of Member States for which information was available for the analysis: 26 (74%)
- Regional population: approximately 950 million
- Life expectancy for Region: average: 75 years; range: 63–82 years

Regional overview

The WHO Region of the Americas comprises 35 Member States. Most (88%) of the 26 countries that responded to the request for information are low- to middle-income countries. The WHO Regional Office for the Americas through the Pan American Health Organization (PAHO) initiated strategies and interventions to contain antimicrobial resistance almost two decades ago. Nevertheless, major gaps remain in some areas.

Only three countries reported having a national plan to address antimicrobial resistance in a multisectoral approach. In 2013, the Regional Technical Advisory Group on Antimicrobial Resistance and Infection Prevention and Control suggested a framework to assist countries in establishing national plans.

Public awareness of antimicrobial resistance was low, and only 10 countries had conducted a public information campaign within the previous 2 years. Overall knowledge about antimicrobial resistance was low in the key sectors of health care, politics and the media.

The Latin American Network for Antimicrobial Resistance Surveillance has helped to improve bacterial surveillance in the Region, specifically in the Latin American countries. A national reference laboratory for testing sensitivity to antibiotics was present in 25 countries (71%). Few countries (13), however, reported having provided a report on surveillance of antimicrobial resistance in humans.

A national IPC programme was reported by 11 countries; four had one in all tertiary hospitals.

Antimicrobial medicines were readily available over the counter in 18 countries, and prescriptions could be regulated in only 11 countries. Ten countries had standard treatment guidelines.

WHO (2006) reported that counterfeit medicines are a problem in the Region, particularly in Latin America. Strong national regulatory authorities and quality standards could weaken the production of counterfeit medicines; however, only 17 countries reported that they had a national regulatory authority, 14 had quality standards, and 14 had the capacity to enforce the standards.

3.1 **Introduction**

The WHO Region of the Americas comprises all of North, Central and South America and the Caribbean islands (Figure 3.1). All except three of the countries that responded to the request for information are lower- to middle-income countries.

The Regional Office recognized the serious threat posed by antimicrobial resistance in the mid-1990s and undertook a programme to improve surveillance and to control antimicrobial re-
AMR ANTIMICROBIAL RESISTANCE

Resistance in the Americas by strengthening laboratory capacity to identify bacteria and test for antimicrobial susceptibility (Periago, 2011).

For the survey, countries identified acute respiratory infections (including pneumonia and TB), gastroenteritis and dengue fever as their main public health challenges. Inappropriate use of antimicrobial medicines is a major driver of antimicrobial resistance in the Region, with self-medication, easy access to these medicines and lack of awareness in several important sectors.

3.2 National plans and other strategies

Few countries reported having a national plan (9%; Figure 3.1). More had a national coordinating mechanism (20%) and a national focal point (20%), but policies and strategies were less frequent. Only 14% of countries had issued a progress report in the previous 5 years.

Developing national plans and strategies is a major area for improvement in the Region, as these are crucial for controlling antimicrobial resistance globally. Many countries recognized that national plans were urgently needed. The Regional Technical Advisory Group on Antimicrobial Resistance and Infection Prevention and Control suggested that a framework be developed to help countries construct national plans (PAHO, 2013a).

Figure 3.1 – Percentages of Member States that had a national antimicrobial resistance plan, coordinating mechanism, focal point, policy or strategy and had prepared a report in the previous 5 years, WHO Region of the Americas (Note: numbers above the bars represent the numbers of responses)
3.3 Surveillance and laboratory capacity

The Americas have a regional surveillance network, the Latin American Network for Antimicrobial Resistance Surveillance, which coordinates surveillance in 21 countries (WHO, 2014). The Network includes many Latin American countries; English-speaking Caribbean countries are invited to contribute data but are not part of the external quality assessment programme. Some countries are also a part of the Sistema de Redes de Vigilancia de los Agentes Responsables de Neumonias y Meningitis Bacterianas, which monitors bacteria that cause vaccine-preventable pneumonia and meningitis (*Neisseria meningitidis*, *Pneumococcus pneumoniae* and *Haemophilus influenzae*).

Surveillance of antimicrobial resistance was performed in 57% of countries in the Region (Figure 3.2).

National reference laboratories for testing sensitivity to antibiotics were present in 25 (71%) countries. This partly reflects the work of the Latin American Network for Antimicrobial Resistance Surveillance, which has strengthened laboratory networks considerably in many countries.

Only 13 countries (37%) had prepared reports on antimicrobial resistance surveillance.
3.4 Access to quality-assured antimicrobial medicines

The Regional Office uses a system based on indicators to classify the Region’s national regulatory authorities. The highest level designates a “national regulatory authority that is competent and efficient in performance of the health regulation functions recommended by PAHO/WHO to guarantee the efficacy, safety and quality of medicines”; it is therefore considered a regional reference authority (PAHO, 2014). The Pan American Network for Drug Regulatory Harmonization was initiated by the Region’s national regulatory authorities and the Regional Office (PAHO, 2013b).

Only 17 (49%) countries reported having a national regulatory authority; 14 (40%) had quality standards, and 14 (40%) could enforce those standards. Most countries (21; 60%) had an essential medicines list. Good initiatives existed in the Region to improve access to safe, high-quality medicines; however, many countries still lacked stringent control. Many reported previously that counterfeit medicines were a significant problem in their country (WHO, 2006).

3.5 Use of antimicrobial medicines

Over 50% of countries reported that antimicrobial medicines were freely available without a prescription. Only about 40% of the countries could prepare standard treatment guidelines. Use of antimicrobial medicines had been monitored in 17% of countries in the previous 5 years (Table 3.1).

Table 3.1 – Use of antimicrobial medicines, WHO Region of the Americas

<table>
<thead>
<tr>
<th></th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Unknown (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial medicines are available without a prescription.</td>
<td>51</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>Restriction of prescription-only medicines can be enforced.</td>
<td>31</td>
<td>20</td>
<td>49</td>
</tr>
<tr>
<td>Standard treatment guidelines could be drawn up.</td>
<td>40</td>
<td>11</td>
<td>49</td>
</tr>
<tr>
<td>Use of antimicrobial medicines was monitored in the previous 5 years.</td>
<td>17</td>
<td>26</td>
<td>57</td>
</tr>
</tbody>
</table>

3.6 Public awareness

Public awareness in the participating countries in the Americas was relatively low; about 29% of countries (10) had conducted a public information campaign in the previous 2 years. Many countries noted that educating the public is important in tackling the problem of antimicrobial resistance but indicated poor general awareness in politics, health care, pharmaceuticals and the media.

3.7 Infection prevention and control programmes

Enhanced IPC programmes are crucial for controlling the spread of infections and antimicrobial-resistant microorganisms within and between health care facilities and via travel and trade. A national IPC programme was present in 11 (42%) countries, and 4 (15%) had an IPC programme in all tertiary hospitals.
4. WHO Eastern Mediterranean Region

Regional facts

Number of Member States: 21

Number of Member States for which information was available for the analysis: 13 (62%)

Regional population: 583 million

Life expectancy in the Region: average: 72 years; range: 60–80 years

Regional overview

The Eastern Mediterranean Region comprises 21, mostly low- to middle-income Member States.

Overall, many gaps were found in addressing antimicrobial resistance in the Region. This is not surprising, given the other emergencies in those countries. None of the countries reported having a national action plan for antimicrobial resistance, which is considered a priority and an outcome indicator for control measures. There was poor awareness of antimicrobial resistance in all sectors included in the survey (national authorities, civil society and people involved in health care and pharmaceuticals). Fragmented information on the safe use of antimicrobial medicines was available, although this is crucial. These medicines were available without a prescription in nine countries. Three countries had conducted a public information campaign in the previous 2 years.

Investment in surveillance of antimicrobial resistance appeared to be low: eight of the 21 countries reported surveillance of resistant bacteria. The laboratories that performed antimicrobial testing generally did not have adequate capacity for accurate, comprehensive testing.

Prevention of nosocomial infections requires strong national IPC programmes. Five countries had an IPC programme in place, and four of these indicated that a programme was functioning in all tertiary hospitals. IPC is important for controlling the spread of infection across borders, especially in view of the numbers of refugees in these countries. Regional collaboration will be essential for sharing data from antimicrobial resistance surveillance. Four countries reported monitoring use of antimicrobial medicines.

Counterfeit medicines are a significant problem in the Region. A few countries had regulations for quality standards but with limited enactment due to lack of capacity to enforce regulations.

4.1 Introduction

The WHO Eastern Mediterranean Region covers the area around the southern Mediterranean Sea and the Middle East, including some countries of North Africa and the Horn of Africa. The countries are mostly lower- to middle-income countries; only two of the countries that participated in the survey are high-income countries.

Many countries in the Region are facing health emergencies, and political turmoil and internal conflicts have resulted in large internally displaced populations, which compete for the attention of health care professionals and policy-makers. The Region is also receiving large numbers of refugees (50% of the world’s total), adding to the complexity of control of antimicrobial resistance and other public health issues. As is to be expected, many of the low-income countries had un-
nderdeveloped or overburdened health care systems that were unable to cope with the additional load of antimicrobial resistance (WHO Regional Office for the Eastern Mediterranean, 2013).

Most countries reported that TB was their major challenge among infectious diseases; however, antimicrobial resistance was not a high priority in the Region (WHO Regional Office for the Eastern Mediterranean, 2013). Countries are being urged to reverse this trend by establishing better antimicrobial resistance surveillance systems and more effective enforcement of regulations.

4.2 National plans and other strategies

National planning is essential for controlling antimicrobial resistance: the draft global action plan relies on countries having and implementing a national plan. As seen in Figure 4.1, none of the participating countries in the Eastern Mediterranean Region reported having a national action plan, although some had a national coordinating mechanism (9%), national focal points (14%) or policies or strategies (9%). No country had prepared a progress report in the previous 5 years.

Figure 4.1. – Percentages of Member States that had a national plan for antimicrobial resistance, coordinating mechanism, focal point, policy or strategy and had prepared a report in the previous 5 years, WHO Eastern Mediterranean Region
(Note: numbers above the bars represent the numbers of responses)
4.3  Surveillance and laboratory capacity

About 38% of countries reported that they performed surveillance of resistant bacteria (Figure 4.2). The percentage was higher (nearly 43%) for M. tuberculosis, as this infection represents a huge public health problem in the Region. Countries in the Region are increasingly concerned about antimicrobial resistance, and regional collaboration is being sought to improve surveillance (WHO Regional Office for the Eastern Mediterranean, 2013).

At the time of the survey, there was little investment in laboratory surveillance of antimicrobial resistance. Less than half the countries in the Region had national reference laboratories for testing sensitivity to antibiotics, and only five participated in external quality assessment. None of the countries reported having prepared a report on surveillance of antimicrobial resistance, and none had data on the prevalence of antimicrobial resistance, which are necessary for quantifying and efficiently addressing the problem.

4.4  Access to quality-assured antimicrobials

Quality-assured antimicrobials are essential for treating infections successfully. Poor-quality, degraded and counterfeit antimicrobial medicines can lead to antimicrobial resistance (WHO Regional Office for the Western Pacific, 2014); counterfeit medicines are a particular problem in the Eastern Mediterranean Region (WHO Regional Office for the Eastern Mediterranean, 2013).

Regulatory agencies can set standards to ensure that medicines are of high quality and available to the entire population. Ten countries had a national regulatory authority, four had quality standards, and the national regulatory authority could enforce standards in seven countries. Nine had a list of essential medicines.
4.5 Use of antimicrobial medicines

In the Region, there is a strong possibility of misuse of antimicrobial medicines in the health sector and little enforcement of the rules and regulations that are in place (Table 4.1). It has been reported that antimicrobial medicines are often prescribed at the request of patients, and pharmacies do not necessarily comply with regulations (Habibzadeh, 2013; WHO Regional Office for the Eastern Mediterranean, 2013). In addition, pharmaceutical companies and distributors promote use of antimicrobial agents (WHO Regional Office for the Eastern Mediterranean, 2013).

Antimicrobial medicines were available without a prescription in nine of the 21 participating countries. There is no uniform access to health care, and many people find it cheaper and easier to obtain antimicrobial medicines themselves, eliminating the cost and time required to see a health care worker (WHO Regional Office for the Eastern Mediterranean, 2013). About half the surveyed countries reported that they could enforce prescription-only regulations and set standard treatment guidelines. Antimicrobial use was monitored in four countries.

There were gaps in knowledge about the policies and practices of use of antimicrobial medicines, as high percentages of “unknown” were recorded in nearly all categories.

Table 4.1 – Use of antimicrobial medicines, WHO Eastern Mediterranean Region

<table>
<thead>
<tr>
<th></th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Unknown (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial medicines are available without a prescription.</td>
<td>43</td>
<td>5</td>
<td>52</td>
</tr>
<tr>
<td>Restriction of prescription-only medicines can be enforced.</td>
<td>33</td>
<td>9</td>
<td>58</td>
</tr>
<tr>
<td>Standard treatment guidelines could be drawn up.</td>
<td>33</td>
<td>9</td>
<td>58</td>
</tr>
<tr>
<td>Use of antimicrobial medicines was monitored in the previous 5 years.</td>
<td>19</td>
<td>24</td>
<td>57</td>
</tr>
</tbody>
</table>

4.6 Public awareness

Overall, public awareness in the Region about the problem of antimicrobial resistance and its causes was poor. Only three (14%) countries had conducted a public information campaign in the previous 2 years. It has been reported that many people in the Region believe that antibiotics help in most ailments (Habibzadeh, 2013). Better public education and changes to systems and policies will be required to curb inappropriate use of antimicrobials.

4.7 Infection prevention and control programmes

Effective IPC programmes are important for managing and containing antimicrobial resistance. Five of the 21 countries had IPC strategies, and four reported that an IPC programme was available in all tertiary hospitals.
5. WHO European Region

Regional facts

Number of Member States: 53
Number of Member States for which information was available for the analysis: 49 (92%)
Regional population: 902 million
Life expectancy for region: average: 77 years; range: 63–83 years

Regional overview

The WHO European Region comprises 53 Member States, 58% of which are high-income countries.

The Region has several plans and strategies to address antimicrobial resistance, and 40% of countries reported having an action plan. Many had a national coordinating mechanism (47%) or national focal point (70%).

Public information campaigns were common in the Region, as 79% of the countries had implemented one in the previous 2 years; however, a survey conducted in 2013 in the European Union indicated that about half the population believed that antibiotics are effective against viruses (European Commission, 2013a). This illustrates that there continues to be a need for targeted information campaigns even in countries with a long-standing effort in this area.

All countries that are members of the European Union undertake surveillance of resistance in bacteria through EARS-Net, which is facilitated by the European Centre for Disease Prevention and Control. Since 2012, countries that are not members of the European Union receive support from the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) network, initiated by WHO and partners to strengthen surveillance of antimicrobial resistance in that part of the Region. The CAESAR network will provide data compatible with that collected by EARS-Net to complete the overview of antimicrobial resistance trends throughout the Region.

About half the countries had a national IPC programme in place; less than 20% had one in every tertiary hospital. IPC programmes are important for preventing the transmission of resistant organisms.

5.1 Introduction

The WHO European Region is a very diverse region comprising 53 countries. More than half (58%) are high-income countries; the remainder are lower to middle-income countries. Good infrastructure is available to combat antimicrobial resistance in the Region, especially in the high-income countries; as a result, many countries can focus on indicators of progress and on optimizing their systems. The Regional Office recognizes the implications of antimicrobial resistance for global public health and has undertaken international and interregional initiatives to address the problem. For example, in 2011, all 53 countries adopted a strategic action plan with the following activity areas and strategic objectives (WHO Regional Office for Europe, 2014): strengthen intersectoral coordination; strengthen surveillance of antibiotic resistance; promote rational use and strengthen surveillance of antibiotic consumption; strengthen infection control and surveillance in health care settings; promote innovation and research on new drugs; and improve awareness, patient safety and partnership.
The Transatlantic Taskforce on Antimicrobial Resistance (2014), a collaboration between the European Union and the United States of America, also encourages appropriate therapeutic use of antimicrobial medicines, prevention of antimicrobial-resistant infections in health care facilities and communities, and strategies to improve the “pipeline” for new antimicrobial medicines. Antimicrobial stewardship programmes to promote adherence to treatment guidelines are used in the European Union to optimize antimicrobial prescribing in health care facilities in order to slow the spread of antimicrobial resistance (Huttner et al., 2013).

5.2 National plans and other strategies

National action plans are important to combat antimicrobial resistance both nationally and globally. Less than half the countries of the Region had an action plan (Figure 5.1); however, 47% had a national coordination mechanism, and 70% had national focal points. Although a number of countries have made good progress in this area for many years, a financed, multisectoral national action plan remains an important means for countries to adopt a comprehensive approach to combat antimicrobial resistance. Less than 40% of countries had policies or strategies in place to counteract antimicrobial resistance, and about 21% had issued a recent report on relevant activities.

Figure 5.1 – Percentages of Member States that had a national plan for antimicrobial resistance, coordinating mechanism, focal point, policy or strategy and had prepared a report in the previous 5 years, WHO European Region
(Note: numbers above the bars represent the numbers of responses)
5.3 Surveillance and laboratory capacity

Figure 5.2 shows that 62% of countries collected data from surveillance of antimicrobial-resistant bacteria. Antimicrobial resistance in the European Union is monitored through EARS-Net, a network of surveillance sites in European Union countries coordinated by the European Centre for Disease Prevention and Control. For the non-European Union countries of the Region, WHO and partners have established the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) network of national surveillance systems, which uses the same methods as EARS-Net. CAESAR connects existing national surveillance systems and builds surveillance in countries that do not yet have established systems. Currently, 16 countries are participating at various stages in CAESAR.

Many countries collect comprehensive data on the prevalence of specific resistant strains (WHO Regional Office for Europe, 2014).

A national reference laboratory for testing sensitivity to antibiotics was present in 36 (68%) countries. In 40 (75%) countries, laboratories participated in external quality assessment.

Surveillance of antimicrobial resistance was reported by 29 (55%) countries.

5.4 Access to quality-assured antimicrobial medicines

The quality of antimicrobial medicines in the Region is high, as 47 (89%) countries had a national regulatory agency, and 49 (92%) had quality standards. In addition, 48 (91%) countries reported that they could enforce the quality standards. Poor-quality and counterfeit medicines may therefore not be a significant cause of antimicrobial resistance in the Region. A list of essential medicines was available in 32 (60%) countries.
5.5 Use of antimicrobial medicines

In 43% of the countries, antimicrobial medicines were sold without a prescription; 55% of countries reported that they could enforce regulations (Table 5.1). Only 43% of countries reported that they could prepare standard guidelines for health care workers treating infections.

Data on antimicrobial use are gathered through the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) from countries in the European Union and the European Economic Area by the European Centre for Disease Prevention and Control; for non-European Union countries, data are collected through the Antimicrobial Medicines Consumption Project Group of the Regional Office. As a result, there is good monitoring of antimicrobial use (Table 5.1).

<table>
<thead>
<tr>
<th>Table 5.1 – Antimicrobial use, WHO European Region</th>
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<tbody>
<tr>
<td>Antimicrobial medicines are available without a prescription.</td>
</tr>
<tr>
<td>Restriction of prescription-only medicines can be enforced.</td>
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<tr>
<td>Standard treatment guidelines could be drawn up.</td>
</tr>
<tr>
<td>Use of antimicrobial medicines was monitored in the previous 5 years.</td>
</tr>
</tbody>
</table>

5.6 Public awareness

The frequency of public information campaigns on antibacterial resistance in the Region was relatively high, as about 79% of Member States (42) reported having organized at least one campaign in the previous 2 years. A European Union survey in 2013 revealed, however, that about half of the population believed that antibiotics are effective against viral infections and therefore expected them to be prescribed for a common cold or influenza (European Commission, 2013a).

5.7 Infection prevention and control programmes

IPC programmes are essential for controlling all infections and especially for halting the transmission of antimicrobial-resistant organisms. These programmes are most useful when there is guidance at national and facility levels. Twenty-seven (51%) countries had a national IPC programme, and eight (15%) reported that all their tertiary hospitals had a facility-specific IPC programme.

Europe is currently the world’s first tourist destination (European Commission, 2013b), which could facilitate the spread of resistant microorganisms across borders. In addition, Europe is experiencing an influx of refugees, mainly from the Syrian Arab Republic (Migration Policy Centre, 2014). More, stronger IPC programmes will help to address cross-border transmission of antimicrobial resistance.
6. WHO South-East Asia Region

Regional facts

- Number of Member States: 11
- Number of Member States for which information was available for the analysis: 11 (100%)
- Regional population: approximately 1.75 billion
- Life expectancy for region: average: 70 years; range: 66–77 years

Regional overview

The WHO South-East Asia Region comprises 11 Member States, all of which are lower- to middle-income countries.

The Region recognizes antimicrobial resistance as a serious threat to public health. The WHO Regional Office for South-East Asia has prepared a regional strategy on prevention and containment of antimicrobial resistance (WHO, 2010), and, in 2011, all health ministers in the Region committed themselves to concerted action by adopting the Jaipur Declaration on Antimicrobial Resistance. In accordance with the Jaipur Declaration and the regional strategy, all Member States are encouraged to have a multisectoral national plan to combat antimicrobial resistance. At the time of the survey, five of the 11 countries in the Region reported having such a plan, and two countries reported that a plan was in preparation. More countries reported having a national coordination mechanism or strategies or policies.

Public awareness in the Region is growing, as five countries reported having conducted a public awareness campaign on antimicrobial resistance in the previous 2 years.

Countries face many challenges in conducting surveillance, but it is recognized as a priority in the regional strategy. Four countries had prepared reports on antimicrobial resistance surveillance, and Member States report annually on progress made in accordance with the Jaipur Declaration.

Monitoring use of antimicrobial medicines was limited, and these medicines were available without a prescription in more than half the countries. Many countries reported that health care workers comply poorly with prescribing standards and guidelines.

IPC programmes are evolving in the Region, with nine of the 11 countries having a national IPC programme and seven with such a programme in all tertiary hospitals.

Nine of the 11 countries had a national regulatory agency, and six had quality standards.

6.1 Introduction

The WHO South-East Asia Region comprises 11 Member States. All the countries are lower- to middle-income countries.

The Region recognizes antimicrobial resistance as a serious global problem that requires a regional response. In 2011, the Region’s health ministers adopted the Jaipur Declaration on Antimicrobial Resistance, which states that combating antimicrobial resistance must be a priority for national governments. To this end, the Regional Office has prepared a strategy (WHO Regional Office for South-East Asia, 2010) to support countries in introducing legislation and policies to govern the use of antimicrobial medicines; establishing laboratory-based networks for surveillance
of antimicrobial resistance; ensuring rational use of antimicrobial medicines in all health care settings; and promoting community awareness about antimicrobial resistance.

Since 2011, policies for containing antimicrobial resistance have become more common (WHO Regional Office for South-East Asia, 2013). The regional strategy also encourages research into the development or improvement of antimicrobial medicines.

The country situation analysis showed that antimicrobial resistance is a major problem in the Region and that nosocomial infections are a particular concern. The main cause of resistance appears to be inappropriate use of antimicrobial medicines, due to both their over-the-counter availability and the poor compliance of health care workers with standards.

### 6.2 National plans and other strategies

Five (45%) of the Region’s Member States had a national plan. Seven (64%) reported having a national coordinating mechanism, and six (55%) reported having policies or strategies (Figure 6.1).

![Figure 6.1](image_url) – Percentages of Member States that had a national plan for antimicrobial resistance, coordinating mechanism, focal point, policy or strategy and had prepared a report in the previous 5 years, WHO South-East Asia Region (Note: numbers above the bars represent the numbers of responses)
6.3 Surveillance and laboratory capacity

Figure 6.2 shows that all 11 countries collected surveillance data on antimicrobial resistance in bacteria. The survey did not include a breakdown by target organism, but the Regional Office (2013) reported a focus on methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci and bacteria that produce extended-spectrum β-lactamases and metallo-β-lactamases.

Figure 6.2 – Percentages of Member States that had conducted surveillance for antimicrobial resistance in bacteria in general and in the causative agents of tuberculosis, malaria, influenza and HIV infection, WHO South-East Asia Region
(Note: numbers above the bars represent the numbers of responses)

Nine countries (82%) had national reference laboratories for testing sensitivity to antibiotics, and six (53%) participated in external quality assessment.

In countries that had prepared reports on antimicrobial resistance surveillance, monitoring in humans was infrequent (36%; four countries).

6.4 Access to quality-assured antimicrobial medicines

A national regulatory agency existed in nine (82%) countries, and six (55%) had quality standards; seven (64%) reported that they could enforce the quality standards. WHO (2010) reported that counterfeit medicines are a significant problem in both the WHO South-East Asia and Western Pacific regions.

All 11 Member States had a list of essential medicines.
6.5 Use of antimicrobial medicines

Antimicrobial medicines were available without a prescription in 64% of countries, and 82% reported that they could enforce regulations (Table 6.1). Few countries had conducted information campaigns on antimicrobial resistance, although all had prepared standard treatment guidelines to raise awareness among health care workers about the treatment of infections. Many countries reported compliance with prescribing regulations. Little monitoring of antimicrobial use was reported in the Region (Table 6.1).

<table>
<thead>
<tr>
<th>Table 6.1 – Antimicrobial use, WHO South-East Asia Region</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yes (%)</strong></td>
</tr>
<tr>
<td>Antimicrobial medicines are available without a prescription.</td>
</tr>
<tr>
<td>Restriction of prescription-only medicines can be enforced.</td>
</tr>
<tr>
<td>Standard treatment guidelines could be drawn up.</td>
</tr>
<tr>
<td>Use of antimicrobial medicines was monitored in the previous 5 years.</td>
</tr>
</tbody>
</table>

6.6 Public awareness

At the time of the survey, five countries (45%) reported having conducted a public information campaign on antimicrobial use in the previous 2 years (Figure 6.7). Further progress has been made, with campaigns now being undertaken in almost all countries. Since World Health Day in 2011, the WHO Regional Office has been distributing material to Member States in the Region to raise awareness.

6.7 Infection prevention and control programmes

IPC programmes address all types of infection and are especially important in slowing the transmission of antimicrobial-resistant organisms. Nine of the Region’s Member States reported a national IPC programme, and seven reported that all their tertiary hospitals had such a programme.
7. WHO Western Pacific Region

Regional facts

<table>
<thead>
<tr>
<th>Number of Member States: 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Member States for which information was available for the analysis: 26 (96%)</td>
</tr>
<tr>
<td>Regional population: 1.85 billion</td>
</tr>
<tr>
<td>Life expectancy for region: average: 73 years; range: 62–84 years</td>
</tr>
</tbody>
</table>

Regional overview

The Western Pacific Region comprises 27 Member States, which are widely diverse socioeconomically and include some of the world’s least developed countries.

The WHO Regional Office for the Western Pacific was the first WHO regional office to implement recommendations for surveillance of antimicrobial resistance, in 1982; however, other competing major public health issues (e.g. severe acute respiratory syndrome in 2003 and avian influenza) have slowed progress.

Four countries (17%) reported having a national action plan. There was lack of awareness about antimicrobial resistance among the general public and in all sectors, including policymaking, and lack of public information on the safe use of antimicrobial medicines. Less than half the countries had conducted a public information campaign in the previous 2 years.

Nearly 70% of countries reported surveillance for antimicrobial resistance in bacteria; this proportion may increase following introduction of the Western Pacific Antimicrobial Resistance Surveillance system in the near future.

More than half the countries (67%) reported having an IPC programme; 59% indicated that a programme was operating in all tertiary hospitals.

There was weak enforcement of regulations on the sale of antimicrobial medicines without prescription and of quality standards. Countries had poor capacity to enforce standards and requirements to promote the rational use of antimicrobial medicines.

7.1 Introduction

The WHO Western Pacific Region covers a vast area, from Mongolia and China in the north and west to New Zealand in the south and French Polynesia in the east; it comprises 37 countries and areas. The Region’s population represents about 25% of the total world population, China itself accounting for approximately three fourths of the population of the Region (United Nations Development Programme, 2014). The Region is one of the most diverse of all the WHO regions, as it includes some of the world’s least developed countries as well as highly developed and rapidly emerging economies. It includes six high-income countries, while the remainder are lower- to middle-income countries (World Bank, 2014). This socioeconomic spread results in wide variation in health care resources and financing and differences in strategies for containing antimicrobial resistance.

The commonest public health threats reported by high-income countries included antimicrobial resistance and health care-associated and vaccine-preventable infections. In the lower-
middle-income countries, the main public health challenges are TB, insect-borne infections (e.g. dengue, malaria), bacterial infections and sexually transmitted infections (including HIV infection).

The Regional Office for the Western Pacific was the first regional office to implement recommendations for surveillance of antimicrobial resistance, in 1982. The scale of the problem of antimicrobial resistance in the Region varies. Some high-income countries reported that it is an issue mainly in hospitals, while many lower- to middle-income countries indicated that inappropriate use of antimicrobial medicines is prevalent.

7.2 National plans and other strategies

Four countries (15%) in the Region reported having a national action plan to contain antimicrobial resistance, and less than half reported having national focal points, national coordinating mechanisms, policies or strategies (Figure 7.1). Six countries (22%) had issued a progress report within the previous 5 years. These data indicate gaps in strategies and policies to contain antimicrobial resistance at country and regional levels, even in many high-income countries.

Figure 7.1 – Percentages of Member States that had a national plan for antimicrobial resistance, coordinating mechanism, focal point, policy or strategy and had prepared a report in the previous 5 years, WHO Western Pacific Region (Note: numbers above the bars represent the numbers of responses)
7.3 Surveillance and laboratory capacity

In 2013, the Regional Office proposed the Western Pacific Antimicrobial Resistance Surveillance (WePARS) network for tracking and early detection of antimicrobial resistance. It identified strengthening laboratory capacity and harmonizing laboratory methods as crucial elements in containing antimicrobial resistance in the Region. The main focus of WePARS will be resistance in bacteria in sectors that are not covered by other vertical disease programmes, such as for MDR-TB.

Just over 70% of countries reported conducting some bacterial surveillance (Figure 7.2).

![Figure 7.2](image)

Figure 7.2 – Percentages of Member States that had conducted surveillance for resistance in bacteria in general and in the causative agents of tuberculosis, malaria, influenza and HIV infection, WHO Western Pacific Region (Note: numbers above the bars represent the numbers of responses)

Bacterial surveillance is successful only if laboratories can ensure the quality of testing and the reliability of the results (i.e. internal quality control). The Clinical and Laboratory Standards Institute in the United States of America and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) both publish standardized testing methods; most countries in the Western Pacific Region use the former (WHO Regional Office for the Western Pacific, 2014).

Eighteen countries in the Region (67%) reported having a national reference laboratory in which sensitivity to antibiotics was tested, and 17 (63%) had laboratories that participated in external quality assessment (Figure 7.3).

More than half (56%; 15) of the countries reported having prepared reports on antimicrobial resistance surveillance; nearly 44% had not or were unsure.
7.4 Access to quality-assured antimicrobial medicines

Seventeen countries reported having a national regulatory authority, and the same number reported that the authority could enforce quality standards. Fifteen (56%) reported having national quality standards; however, some reported that although they had a national regulatory authority they were unable to enforce standards, while others reported that they could enforce standards but did not have a regulatory authority.

A list of essential medicines was available in 92% (24) of participating countries.

7.5 Use of antimicrobial medicines

A few countries reported that a national system was in place to monitor rational use of antimicrobial medicines. The Regional Office is strengthening countries’ national monitoring systems, and the data obtained will be used to track progress towards appropriate use of antimicrobial medicines and to inform policy-makers in establishing national plans and policies (see section 7.2). The public could buy antimicrobial medicines without a prescription in 52% of the countries (Table 7.1). Only 59% of the countries reported that they could prepare standard treatment guidelines. Half the responding countries reported monitoring use of antimicrobial medicines in humans.

Table 7.1 – Antimicrobial use, Western Pacific Region

<table>
<thead>
<tr>
<th></th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Unknown (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial medicines are available without a prescription.</td>
<td>52</td>
<td>41</td>
<td>7</td>
</tr>
<tr>
<td>Restriction of prescription-only medicines can be enforced.</td>
<td>85</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Standard treatment guidelines could be drawn up.</td>
<td>59</td>
<td>26</td>
<td>15</td>
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<td>Use of antimicrobial medicines was monitored in the previous 5 years.</td>
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7.6 Public awareness

Public information about appropriate antimicrobial use is especially important in areas where these medicines are available without a prescription, and 52% of the countries reported that this was the case (see section 7.5). Just over one third the Member States (10 countries) had conducted a public information campaign within the previous 2 years.

7.7 Infection prevention and control programmes

More than half the countries (81; 67%) reported having an IPC programme, and 16 indicated that a programme was present in all tertiary hospitals.
8. Conclusions

Although antimicrobial resistance is a natural phenomenon, it is being propagated by misuse of antimicrobial medicines, poor-quality medicines, weak laboratory capacity and surveillance, insufficient regulation of the use of these medicines and inadequate or inexistent programmes for IPC. This initial “country situation analysis” was conducted in 2013 in Member States in each of the six WHO regions to determine the extent to which effective practices and structures to address antimicrobial resistance are already in place and where gaps remain. As widely different proportions of countries in each Region provided information, caution should be exercised in interpreting the results and in comparing the results among regions.

The survey addressed the key elements for combating antimicrobial resistance: a comprehensive national plan, laboratory capacity to undertake surveillance for resistant microorganisms, access to safe, effective antimicrobial medicines, control of the misuse of antimicrobial medicines, awareness and understanding among the general public and effective IPC programmes.

1. Only a few countries reported having a comprehensive national plan based on a multisectoral approach and with sustainable financing. More countries reported having a national focal point for antimicrobial resistance and a national coordination mechanism; others had put in place relevant strategies and policies. Progress is to be made even in countries with strong health-care systems.

2. Surveillance of antimicrobial resistance varied by type of resistance and by country in all WHO regions; in many, poor laboratory capacity, infrastructure and data management prevented effective surveillance. A national reference laboratory capable of testing for antibiotic sensitivity was present in each region; however, many of the laboratories did not participate in external quality assessment schemes. Monitoring of antimicrobial resistance was infrequent, although, in three regions, more than half the responding countries had prepared reports on surveillance of antimicrobial resistance in humans.

3. Regions in which there are many high-income countries, such as the European and the Western Pacific regions, reported higher rates of access to high-quality medicines. In the regions in which there were problems of low-quality and/or counterfeit medicines, few countries had a national regulatory authority, national standards or the capacity to enforce them.

4. The sale of antimicrobial medicines without prescription was widespread, and many countries lacked standard treatment guidelines for health care workers. Thus, overuse of antimicrobial medicines by the public and by the medical profession was a potential problem in all regions. Few countries reported a system for monitoring the use of antimicrobial medicines; tracking of prescribing patterns and over-the-counter sales is therefore a significant challenge. Furthermore, regulations on the sale of prescription-only medicines could not be widely enforced in several regions.

5. Public awareness of antimicrobial resistance was generally low in all regions. Even in some countries in which national public awareness campaigns had been conducted, there was still widespread belief that antibiotics are effective against viral infections. The level of awareness about antimicrobial resistance was also low in the sectors of health care, politics, the media and academia. More education and collaborative awareness-raising campaigns in these sectors will be required. If these sectors are not well informed, the appropriate regulations and standards will not be legislated, and the other sectors will not have the information to implement them effectively.

6. Half the Member States in the European, South-East Asia and Western Pacific regions that responded to the survey reported having a national IPC programme; fewer had IPC programmes in all tertiary hospitals.
This first country situation analysis provides an overview of existing structures and policies to address antimicrobial resistance in 133 Member States. The survey summarized in this report can inform future global efforts to tackle antimicrobial resistance and form the basis for a monitoring framework to assess progress in countries.
References and further reading


Annex 1.

A
Afghanistan
Albania
Antigua and Barbuda
Argentina
Armenia
Australia
Austria
Azerbaijan

B
Bahrain
Bangladesh
Barbados
Belarus
Belgium
Belize
Bhutan
Bolivia (Plurinational State of)
Bosnia and Herzegovina
Brazil
Brunei Darussalam
Bulgaria
Burkina Faso

C
Cambodia
Canada
Central African Republic
Chile
China
Colombia
Cook Islands
Costa Rica
Croatia
Cuba
Cyprus
Czech Republic

D
Democratic People’s Republic of Korea
Denmark
Dominica
Dominican Republic

E
Ecuador
Egypt
El Salvador
Estonia

F
Fiji
France

G
Gambia
Georgia
Germany
Ghana
Greece
Guatemala
Guyana

H
Honduras
Hungary

I
Iceland
India
Indonesia
Iran (Islamic Republic of)
Ireland
Israel
Italy

J
Jamaica
Japan
Jordan

K
Kazakhstan
Kiribati
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GLOBAL ACTION PLAN
ON ANTIMICROBIAL RESISTANCE
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# Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreword</td>
<td>VII</td>
</tr>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Scope</td>
<td>2</td>
</tr>
<tr>
<td>The challenge</td>
<td>3</td>
</tr>
<tr>
<td>The way forward</td>
<td>5</td>
</tr>
<tr>
<td>Consultative process</td>
<td>7</td>
</tr>
<tr>
<td>Strategic objectives</td>
<td>8</td>
</tr>
<tr>
<td>Objective 1: Improve awareness and understanding of antimicrobial resistance through effective communication, education and training</td>
<td>8</td>
</tr>
<tr>
<td>Objective 2: Strengthen the knowledge and evidence base through surveillance and research</td>
<td>8</td>
</tr>
<tr>
<td>Objective 3: Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures</td>
<td>9</td>
</tr>
<tr>
<td>Objective 4: Optimize the use of antimicrobial medicines in human and animal health</td>
<td>10</td>
</tr>
<tr>
<td>Objective 5: Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions</td>
<td>11</td>
</tr>
<tr>
<td>Framework for action on antimicrobial resistance</td>
<td>12</td>
</tr>
</tbody>
</table>
Foreword

Antimicrobial resistance threatens the very core of modern medicine and the sustainability of an effective, global public health response to the enduring threat from infectious diseases. Effective antimicrobial drugs are prerequisites for both preventive and curative measures, protecting patients from potentially fatal diseases and ensuring that complex procedures, such as surgery and chemotherapy, can be provided at low risk. Yet systematic misuse and overuse of these drugs in human medicine and food production have put every nation at risk. Few replacement products are in the pipeline. Without harmonized and immediate action on a global scale, the world is heading towards a post-antibiotic era in which common infections could once again kill.

Alert to this crisis, the May 2015 World Health Assembly adopted a global action plan on antimicrobial resistance, which outlines five objectives:

- to improve awareness and understanding of antimicrobial resistance through effective communication, education and training;
- to strengthen the knowledge and evidence base through surveillance and research;
- to reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures;
- to optimize the use of antimicrobial medicines in human and animal health;
- to develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions.

This action plan underscores the need for an effective “one health” approach involving coordination among numerous international sectors and actors, including human and veterinary medicine, agriculture, finance, environment, and well-informed consumers. The action plan recognizes and addresses both the variable resources nations have to combat antimicrobial resistance and the economic factors that discourage the development of replacement products by the pharmaceutical industry.

An all-out effort is needed. WHO will work with the United Nations to tackle antimicrobial resistance at the political level. Our strong collaboration with FAO and OIE will continue. A framework for monitoring and evaluating national activities is being developed. The objective is to have multisectoral national action plans in place by the 2017 World Health Assembly.

Antimicrobial resistance is a crisis that must be managed with the utmost urgency. As the world enters the ambitious new era of sustainable development, we cannot allow hard-won gains for health to be eroded by the failure of our mainstay medicines.

Dr Margaret Chan
Director-General
World Health Organization
Introduction

1. When microbes become resistant to medicines, the options for treating the diseases they cause are reduced. This resistance to antimicrobial medicines is happening in all parts of the world for a broad range of microorganisms with an increasing prevalence that threatens human and animal health. The direct consequences of infection with resistant microorganisms can be severe, including longer illnesses, increased mortality, prolonged stays in hospital, loss of protection for patients undergoing operations and other medical procedures, and increased costs. Antimicrobial resistance affects all areas of health, involves many sectors and has an impact on the whole of society.

2. The indirect impact of antimicrobial resistance, however, extends beyond increased health risks and has many public health consequences with wide implications, for instance on development. Antimicrobial resistance is a drain on the global economy with economic losses due to reduced productivity caused by sickness (of both human beings and animals) and higher costs of treatment. To counter it needs long-term investment, such as financial and technical support for developing countries and in development of new medicines, diagnostic tools, vaccines and other interventions, and in strengthening health systems to ensure more appropriate use of and access to antimicrobial agents.

3. The development of this global action plan on antimicrobial resistance, requested by the Health Assembly in resolution WHA67.25 in May 2014, reflects a global consensus that antimicrobial resistance poses a profound threat to human health. It reflects the input received to date from broad multisectoral and Member States’ consultations.

4. The goal of the global action plan is to ensure, for as long as possible, continuity of successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them. It is expected that countries will develop their own national action plans on antimicrobial resistance in line with the global plan.

5. To achieve this goal, the global action plan sets out five strategic objectives: (1) to improve awareness and understanding of antimicrobial resistance; (2) to strengthen knowledge through surveillance and research; (3) to reduce the incidence of infection; (4) to optimize the use of antimicrobial agents; and (5) to ensure sustainable investment in countering antimicrobial resistance. These objectives can be attained through the implementation of clearly identified actions by Member States, the Secretariat, and international and national partners across multiple sectors. The actions to optimize use of antimicrobial medicines and to renew investment in research and development of new products must be accompanied by actions to ensure affordable and equitable access by those who need them.

6. With this approach, the main goal of ensuring treatment and prevention of infectious diseases with quality-assured, safe and effective medicines is achievable.

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1 See resolution WHA68.7.
Antibiotic resistance develops when bacteria adapt and grow in the presence of antibiotics. The development of resistance is linked to how often antibiotics are used. Because many antibiotics belong to the same class of medicines, resistance to one specific antibiotic agent can lead to resistance to a whole related class. Resistance that develops in one organism or location can also spread rapidly and unpredictably, through, for instance, exchange of genetic material between different bacteria, and can affect antibiotic treatment of a wide range of infections and diseases. Drug-resistant bacteria can circulate in populations of human beings and animals, through food, water and the environment, and transmission is influenced by trade, travel and both human and animal migration. Resistant bacteria can be found in food animals and food products destined for consumption by humans.

Some of these features also apply to medicines that are used to treat viral, parasitic and fungal diseases; hence the broader term antimicrobial resistance.

The global action plan covers antibiotic resistance in most detail but also refers, where appropriate, to existing action plans for viral, parasitic and bacterial diseases, including HIV/AIDS, malaria and tuberculosis. Many of the actions proposed in this plan are equally applicable to antifungal resistance in addition to resistance in those other microorganisms.

Antimicrobial resistance (and particularly antibiotic resistance) is spreading, and there are few prospects for the development of new classes of antibiotics in the short term. However, there is today considerable awareness of the need for, and political support for, action to combat antimicrobial resistance. Support is multisectoral, and there is increasing collaboration among the relevant sectors, in particular, human health, animal health and agriculture (including a tripartite collaboration agreed by FAO, OIE and WHO). The need for urgent action is consistent with a precautionary approach, and national and international multisectoral action and collaboration should not be impeded by gaps in knowledge.

This global action plan provides the framework for national action plans to combat antimicrobial resistance. It sets out the key actions that the various actors involved should take, using an incremental approach over the next 5-10 years to combat antimicrobial resistance. These actions are structured around the five strategic objectives set out in paragraphs 29-47.

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12. Improvements in global health over recent decades are under threat because the microorganisms that cause many common human diseases and medical conditions – including tuberculosis, HIV/AIDS, malaria, sexually transmitted diseases, urinary tract infections, pneumonia, blood-stream infections and food poisoning – have become resistant to a wide range of antimicrobial medicines. Doctors must increasingly use “last-resort” medicines that are more costly, may have more side effects and are often unavailable or unaffordable in low- and middle-income countries. Some cases of tuberculosis and gonorrhoea are now resistant even to antibiotics of last resort.

13. Resistance develops more rapidly through the misuse and overuse of antimicrobial medicines. Antibiotic use for human health is reported to be increasing substantially. Surveys in a wide range of countries show that many patients believe that antibiotics will cure viral infections that cause coughs, colds and fever. Antibiotics are needed to treat sick animals but are also widely used in healthy animals to prevent disease and, in many countries, to promote growth through mass administration to herds. Antimicrobial agents are commonly used in plant agriculture and commercial fish and seafood farming. The potential impact of antimicrobials in the environment is also of concern to many.

14. Antimicrobial resistance can affect all patients and families. Some of the commonest childhood diseases in developing countries – malaria, pneumonia, other respiratory infections, and dysentery – can no longer be cured with many older antibiotics or medicines. In lower-income countries, effective and accessible antibiotics are crucial for saving the lives of children who have those diseases, as well as other conditions such as bacterial blood infections. In all countries, some routine surgical operations and cancer chemotherapy will become less safe without effective antibiotics to protect against infections.

15. Health care workers have a vital role in preserving the power of antimicrobial medicines. Inappropriate prescribing and dispensing can lead to their misuse and overuse if medical staff lack up-to-date information, cannot identify the type of infection, yield to patient pressure to prescribe antibiotics, or benefit financially from supplying the medicines. Inadequate hygiene and infection prevention and control in hospitals help to spread infections. Hospital patients infected with methicillin-resistant Staphylococcus aureus have a higher risk of dying than those infected by a non-resistant form of the bacteria.

16. For farmers, animal husbandry and the food industry, the loss of effective antimicrobial agents to treat sick animals damages food production and family livelihoods. An additional risk for livestock workers is exposure to animals carrying resistant bacteria. For example, farmers working with cattle, pigs and poultry that are infected with methicillin-resistant Staphylococcus aureus have a much higher risk of also being colonized or infected with these bacteria. Food is one of the possible vehicles for transmission of resistant bacteria from animals to human beings and human consumption of food carrying antibiotic-resistant bacteria has led to acquisition of antibiotic-resistant infections. Other risks for infection with resistant organisms include exposure to crops treated with antimicrobial agents or contaminated by manure or slurry, and farmyard run-offs into groundwater.
17. Reducing antimicrobial resistance will require the political will to adopt new policies, including controlling the use of antimicrobial medicines in human health and animal and food production. In most countries, antibiotics can be purchased in markets, shops, pharmacies or over the Internet without prescription or involvement of a health professional or veterinarian. Poor quality medical and veterinary products are widespread, and often contain low concentrations of active ingredients, encouraging emergence of resistant microbes. Laws to ensure that medicines are of assured quality, safe, effective and accessible to those who need them need to be enacted and enforced.

18. The World Economic Forum has identified antibiotic resistance as a global risk beyond the capacity of any organization or nation to manage or mitigate alone, but in general there is little awareness of the potential social, economic and financial impacts of drug resistance. In developed economies, these include higher health care costs and decreases in labour supply, productivity, household incomes, and national income and tax revenues. In the European Union alone, a subset of drug-resistant bacteria is responsible annually for some 25,000 deaths, with extra health care costs and lost productivity due to antimicrobial resistance amounting to at least €1500 million. Similar analyses are needed for low- and middle-income countries. Resistance to common veterinary antimicrobial medicines also causes food production losses, poor animal welfare and extra costs. Antimicrobial resistance is sapping the global economy and the full economic case needs to be made for long-term sustainable investment to tackle the problem, including the ensuring of access to financial and technical support for developing countries.

19. For the pharmaceutical sector, medicines that are no longer effective lose their value. Industry leaders are important partners in combating antimicrobial resistance, both by supporting the responsible use of antimicrobial resistance, in order to prolong their effectiveness and through research and development of innovative medicines and other tools to combat resistance. No major new class of antibiotics has been discovered since 1987 and too few antibacterial agents are in development to meet the challenge of multidrug resistance. New concepts are needed for providing incentives for innovation and promoting cooperation among policy-makers, academia and the pharmaceutical industry to ensure that new technologies are available globally to prevent, diagnose and treat resistant infections. Public sector partnerships with the private sector are also important to help to ensure equitable access to quality-assured products and other related health technologies, through fair pricing and donations for the poorest populations.

The way forward

20. Despite proposals and initiatives over many years to combat antimicrobial resistance, progress has been slow, in part because of, on the one hand, inadequate monitoring and reporting at national, regional and global levels, and, on the other, inadequate recognition by all stakeholders of the need for action in their respective areas.

21. At the national level, operational action plans to combat antimicrobial resistance are needed to support strategic frameworks. All Member States are urged to have in place, within two years of the endorsement of the action plan by the Health Assembly, national action plans on antimicrobial resistance that are aligned with the global action plan and with standards and guidelines established by intergovernmental bodies such as the Codex Alimentarius Commission, FAO and OIE. These national action plans are needed to provide the basis for an assessment of the resource needs, and should take into account national and regional priorities. Partners and other stakeholders, including FAO, OIE, the World Bank, industry associations and foundations, should also put in place and implement action plans in their respective field of responsibility to counter antimicrobial resistance, and report progress as part of their reporting cycles. All action plans should reflect the following principles:

1. **Whole-of-society engagement including a one-health approach.** Antimicrobial resistance will affect everybody, regardless of where they live, their health, economic circumstances, lifestyle or behaviour. It will affect sectors beyond human health, such as animal health, agriculture, food security and economic development. Therefore, everybody – in all sectors and disciplines – should be engaged in the implementation of the action plan, and in particular in efforts to preserve the effectiveness of antimicrobial medicines through conservation and stewardship programmes.

2. **Prevention first.** Every infection prevented is one that needs no treatment. Prevention of infection can be cost effective and implemented in all settings and sectors, even where resources are limited. Good sanitation, hygiene and other infection prevention measures that can slow the development and restrict the spread of difficult-to-treat antibiotic-resistant infections are a “best buy”.

3. **Access.** The aim to preserve the ability to treat serious infections requires both equitable access to, and appropriate use of, existing and new antimicrobial medicines. Effective implementation of national and global action plans to address antimicrobial resistance depends also on access, inter alia, to health facilities, health care professionals, veterinarians, preventive technologies, diagnostic tools including those which are “point of care”, and to knowledge, education and information.

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6 The Secretariat has worked with Member States to collate information on the status of national action plans on antimicrobial resistance and on regulations and policies for use of antimicrobial medicines. A report based on these data provides a baseline against which future progress at national and global levels can be monitored and reported, see http://www.who.int/drugresistance/documents/situationanalysis/en/ (accessed 9 September 2015).
(4) **Sustainability.** All countries should have a national action plan on antimicrobial resistance that includes an assessment of resource needs. The implementation of these plans will require long-term investment, for instance in surveillance, operational research, laboratories, human and animal health systems, competent regulatory capacities, and professional education and training, in both the human and animal health sectors. Political commitment and international collaboration are needed to promote the technical and financial investment necessary for effective development and implementation of national action plans.

(5) **Incremental targets for implementation.** Member States are at very different stages in terms of developing and implementing national plans to combat antimicrobial resistance. To enable all countries to make the most progress towards implementing the global action plan on antimicrobial resistance, flexibility will be built into the monitoring and reporting arrangements in order to allow each country to determine the priority actions that it needs to take in order to attain each of the five strategic objectives and to implement the actions in a stepwise manner that meets both local needs and global priorities.
22. In May 2014, the Sixty-seventh World Health Assembly adopted resolution WHA67.25 on antimicrobial resistance, in which it requested, inter alia, the Director-General, to develop a draft global action plan to combat antimicrobial resistance, including antibiotic resistance, and to submit the draft to the Sixty-eighth World Health Assembly, through the Executive Board.

23. To initiate the preparation of a draft global action plan, the Secretariat used the recommendations of the Strategic and Technical Advisory Group on antimicrobial resistance, existing national and regional action plans, WHO’s guidance and action plans on related subjects, as well as other available evidence and analysis. The Secretariat regularly consulted FAO and OIE, for example through meetings as part of the tripartite collaboration and through their participation in other consultations, to ensure a one-health approach and consistency with Codex Alimentarius and OIE international standards and guidelines.

24. At its second meeting (Geneva, 14–16 April 2014), the Strategic and Technical Advisory Group considered input from more than 30 additional participants, including representatives of intergovernmental organizations, civil society, public health and regulatory agencies, industry associations, professional organizations and patient groups. At a subsequent meeting (Geneva, 17 October 2014), the Advisory Group reviewed the text of the draft global action plan. The Strategic and Technical Advisory Group recently held its fourth meeting (Geneva, 24 and 25 February 2015) in order to provide advice to the Secretariat on finalization of the draft global action plan.

25. During July and August 2014 the Secretariat held a web-based consultation for Member States and other relevant stakeholders, attracting 130 comments and contributions, including 54 from Member States, 40 from nongovernmental organizations and 16 from private-sector entities.

26. Between June and November 2014, Member States, stakeholders and the Secretariat convened additional high-level technical, political and interagency discussions to contribute to the action plan. These included the Ministerial Conference on Antibiotic Resistance: joining forces for future health (The Hague, 25 and 26 June 2014); a meeting on the Global Health Security Agenda, including antimicrobial resistance (Jakarta, 20 and 21 August 2014); an informal Member States consultation to provide direct input on the draft plan (Geneva, 16 October 2014); a meeting on the responsible use of antibiotics (Oslo, 13 and 14 November 2014); and a meeting on global surveillance capacity, systems and standards (Stockholm, 2 and 3 December 2014).


8 Details of national and regional action plans, WHO guidance and action plans for specific diseases and health topics including antimicrobial resistance, standards and guidelines established by intergovernmental organizations such as FAO and OIE, and other information taken into account are documented in supplementary material, see http://www.who.int/drugresistance/documents/situationanalysis/en/ (accessed 9 September 2015).


Strategic objectives

27. The overall goal of the action plan is to ensure, for as long as possible, continuity of the ability to treat and prevent infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them.

28. To achieve this overall goal, five strategic objectives have been identified. These are set out below with the corresponding actions for Member States, the Secretariat (including actions for FAO, OIE and WHO within the tripartite collaboration), and international organizations and other partners, in the tables following paragraph 50. It is expected that countries will develop their own national action plans on antimicrobial resistance in line with the global plan.

Objective 1: Improve awareness and understanding of antimicrobial resistance through effective communication, education and training

29. Steps need to be taken immediately in order to raise awareness of antimicrobial resistance and promote behavioural change, through public communication programmes that target different audiences in human health, animal health and agricultural practice as well as consumers. Inclusion of the use of antimicrobial agents and resistance in school curricula will promote better understanding and awareness from an early age.

30. Making antimicrobial resistance a core component of professional education, training, certification, continuing education and development in the health and veterinary sectors and agricultural practice will help to ensure proper understanding and awareness among professionals.

Objective 2: Strengthen the knowledge and evidence base through surveillance and research

31. Actions and investments to tackle antimicrobial resistance should be supported by clear rationales of their benefit and cost-effectiveness. National governments, intergovernmental organizations, agencies, professional organizations, nongovernmental organizations, industry and academia have important roles in generating such knowledge and translating it into practice.

32. Particularly important gaps in knowledge that need to be filled include the following:

- Information on: the incidence, prevalence, range across pathogens and geographical patterns related to antimicrobial resistance is needed to be made accessible in a timely manner in order to guide the treatment of patients; to inform local, national and regional actions; and to monitor the effectiveness of interventions;

- Understanding how resistance develops and spreads, including how resistance circulates within and between humans and animals and through food, water and the environment, is important for the development of new tools, policies and regulations to counter antimicrobial resistance;

- The ability rapidly to characterize newly emerged resistance in microorganisms and elucidate the underlying mechanisms; this knowledge is necessary to ensure that surveillance and diagnostic tools and methods remain current;
Understanding social science and behaviour, and other research needed to support the achievement of Objectives 1, 3 and 4, including studies to support effective antimicrobial stewardship programmes in human and animal health and agriculture;

Research, including clinical studies conducted in accordance with relevant national and international governance arrangements, on treatments and prevention for common bacterial infections, especially in low resource settings;

Basic research and translational studies to support the development of new treatments, diagnostic tools, vaccines and other interventions;

Research to identify alternatives to nontherapeutic uses of antimicrobial agents in agriculture and aquaculture, including their use for growth promotion and crop protection;

Economic research, including the development of models to assess the cost of antimicrobial resistance and the costs and benefits of this action plan.

WHO’s global report on surveillance of antimicrobial resistance also revealed many gaps in information on antimicrobial resistance in pathogens of major public health importance. International standards on harmonization of national antimicrobial resistance surveillance and monitoring programmes were adopted by OIE’s members in 2012, but there are no internationally agreed standards for collection of data and reporting on antibacterial resistance in human health, and no harmonizing standards across medical, veterinary and agricultural sectors. In addition, there is no global forum for the rapid sharing of information on antimicrobial resistance.

In 2013, some Member States of the European Union published a strategic research agenda on antimicrobial resistance through a joint programming initiative. This initiative, which includes some countries outside the European Union, could provide an initial framework for further development of a global strategic research agenda.

Objective 3: Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures

Many of the most serious and difficult-to-treat antibiotic-resistant infections occur in health care facilities, not only because that is where patients with serious infections are admitted but also because of the intensive use therein of antibiotics. Although the development of resistance in such situations may be a natural consequence of necessary antimicrobial use, inadequate measures to prevent and control infection may contribute to the spread of microorganisms resistant to antimicrobial medicines.

Better hygiene and infection prevention measures are essential to limit the development and spread of antimicrobial-resistant infections and multidrug-resistant bacteria. Effective prevention of infections transmitted through sex or drug injection as well as better sanitation, hand washing, and food and water safety must also be core components of infectious disease prevention.

Vaccination, where appropriate as an infection prevention measure, should be encouraged. Immunization can reduce antimicrobial resistance in three ways:

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Existing vaccines can prevent infectious diseases whose treatment would require antimicrobial medicines;

Existing vaccines can reduce the prevalence of primary viral infections, which are often inappropriately treated with antibiotics, and which can also give rise to secondary infections that require antibiotic treatment;

Development and use of new or improved vaccines can prevent diseases that are becoming difficult to treat or are untreatable owing to antimicrobial resistance.

38. Much antibiotic use is linked to animal production. Antibiotics are sometimes used to prevent infections, to prevent the spread of diseases within a herd when infection occurs, and as a growth stimulant, and are often administered through feed and water. Sustainable husbandry practices, including the use of vaccines, can reduce infection rates and dependence on antibiotics as well as the risk that antibiotic-resistant organisms will develop and spread through the food chain.

Objective 4: Optimize the use of antimicrobial medicines in human and animal health

39. Evidence that antimicrobial resistance is driven by the volume of use of antimicrobial agents is compelling. High antibiotic use may reflect over-prescription, easy access through over-the-counter sales, and more recently sales via the Internet which are widespread in many countries. Despite measures taken by some Member States, antibiotic use in humans, animals and agriculture is still increasing globally. The projected increase in demand for animal food products may lead to yet further increases in antibiotic use.

40. Data on antibiotic use are collected and analysed in many high- and middle-income countries and OIE is developing a database on antibiotic use in animals. However, data are lacking on antibiotic use in human beings at the point of care and from lower-income countries.

41. More widespread recognition of antimicrobial medicines as a public good is needed in order to strengthen regulation of their distribution, quality and use, and encourage investment in research and development. In some cases, industry spending on promoting products is greater than governmental investment in promoting rational use of antimicrobial medicines or providing objective information.

42. Decisions to prescribe antibiotics are rarely based on definitive diagnoses. Effective, rapid, low-cost diagnostic tools are needed for guiding optimal use of antibiotics in human and animal medicine, and such tools should be easily integrated into clinical, pharmacy and veterinary practices. Evidence-based prescribing and dispensing should be the standard of care.

43. Regulation of the use of antimicrobial agents is inadequate or poorly enforced in many areas, such as over-the-counter and Internet sales. Related weaknesses that contribute to development of antimicrobial resistance include poor patient and health care provider compliance, the prevalence of substandard medicines for both human and veterinary use, and inappropriate or unregulated use of antimicrobial agents in agriculture.
Objective 5: Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions

44. The economic case must reflect the need for capacity development, including training in low-resource settings, and the need for the evidence-based use of interventions across human and animal health care systems including medicines, diagnostic tools and vaccines.

45. Economic impact assessments are needed on the health and broader socioeconomic burden of antimicrobial resistance, and should compare the cost of doing nothing against the cost and benefit of action. Lack of such data hindered implementation of the 2001 Global Strategy for Containment of Antimicrobial Resistance. The few studies on the economic cost of antimicrobial resistance are limited chiefly to developed countries.

46. Investment in the development of new antimicrobial medicines, as well as in diagnostic tools and vaccines, is needed urgently. Lack of such investment reflects, in part, fears that resistance will develop rapidly and that returns on investment will be limited because of restrictions in use. Thus research and development of new antibiotics is seen as a less attractive business investment than that of medicines for chronic diseases. Currently most major pharmaceutical companies have stopped research in this area, a situation described by WHO’s Consultative Expert Working Group on Research and Development: Financing and Coordination as “a serious market failure” and “a particular cause for concern”. New processes are needed both to facilitate renewed investment in research and development of new antibiotics, and to ensure that use of new products is governed by a public health framework of stewardship that conserves the effectiveness and longevity of such products. The cost of investment in research and development may need to be de-linked from price and the volume of sales to facilitate equitable and affordable access to new medicines, diagnostic tools, vaccines and other results from research and development in all countries. Many forums have been created in recent years to discuss these issues.

47. Antibiotics must also be supplemented by affordable, point-of-care diagnostic tools to inform health practitioners and veterinarians of the susceptibility of the pathogens to available antibiotics. The applicability and affordability of these techniques in low- and middle-income countries must be considered.
48. The framework presented below tabulates the actions that the Member States, Secretariat and international and national partners need to take in order to attain the goal and meet the objectives of the global plan.

49. All Member States are urged to have in place, within two years of the endorsement of the action plan by the Health Assembly, national action plans on antimicrobial resistance that are aligned with the global action plan and with standards and guidelines established by intergovernmental bodies such as the Codex Alimentarius Commission, FAO and OIE. These national action plans should provide the basis for an assessment of the resource needs, take into account national and regional priorities, and address relevant national and local governance arrangements. The Secretariat will facilitate this work by:

- Supporting countries to develop, implement and monitor national plans;
- Leading and coordinating support to countries for assessment and implementation of investment needs, consistent with the principle of sustainability (subparagraph 21(4) above);
- Monitoring development and implementation of action plans by Member States and other partners;
- Publishing biennial progress reports, including an assessment of countries and organizations that have plans in place, their progress in implementation, and the effectiveness of action at regional and global levels; and including an assessment of progress made by FAO, OIE and WHO in implementing actions undertaken within the organizations’ tripartite collaboration will also be included in these reports.

50. The Secretariat will also work with the Strategic and Technical Advisory Group on antimicrobial resistance, Member States, FAO and OIE, and other relevant partners to develop a framework for monitoring and evaluation, including the identification of measurable indicators of implementation and effectiveness of the global action plan. Examples of such indicators of effectiveness (impact) that could be applied for each of the strategic objectives are shown in the tabulated framework.
Objective 1: Improve awareness and understanding of antimicrobial resistance through effective communication, education and training

Potential measures of effectiveness: extent of reduction in global human consumption of antibiotics (with allowance for the need for improved access in some settings), and reduction in the volume of antibiotic use in food production

I. Member State action

i. Increase national awareness of antimicrobial resistance through public communication programmes that target the different audiences in human health, animal health and agricultural practice, including participation in an annual world antibiotic awareness campaign.

ii. Establish antimicrobial resistance as a core component of professional education, training, certification and development for the health and veterinary sectors and agricultural practice.

iii. Include antimicrobial use and resistance in school curricula in order to promote better understanding and awareness, and provide the public media with accurate and relevant information so that public information and reporting reinforce key messages.

iv. Recognize antimicrobial resistance as a priority need for action across all government ministries through inclusion in national risk registers or other effective mechanisms for cross-government commitment.

v. Promote and support establishment of multisectoral (one-health) coalitions to address antimicrobial resistance at local or national level, and participation in such coalitions at regional and global levels.

II. Secretariat action

i. Develop and implement global communication programmes and campaigns, including an annual world antibiotic awareness campaign, building on existing regional and national campaigns and in partnership with other organizations (e.g. UNESCO and UNICEF). Provide core communication materials and tools (including those for social media and for assessing public awareness and understanding) that can be adapted and implemented by Member States and others.

ii. Develop, with FAO and OIE through the tripartite collaboration, core communication, education and training materials that can be adapted and implemented regionally and nationally, on subjects that include the need for responsible use of antibiotics, the importance of infection prevention in human and animal health and agricultural practice, and measures to control spread of resistant organisms through food and the environment. Provide support to Member States with the integration of education on antimicrobial resistance into professional training, education and registration.

iii. Publish regular reports on progress in implementing the global action plan and progress towards meeting impact targets, in order to maintain commitment to reducing antimicrobial resistance.

iv. Maintain antimicrobial resistance as a priority for discussion with Member States through the regional committees, the Executive Board and Health Assembly, and with other intergovernmental organizations, including the United Nations.

III. International and national partners’ action

i. Professional organizations and societies should establish antimicrobial resistance as a core component of education, training, examination, professional registration or certification, and professional development.

ii. OIE should continue to support its members in implementing OIE standards including veterinary professional standards and training, applying its Performance of Veterinary Services Pathway\(^ \text{16}\) and updating of legislation.

iii. FAO should support awareness-raising on antimicrobial resistance and promote good animal production and hygiene practices among animal production and health workers, animal producers, and other stakeholders in the food and agriculture sectors.

iv. Intergovernmental organizations, including FAO, OIE and the World Bank, should raise awareness and understanding of antimicrobial resistance and, in collaboration with WHO, should mirror the actions of the Secretariat within their constituencies.

v. Other stakeholders – including civil society organizations, trade and industry bodies, employee organizations, foundations with an interest in science education, and the media – should help to promote public awareness and understanding of infection prevention and use of antimicrobial medicines across all sectors.

vi. WHO, FAO, OIE and other international stakeholders should encourage and support Member States in forging in-country as well as regional/global coalitions and alliances.

Objective 2: Strengthen the knowledge and evidence base through surveillance and research

Potential measure of effectiveness: extent of reduction in the prevalence of antimicrobial resistance, based on data collected through integrated programmes for surveillance of antimicrobial resistance in all countries

I. Member State action

i. Develop a national surveillance system for antimicrobial resistance that:
   - includes a national reference centre with the ability systematically to collect and analyse data – including those on a core set of organisms and antimicrobial medicines from both health care facilities and the community – in order to inform national policies and decision-making;
   - includes at least one reference laboratory capable of susceptibility testing to fulfil the core data requirements, using standardized tests for identification of resistant microorganisms and operating to agreed quality standards;
   - strengthens surveillance in animal health and agriculture sectors by implementation of the recommendations of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance for antimicrobial susceptibility testing of foodborne pathogens, the standards published in the OIE terrestrial and aquatic animal codes including the monitoring of resistance and antimicrobial use; the FAO/WHO Codex Alimentarius Code of Practice to Minimize and Contain Antimicrobial Resistance and the Codex Alimentarius Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance;

II. Secretariat action

i. Develop and implement a global programme for surveillance of antimicrobial resistance in human health, including surveillance and reporting standards and tools, case definitions, external quality assessment schemes, and a network of WHO Collaborating Centres to support surveillance of antimicrobial resistance and external quality assessment in each WHO region.


iv. Work with FAO and OIE, within the tripartite collaboration, to support integrated surveillance and reporting of antimicrobial resistance in human and animal health and agriculture, and develop measures of antimicrobial resistance in the food chain for use as indicators of risk to human health.

v. Develop a framework for monitoring and reporting on antimicrobial consumption in human health, including standards for collection and reporting of data on use in different settings, building on the work of OECD.

vi. With FAO and OIE, within the tripartite collaboration, collect, consolidate and publish information on the global consumption of antimicrobial medicines.

III. International and national partners’ action

i. FAO, with WHO, should review and update regularly the FAO/WHO Codex Alimentarius Code of Practice to minimize and contain antimicrobial resistance and the Codex Alimentarius guidelines for risk analysis of foodborne antimicrobial resistance.

ii. The international research community and FAO should support studies to improve understanding of the impact of antimicrobial resistance on agriculture, animal production and food security, as well as the impacts of agricultural practices on development and spread of antimicrobial resistance, and to reduce non-therapeutic use of antimicrobial agents in agriculture through the development of sustainable husbandry practices.

iii. OIE should regularly update the terrestrial and aquatic animal codes (particularly with reference to antimicrobial resistance), revise the guideline on laboratory methods for bacterial antimicrobial susceptibility testing, and support the establishment of veterinary laboratory services through its Performance of Veterinary Services Pathway.

iv. Global health donors, international development bodies, and aid and technical agencies should support developing countries to build capacity to collect and analyse data on the prevalence of antimicrobial resistance and share or report such data.

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Objective 2 (cont.): Strengthen the knowledge and evidence base through surveillance and research

**Potential measure of effectiveness:** extent of reduction in the prevalence of antimicrobial resistance, based on data collected through integrated programmes for surveillance of antimicrobial resistance in all countries

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<tr>
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<td>- promotes participation in regional and global networks and sharing of information so that national, regional and global trends can be detected and monitored;</td>
<td>- vii. Consult Member States and other multisectoral stakeholders for the development of a global public health research agenda for filling major gaps in knowledge on antimicrobial resistance, including methods to assess the health and economic burdens of antimicrobial resistance, cost-effectiveness of actions, mechanisms of development and spread of resistance, and research to underpin development of new interventions, diagnostic tools and vaccines. Monitor and report on implementation of the research agenda, for instance through the use of WHO’s Global Health Research and Development Observatory.</td>
<td>- v. Research funding organizations and foundations should support implementation of the agreed global public health research agenda on antimicrobial resistance.</td>
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<td>- has the capacity to detect and report newly emerged resistance that may constitute a public health emergency of international concern, as required under the International Health Regulations (2005).</td>
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<td>ii. Collect and report data on use of antimicrobial agents in human and animal health and agriculture so that trends can be monitored and the impact of action plans assessed.</td>
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<td>iii. Consider implementing an agreed global public health research agenda on antimicrobial resistance, including: research to promote responsible use of antimicrobial medicines; defining improved practices for preventing infection in human and animal health and agricultural practice; and encouraging development of novel diagnostic tools and antimicrobial medicines.</td>
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<td></td>
<td>viii. Work with partners to establish a sustainable repository for information on antimicrobial resistance and on the use and efficacy of antimicrobial medicines that is integrated with the global health research and development observatory and with a programme for independent evidence assessment and evaluation.</td>
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**Objective 3: Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures**

**Potential measures of effectiveness:** extent of reduction in the prevalence of preventable infections, and in particular the incidence of drug-resistant infections in health care settings

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| i. Member States may consider the following actions:  
  ▶ take urgent action to implement and strengthen hygiene and infection prevention and control;  
  ▶ include training and education in hygiene and infection prevention and control as core (mandatory) content in training and education for health care and veterinary professionals and in their continuing professional development and accreditation or registration.  
  ▶ develop or strengthen national policies and standards of practice regarding infection prevention and control activities in health facilities and monitor implementation of and adherence to these national policies and standards.  
  ii. Include within national surveillance of antimicrobial resistance the collection and reporting of data on antimicrobial susceptibility of microorganisms causing health care-associated infections.  
  iii. Strengthen animal health and agricultural practices through implementation of the standards published in the OIE Terrestrial and Aquatic Animal Health Codes and FAO/WHO Codex Alimentarius Code of Practice to Minimize and Contain Antimicrobial Resistance.  
  iv. Promote vaccination as a method of reducing infections in food animals. | i. Facilitate the design and implementation of policies and tools to strengthen hygiene and infection prevention and control practices, particularly to counter antimicrobial resistance, and promote the engagement of civil society and patient groups in improving practices in hygiene and infection prevention and control.  
  ii. Ensure that policy recommendations for new and existing vaccines take into account the prospects for restricted treatment options because of antimicrobial resistance, and the additional benefits of reduced use of antimicrobial agents, including antibiotics.  
  iii. Work with partners and other organizations to facilitate the development and clinical evaluation of specific priority vaccines for the prevention of difficult-to-treat or untreatable infections.  
  iv. Work with FAO and OIE, within the tripartite collaboration, to develop recommendations for the use of vaccines in food-producing animals, including recommendations for new vaccines, as a means to prevent foodborne diseases in humans and animals and reduce antimicrobial use. | i. Professional societies and accreditation bodies should support training and education on infection-prevention measures as a mandatory requirement in professional development, accreditation and registration.  
  ii. OIE should update its codes and manuals to take account of new developments in vaccines.  
  iii. FAO should continue to engage and support producers and stakeholders in the food and agriculture sectors in adopting good practices in animal husbandry and health aimed at reducing the use of antibiotics and the risk of development and spread of antimicrobial resistance. |

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Objective 4: Optimize the use of antimicrobial medicines in human and animal health

Potential measure of effectiveness: extent of reduction in global human consumption of antibiotics (with allowance for the need for improved access in some settings), the consumption of antibiotics used in food production (terrestrial and aquatic livestock, and other agricultural practices), and the use of medical and veterinary antimicrobial agents for applications other than human and animal health

I. Member State action

i. Develop and implement comprehensive action plans on antimicrobial resistance that incorporate the following elements:
   - distribution, prescription, and dispensing of antimicrobials is carried out by accredited health or veterinary professionals under statutory body supervision or other suitably trained person authorized in accordance with national legislation;
   - marketing authorization is given only to antimicrobial agents that are quality assured, safe and efficacious;
   - development and implementation of national and institutional essential medicine lists guided by the WHO Model Lists of Essential Medicines, reimbursement lists and standard treatment guidelines to guide purchasing and prescribing of antimicrobial medicines, and regulation and control of promotional practices by industry;
   - laboratory capacity to identify pathogens and their antimicrobial susceptibility in order to guide optimal use of antimicrobial medicines in clinical practice;
   - provision of stewardship programmes that monitor and promote optimization of antimicrobial use at national and local levels in accordance with international standards in order to ensure the correct choice of medicine at the right dose on the basis of evidence;
   - identification and elimination of economic incentives in all sectors that encourage inappropriate use of antimicrobial agents, and introduction of incentives to optimize use;

II. Secretariat action

i. Strengthen and align, within the tripartite collaboration with FAO and OIE, the concepts of critically important antibiotics for human and animal health, and ensure that these concepts include use of new antibiotics so that a common position on restriction of antimicrobial medicines for human use can be established.

ii. Provide support to Member States in the development and enforcement of relevant regulations so that only, quality assured, safe and effective antimicrobial products reach users.

iii. Develop technical guidelines and standards to support access to, and evidence-based selection and responsible use of, antimicrobial medicines, including follow-up to treatment failure.

iv. Provide leadership to strengthen medicines regulatory systems at national and regional levels, so that appropriate practices for optimizing use of antimicrobial medicines are supported by appropriate and enforceable regulation, and that promotional practices can be adequately regulated.

v. Consult with Member States and pharmaceutical industry associations on innovative regulatory mechanisms for new antimicrobial medicines, for example considering them as a class of medicine that will require a different set of regulatory controls, and on new approaches to product labelling that focus on public health needs rather than marketing claims, in order to address the need for preservation of effectiveness and for global access.

III. International and national partners’ action

i. OIE should regularly update its Terrestrial and Aquatic Animal Health Codes, particularly with reference to antimicrobial resistance.

ii. FAO, in collaboration with WHO, should regularly review and update the FAO/WHO Codex Alimentarius Code of Practice to Minimize and Contain Antimicrobial Resistance to take into account not only residues in food but also the need for standards to minimize and control use of antimicrobial agents in agricultural practice.

iii. OIE, supported by FAO and WHO within the tripartite collaboration, should build and maintain a global database on the use of antimicrobial medicines in animals.

iv. The research community in both the public and private sectors, including the pharmaceutical industry, should invest in the development of effective and low-cost tools for diagnosis of infectious diseases and antimicrobial susceptibility testing for use in human and animal health at points of care and dispensing (pharmacies).

v. Donors, philanthropic and other nongovernmental organizations and civil society should ensure that their efforts to increase access to antimicrobial medicines are accompanied by measures to protect the continued efficacy of such medicines.
Objective 4 (cont.): Optimize the use of antimicrobial medicines in human and animal health

**Potential measure of effectiveness:** extent of reduction in global human consumption of antibiotics (with allowance for the need for improved access in some settings), the consumption of antibiotics used in food production (terrestrial and aquatic livestock, and other agricultural practices), and the use of medical and veterinary antimicrobial agents for applications other than human and animal health

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<td>© effective and enforceable regulation and governance for licensing, distribution, use and quality assurance of antimicrobial medicines in human and animal health, including a regulatory framework for preservation of new antibiotics;</td>
<td>vi. Develop standards and guidance (within the tripartite collaboration with FAO and OIE), based on best available evidence of harms, for the presence of antimicrobial agents and their residues in the environment, especially in water, wastewater and food (including aquatic and terrestrial animal feed).</td>
<td>vi. Professional bodies and associations, including industry associations, health insurance providers and other payers, should develop a code of conduct for appropriate training in, education about, and marketing, purchasing, reimbursement and use of antimicrobial agents. This code should include commitment to comply with national and international regulations and standards, and to eliminate dependence on the pharmaceutical industry for information and education on medicines and, in some cases, income.</td>
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<td>© policies on use of antimicrobial agents in terrestrial and aquatic animals and agriculture, including: implementation of Codex Alimentarius and OIE international standards and guidelines as well as WHO/OIE guidance on the use of critically important antibiotics; phasing out of use of antibiotics for animal growth promotion and crop protection in the absence of risk analysis; and reduction in nontherapeutic use of antimicrobial medicines in animal health.</td>
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**Objective 5: Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions**

**Potential measures of effectiveness:** extent of increase in sustainable investment in capacity to counter antimicrobial resistance for all countries, including investment in development of new medicines, diagnostics and other interventions

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<tr>
<td>i. Member States should consider assessing investment needs for implementation of their national action plans on antimicrobial resistance, and should develop plans to secure and apply the required financing.</td>
<td>i. Work with the United Nations Secretary-General and bodies in the United Nations system to identify the best mechanism(s) to realize the investment needed to implement the global action plan on antimicrobial resistance, particularly with regard to the needs of developing countries.</td>
<td>i. Partners in the finance and economic sectors should define the economic case for national and global investment in combating antimicrobial resistance, including an assessment of the cost of implementing this action plan and the consequential cost of no action; this work could be led by the World Bank.</td>
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<td>ii. Member States are encouraged to participate in international collaborative research to support the development of new medicines, diagnostic tools and vaccines through:</td>
<td>ii. Work with the World Bank and with other development banks to develop and implement a template or models to estimate the investment needed to implement national action plans on antimicrobial resistance, and to collate and summarize these needs.</td>
<td>ii. FAO, OIE and other partners should support appropriate analyses to establish the case for investment and to inform the selection of interventions to improve animal husbandry, management, health, hygiene and biosecurity practices aimed at reducing antimicrobial use (and antimicrobial resistance) in different production settings.</td>
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<td>¦ prioritization and support of basic scientific research on infectious diseases, and promoting partnerships between research institutions in developed and developing countries;</td>
<td>iii. Work with the World Bank and with FAO and OIE, within the tripartite collaboration, to assess the economic impact of antimicrobial resistance and of implementation of the action plan in animal health and agriculture.</td>
<td>¦ Explore with Member States, intergovernmental organizations, industry associations and other stakeholders, options for the establishment of a new partnership or partnerships:</td>
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<td>¦ collaboration, based on fair and equitable benefit sharing as mutually agreed, in the investigation of natural sources of biodiversity and biorepositories as sources for the development of new antibiotics;</td>
<td>iv. Explore with Member States, intergovernmental organizations, industry associations and other stakeholders, options for the establishment of a new partnership or partnerships:</td>
<td>¦ to coordinate the work of many unlinked initiatives aiming to renew investment in research and development of antibiotics (including follow-up initiatives from the Consultative Expert Working Group on Research and Development);</td>
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<td>¦ strengthening existing and creating new public-private partnerships for encouraging research and development of new antimicrobial agents and diagnostics;</td>
<td>¦ to identify priorities for new treatments, diagnostics and vaccines on the basis of emergence and prevalence of serious or life-threatening infections caused by resistant pathogens;</td>
<td>¦ to act as the vehicle(s) for securing and managing investment in new medicines, diagnostics, vaccines and other interventions;</td>
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<td>¦ piloting of innovative ideas for financing research and development and for the adoption of new market models to encourage investment and ensure access to new antimicrobial products.</td>
<td>¦ to facilitate affordable and equitable access to existing and new medicines and other products while ensuring their proper and optimal use;</td>
<td>¦ to establish open collaborative models of research and development in a manner that will support access to the knowledge and products from such research, and provide incentives for investment.</td>
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25 Many of the actions that can support affordable and equitable access to medicines are set out in the Global strategy and plan of action on public health, innovation and intellectual property. Geneva: World Health Organization; 2011.
Expert Consensus on Metrics to Assess the Impact of Patient-Level Antimicrobial Stewardship Interventions in Acute-Care Settings

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Duke University Medical Center, Department of Medicine, Division of Infectious Diseases, and Duke Antimicrobial Stewardship Outreach Network, Durham, North Carolina; Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia

Antimicrobial stewardship programs (ASPs) positively impact patient care, but metrics to assess ASP impact are poorly defined. We used a modified Delphi approach to select relevant metrics for assessing patient-level interventions in acute-care settings for the purposes of internal program decision making. An expert panel rated 90 candidate metrics on a 9-point Likert scale for association with 4 criteria: improved antimicrobial prescribing, improved patient care, utility in targeting stewardship efforts, and feasibility in hospitals with electronic health records. Experts further refined, added, or removed metrics during structured teleconferences and re-rated the retained metrics. Six metrics were rated >6 in all criteria: 2 measures of Clostridium difficile incidence, incidence of drug-resistant pathogens, days of therapy over admissions, days of therapy over patient days, and redundant therapy events. Fourteen metrics rated >6 in all criteria except feasibility were identified as targets for future development.

Keywords. antimicrobial stewardship; patient safety; process measure; outcome measure; quality metrics.

The primary goal of hospital antimicrobial stewardship programs (ASPs) is to improve patient care. Evidence-based strategies involve individualized review of patient-specific clinical data and prescriber-targeted, active interventions to positively impact decisions about antimicrobials (eg, restriction and preauthorization, postprescription audit and feedback) [1, 2]. Metrics to assess the impact of patient-level interventions are poorly defined for hospital ASPs for many reasons. First, the care of patients with suspected infections is complex, involves nuanced decision making, and contains multiple components (eg, whether treatment is indicated, selection of agent[s], dose, duration). Second, patient safety outcomes and resistant infection events are infrequent and may have multiple confounding factors that are either not modifiable or not attributable to the quality of inpatient antimicrobial stewardship. Third, the effort required to extract metrics for ASPs from the electronic health record, complete meaningful analyses, and then translate the analyses into actionable conclusions for program decisions may seem insurmountable. Many potential metrics for hospital ASPs have been proposed, but few have been adequately validated to warrant incorporation into routine program assessments [3, 4]. Furthermore, prior studies that have demonstrated reduced cost and improved processes of care through ASPs are not compelling from a patient care and safety perspective.

We aimed to gain expert consensus on a list of metrics both useful for assessing the impact of patient-level antimicrobial stewardship interventions and feasible to measure in acute-care hospitals with an electronic health record. The goals of this study were not to identify quality metrics to be used for external comparisons or value-based incentives, but rather to identify metrics most pertinent for internal ASP decisions.

METHODS

We performed a modified Delphi, expert consensus-building process to identify metrics useful for tracking the impact of patient-level antimicrobial stewardship interventions. The method differed from the Delphi process developed by the RAND Corporation because it did not include face-to-face meetings [5]. Rather, Web-based teleconferences and electronic surveys enabled the geographically diverse group of experts to participate without logistical barriers. The steps of the process included a comprehensive literature review to develop a candidate metrics list, 2 rounds of electronic surveys for metric rating, data collection, analyses, and feedback to the panel members, and structured, Web-based teleconference discussions between the electronic survey rounds.
A set of candidate metrics was compiled from a comprehensive review of published literature on antimicrobial stewardship outcomes and process measurement. First, a PubMed search was conducted using the following search terms for the time period prior to April 2015:

[(("antimicrobial management") OR ("antibiotic management") OR ("antimicrobial utilization") OR ("antibiotic utilization") OR ("antimicrobial utilisation") OR ("antibiotic utilisation") OR ("antimicrobial stewardship") OR ("antibiotic stewardship") OR ("academic detailing") AND antibiotic OR antibiotics OR ("Anti-Infective Agents"[Mesh]) OR "Anti-Bacterial Agents"[Mesh]) OR (patient safety OR patient outcome OR patient outcomes OR "Outcome and Process Assessment (Health Care)"[Mesh]).

Second, abstracts were screened by 2 physician and 1 pharmacist investigators (R. W. M., D. J. A., E. D. A.) to apply inclusion and exclusion criteria. Publications met inclusion criteria if they intended to measure the effect of a patient-level stewardship intervention, which was defined as involving (1) a patient-level clinical review (either medical record review or verbal review with a primary provider) and (2) recommendation(s) made to adjust antimicrobial therapy for a specific patient. Publications were limited to inpatient, acute-care ASPs. Exclusion criteria were as follows: (1) the publication was not related to antimicrobial stewardship, which targets adjustment, discontinuation, or optimization of antimicrobial therapy; or (2) the study intervention involved a "guideline" or "education" activity that did not include individual patient-level review and patient-specific intervention. The goal of the literature review was to capture a broad array of possible patient-level ASP metrics. Some publications included proposed metrics based on expert opinion; others directly measured and applied the metric in a study of intervention effect.

The third step of developing the preliminary metric list included review of each publication for extraction of proposed and utilized metrics. Each metric was placed into 1 of 5 metric categories: clinical outcomes, unintended consequences, utilization, process measure, or financial outcomes [6]. Primary references were added to the list for metric extraction as necessary. Duplicate entries were removed. Similar metrics were combined and summarized into a single description.

Assembly of the Expert Panel
The Structured Taskforce of Experts Working at Reliable Standards for Stewardship (STEWARDS) panel was assembled from geographically diverse areas of the United States (Table 1). All 19 invited experts agreed to participate and completed the modified Delphi process from September through December 2015. The panel included adult and pediatric infectious disease physicians and pharmacists with dedicated active practice in antimicrobial stewardship, healthcare epidemiologists, academic researchers, Veterans Affairs representatives, and Centers for Disease Control and Prevention (CDC) stewardship experts.

Methods for Comprehensive Literature Review and Development of a Preliminary List of Metrics

Methods for Electronic Survey, Expert Panel Discussions, and Data Analysis

The preliminary list of metrics were compiled into a Web-based, electronic survey via Research Electronic Data Capture (REDCap) software hosted at Duke University [7]. Experts were asked to evaluate each metric using a 9-point Likert scale by rating their agreement in 4 separate criteria based on their expert opinion:

1. This metric is associated with improved antimicrobial prescribing.
2. This metric is associated with improved patient care.
3. This metric is useful in targeting antimicrobial stewardship efforts.
4. This metric is feasible to monitor in any hospital with an electronic health record.

Experts were encouraged to (1) submit free text comments on each metric or the group of metrics in each category and (2) add additional metrics that they believed should be considered for inclusion in subsequent rounds. The electronic survey also elicited experts’ suggestions for refinement of wording or description of each metric.

A priori rejection and retention criteria were used to analyze the results from the first electronic survey. Mean and 95% confidence intervals (CIs) were calculated for each metric and criterion. Ratings with a mean upper 95% CI bound <4 were deemed to have consensus to reject; ratings with a lower 95% CI bound >6 were deemed to have consensus to retain. Metrics that met criteria for consensus to reject in 3 or 4 criteria were removed. Metrics that met criteria for consensus to retain in 3 or 4 criteria were carried forward to the discussion and round 2 survey. All other metrics were considered “equivocal” and open for discussion, refinement, or reevaluation. All analyses and summaries of written comments were presented back to panel members by email prior to discussions.

Two Web conferences were held, each with half of the members of the expert panel in attendance. The discussion reviewed results for all metrics from the initial survey, confirmed agreement with retention of metrics by the a priori criteria, and allowed the panel to determine retention or removal of equivocal metrics. Discussions were moderated by a CDC qualitative research specialist (R. L. C.), who assured that every panel member was given opportunity to participate using a standardized script. Verbal consensus from the group was sought for final decisions to remove metrics, refine their description, suggest additional metrics, or retain metrics for rating in the next survey round.
A second electronic survey of the retained metrics was conducted using the same methods and criteria as round 1. The final list of accepted metrics deemed ready for immediate use and tracking was defined based on consensus acceptance in all 4 criteria. A second list of metrics identified for future study was defined based on acceptance in all criteria except the fourth feasibility criterion.

For all statistical analyses, SAS version 9.4 (SAS Institute, Cary, North Carolina) was used. The Duke University Institutional Review Board approved this activity as exempt.

RESULTS

Figure 1 details the process of literature and metric review based on prespecified exclusion criteria. The initial electronic survey included 90 metrics for rating by the panel. Round 1 survey format separated the numerator and denominator metrics in the utilization category (eg, days of therapy numerator was rated separately from the patient days denominator; Supplementary Table 1). All 19 panel members participated in the round 1 electronic survey. Round 1 survey ratings resulted in consensus to retain 14 metrics; the remaining 76 metrics were considered equivocal based on the a priori criteria and no metrics were removed. Eighteen panel members (95%) participated in the Web-based conferences. The discussions resulted in consensus to remove all 18 metrics in the financial outcomes category. This category was generally rated negatively during round 1, and the panel deemed these metrics as not relevant for patient safety (criterion 1). The panel removed an additional 30 metrics deemed to be difficult to interpret, unlikely to be meaningful for ASP decision making, better represented by other metrics under consideration, or too infeasible to capture and interpret. An additional 8 metrics were added for rating in round 2. Eight metrics were refined for the subsequent rating survey including defining utilization metrics as specific numerator/denominator pairings.

The round 2 electronic survey included 41 metrics for the panel to reevaluate: 5 clinical outcomes, 6 unintended consequences, 10 utilization measures, and 20 process measures...
The STEWARDS panel achieved consensus in identifying metrics for acute-care hospital ASPs to assess the impact of patient-level interventions for the purposes of internal program decision making. The panel identified 6 metrics ready for immediate use and tracking: 2 metrics capturing incidence of *Clostridium difficile* infection (hospital-onset and healthcare facility–associated infections), incidence of drug-resistant infection, 2 measures of antimicrobial utilization (days of therapy in rates per patient admission and per patient-days), and 1 process measure (redundant therapy events). An additional 14 metrics were identified that may prove useful for ASPs in the future, but currently have feasibility barriers that prevent their widespread use.

Prior expert consensus processes that focused on selecting metrics for antimicrobial stewardship have not specifically focused on the impact of patient-level interventions and the goal of informing internal program decision making. In contrast, other panels have attempted to select quality indicators to be used for external comparisons or focused on appropriateness of antibiotic use alone [8, 9]. Morris et al convened a panel of 10 US and Canadian experts to define quality improvement metrics for ASPs, including 2 measures to be used for public reporting [8]. The conclusions of this panel had some similarities to the STEWARDS panel: Both selected incidence of drug-resistant infection, including *C. difficile* infections, and antimicrobial utilization, specifically, days of therapy. In contrast to Morris et al, the STEWARDS panel did not select clinical outcomes such as 30-day unplanned readmissions or mortality due to drug-resistant organisms. The reluctance to use clinical outcomes as metrics for evaluating ASP impact in routine practice has also been demonstrated in a voluntary survey of physicians, administrators, and pharmacists [10].

The lack of acceptance of clinical outcomes as metrics ready for active use by inpatient ASPs is important. Many clinically important patient outcomes (eg, in-hospital mortality, length of stay, 30-day readmission) are already actively tracked by hospitals for quality improvement and thus do not have feasibility barriers like other proposed metrics. Members of the STEWARDS panel expressed a desire to demonstrate impact on clinical outcomes from ASP interventions. Their reluctance to include these metrics in assessments of patient-level stewardship interventions included concerns with the ability to detect changes in these events and then attribute this change directly to stewardship interventions. Namely, panel members expressed concern about the need for risk adjustment for confounding factors (eg, severity of illness, patient case mix, concurrent infection control activities). Also, clinical outcomes may be insensitive to change as a result of improvements in patient-level stewardship, especially for rare outcomes such as death. Clinical outcomes that may be more responsive to improvements in stewardship included infection-related mortality or

(Supplementary Table 1). All 19 panel members participated in the round 2 survey. Round 2 rating resulted in 6 metrics accepted in all 4 criteria and deemed ready for immediate tracking and use by hospital ASPs (Table 2). Fourteen additional metrics were accepted in all criteria except feasibility. These metrics were identified as needing further development in determining standard definitions, method of measurement, and implementation study before active use by ASPs could be recommended. The remaining 21 metrics did not receive expert consensus ratings high enough for acceptance as relevant and feasible metrics for antimicrobial stewardship.

### DISCUSSION

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readmission related to infectious diagnoses. These metrics, however, were not accepted by the STEWARDS panel in the feasibility criterion due to lack of standardized definitions and the need for more experience in measurement utilizing electronic health records. Furthermore, infection-related events are a subset of total deaths and readmissions, which would make it even more difficult to detect a change. Thus, the need for complicated analyses, large sample size, and therefore limitations in translating these data into actionable conclusions hampers the ability to adopt these metrics into routine surveillance practice for ASPs. Some STEWARDS panel members suggested that clinical outcomes may be more useful to prove “no harm” came from ASP interventions that aim to shorten duration, provide more narrow therapy, or avoid intravenous therapy. Clinical outcomes could be utilized as a complementary metric to reassure providers that interventions did not cause unintended negative clinical consequences. Although the ultimate goal for ASPs is to positively impact clinical and patient safety outcomes, members of STEWARDS acknowledged that perhaps a more practical place for individual ASPs to demonstrate impact is through measures of utilization and process.

Many metrics evaluated by the panel in the utilization and process measure category were rated in the neutral range due to experts’ limited experience with the metrics or the lack of a clear, previously validated, standard definition. Furthermore, several process measures did not reach acceptance in the feasibility criterion due to perceived barriers in capturing the required data elements from electronic health records. For example, de-escalation from broad to narrow antimicrobial therapy is an accepted, basic principle of antimicrobial stewardship that should be responsive to patient-level interventions. This metric was accepted in all criteria except the feasibility criterion due to the state of preliminary work in defining spectrum scores [11] and de-escalation events [12] from electronic data, the need for validation of these definitions in other study populations, and the need for more experience in implementing these metrics into routine practice. As another example, the panel achieved consensus that a days of therapy numerator over dominators of either patient-days or admissions were useful to capture in hospitals with electronic health records; however, several members voiced knowledge that many facilities lack the information technology resources to capture these data. The metric used in the National Healthcare Safety Network Antibiotic Use module includes days of therapy over days present, which several STEWARDS members deemed important given its adoption by the CDC for the US national surveillance system [13]. This metric was rated with uncertain feasibility due to experts’ experiences in the complexity of capturing patient movement data. The traditional denominator metric of patient-days, which is currently used for infection prevention surveillance, considers
the count of patients housed on a unit measured at a certain time each day (eg, midnight census) as days at risk [14]. In contrast, days present counts the number of patients housed on a unit for any portion of a calendar day as days at risk [13]. Thus, the days present metric requires detailed information on patient movements throughout the calendar day. This feasibility barrier is slowly being addressed as more electronic health record vendors move toward adding antibiotic use reporting to their products. This and the other metrics that received an uncertain feasibility rating should be evaluated in future studies focused on measurement from electronic data (Table 2, group 2).

This study has limitations. First, the STEWARDS panel consisted of US physicians and pharmacists with infectious disease training, particularly those with antimicrobial stewardship expertise, public health interest, and healthcare epidemiology and antimicrobial stewardship research experience. Thus, the experts’ opinions and self-reported experiences may not reflect those of stewards working in other practice settings and systems. Second, the panel process did not include a face-to-face meeting, but instead involved 2 Web-based teleconferences, each with approximately half of the panel members in attendance due to scheduling limitations. This logistical barrier may have led to a reduction in direct sharing of ideas, but it did not result in failure to meet consensus on the final list of selected metrics. Finally, an important limitation in the output of this study is a continued generality or ambiguity in descriptions of some metrics selected in the final consensus list. For example, the STEWARDS panel did not come to a final recommendation for which measures of incidence of drug-resistant infections should be tracked or how they should be specifically defined and calculated. Based on knowledge of the many possible ways that drug-resistant events can be measured [15, 16], we believe that specific recommendations relevant to ASPs will need dedicated consensus building work in the future. Similar future work in standardized definition development will be required for multiple metrics with feasibility barriers identified during this process (Table 2, group 2).

CONCLUSIONS

The STEWARDS panel developed a list of 6 recommended metrics ready for active use and tracking for acute-care ASPs seeking to assess the impact of patient-level interventions. The selected measures align well with national priorities in improving and measuring antibiotic use and preventing drug resistance [17]. Measurement is a required task in both The Joint Commission antibiotic stewardship accreditation standard and the Centers for Medicare and Medicaid Services proposed antibiotic stewardship condition of participation [18, 19]. The metrics identified by this panel form a core set of measures that ASPs can start using immediately to both meet the measurement requirements and, more importantly, assess the impact of their efforts.

In addition, the panel identified 14 metrics for future study. Future work should focus on standard definition development and overcoming feasibility barriers for metrics that are based on electronic data elements. To this end, The Duke Antimicrobial Stewardship Outreach Network is partnering with CDC and the CDC Foundation to assess the most promising of these additional metrics. Lessons learned from these efforts will help guide the implementation of the next generation of antibiotic stewardship metrics.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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An international cross-sectional survey of antimicrobial stewardship programmes in hospitals

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Objectives: To report the extent and components of global efforts in antimicrobial stewardship (AMS) in hospitals.

Methods: An Internet-based survey comprising 43 questions was disseminated worldwide in 2012.

Results: Responses were received from 660 hospitals in 67 countries: Africa, 44; Asia, 50; Europe, 361; North America, 72; Oceania, 30; and South and Central America, 103. National AMS standards existed in 52% of countries, 4% were planning them and 58% had an AMS programme. The main barriers to implementing AMS programmes were perceived to be a lack of funding or personnel, a lack of information technology and prescriber opposition. In hospitals with an existing AMS programme, AMS rounds existed in 64%; 81% restricted antimicrobials (carbapenems, 74.3%; quinolones, 64%; and cephalosporins, 58%); and 85% reported antimicrobial usage, with 55% linking data to resistance rates and 49% linking data to infection rates. Only 20% had electronic prescribing for all patients. A total of 89% of programmes educated their medical, nursing and pharmacy staff on AMS. Of the hospitals, 38% had formally reviewed their AMS programme: reductions were reported by 96% of hospitals for inappropriate prescribing, 86% for broad-spectrum antibiotic use, 80% for expenditure, 71% for healthcare-acquired infections, 65% for length of stay or mortality and 58% for bacterial resistance.

Conclusions: The worldwide development and implementation of AMS programmes varies considerably. Our results should inform and encourage the further evaluation of this with a view to promoting a worldwide stewardship framework. The prospective measurement of well-defined outcomes of the impact of these programmes remains a significant challenge.

Keywords: antibiotic prescription, antibiotic policy, antibiotic management

Introduction

Antimicrobial resistance is growing and the pipeline for new antibiotics is running dry.1,2 This is especially a problem with multiresistant Gram-negative bacteria.1 Two main approaches are suggested to address this problem, namely an investment in new antibiotic discovery and improved antimicrobial stewardship (AMS).1–3 The earliest described organized AMS activities go back to the early 1970s.4 The term ‘antimicrobial stewardship’ was first coined in 1997 as describing a collection of strategies, policies, guidelines or tools that could improve antimicrobial prescribing with the aim of decreasing antimicrobial resistance and use.5 Many definitions have been suggested for AMS across the world, but agreement has not been reached on one definition. While studies to investigate AMS have previously been undertaken, the vast majority have only been conducted on a national scale (e.g. in the USA,6,7 the UK8 and Belgium9) and good quality information from all continents is lacking. Nonetheless, all the studies to date describe varying levels of maturity of stewardship, different priorities or strategies and a different impact on measured outcomes. A European survey of 32 countries10 focused around hospital antibiotic consumption and information about the presence of policies and practices again revealed much variation across countries. The aim of this global cross-sectional survey was to investigate the depth and penetration of AMS across the world. The survey collected outcome data for the relevant strategies...
employed and information about the main perceived barriers found in different regions. Learning about these barriers and facilitators for stewardship may identify opportunities for improving practice globally.

Methods

In March 2011, the ESCMID Study Group for Antibiotic Policies (ESGAP) launched a global survey of AMS. To achieve worldwide coverage, agreement was reached to form a joint working party with the AMS group of the International Society of Chemotherapy (ISC).

A literature search was undertaken of published standards and surveys on AMS using Medline, Embase and Google Scholar (articles published in English). Search terms were ‘antimicrobial’ or ‘antibiotic’ and ‘stewardship’ or ‘control’. The working party also shared surveys not identified within the literature search.

From the literature, a draft questionnaire was developed using the components of AMS that had been identified, and from questions asked in other surveys that would capture the breadth of activities undertaken. Published recommendations for the development and implementation of web-based surveys were applied prospectively to the design of our research survey.

A web-based survey tool (SurveyMonkey) was used. The initial survey was distributed in October 2011 to key opinion leaders in AMS in all six continents to test the readability and clarity of the questions, especially in countries where English was not the main language, and to reach consensus on the questions. It was decided to restrict the survey to hospital AMS activities and exclude ambulatory care.

The survey was piloted in 11 countries in six continents. The final survey was 18 pages long with 45 questions (the questionnaire is available as Supplementary data at JAC Online). In order to decrease the time taken to complete the survey, it used page and question logic that missed out pages or questions asking for more information depending on the answers.

An invitation letter was sent to regional and country contacts within the ISC and ESCMID for distribution via their infectious diseases, microbiology and antimicrobial pharmacy networks for each continent and country in March 2012. Further advertising took place during the 2012 ECCMID conference, through newsletters and the use of Twitter and other infection and antimicrobial pharmacy networks. The survey was distributed in October 2011 to key opinion leaders in AMS in all six continents to test the readability and clarity of the questions, especially in countries where English was not the main language, and to reach consensus on the questions. It was decided to restrict the survey to hospital AMS activities and exclude ambulatory care.

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Only one IP address was allowed per hospital, but the survey could be accessed again to update the answers if not all the information was complete at the time of entry.

Descriptive data analysis was undertaken using IBM SPSS version 19 (Chicago, IL, USA). Duplicates were identified by duplicate hospital names and addresses. Where there were duplicate entries, these were amalgamated. Due to the size and complexity of the questionnaire, it was decided to use all entries that contained information about AMS activities, even if there were missing answers for some questions.

Results

There were 722 survey returns but 62 entries had to be excluded: 10 did not record any demographic information and 52 were duplicated entries from the same hospital. There were 660 eligible responses (67 countries from six continents): Africa, 44; Asia, 50; Europe, 361; North America, 72; Oceania, 30; and South America, 103 (Table 1). A total of 507/660 (77%) hospitals fully completed the questionnaire. Tertiary teaching hospitals accounted for 48% (319/660) of the returns, district or general hospitals for 24% (161/660) and community or private (not state-funded) hospitals for 8% (56/660) each. Hospitals with up to 500 overnight beds accounted for 48% (314/660), those with 501–1000 beds for 33% (217/660) and those with over 1000 beds for 20% (129/660) of the total.

AMS standards and structures

National AMS standards existed in 52% (35/67) of the countries, and a further 4% (3/67) planned to introduce them. Of the hospitals, 58% (367/636) had a local AMS programme with a median duration of 3 years and 22% (143/636) planned to introduce one. The AMS programmes of European hospitals had been running longer (Table 2).

Although the majority of hospitals reported the existence of drug and therapeutic committees (85%, 543/637), only 62% (396/637) had a specific AMS committee, with variation across the continents: from 12% (5/43) in Africa to 77% (267/348) in Europe. A total of 46% (293/637) of hospitals reported a specific overarching AMS strategy or code of practice. Only 38% (232/616) published an annual report on AMS and 29% (179/612) had a published AMS work plan.

AMS programme objectives, resources and barriers to effective implementation

Hospitals were asked the three main objectives of their AMS programmes. Reducing antimicrobial resistance was the most frequent reason across all continents. Improving patient outcomes, reducing antimicrobial prescribing, reducing *Clostridium difficile* infections and other healthcare-acquired infections and then

<table>
<thead>
<tr>
<th>Continent</th>
<th>Number of countries returning questionnaires</th>
<th>Hospital returns by continent</th>
<th>Mean hospital returns by country (range)</th>
<th>Median hospital returns by country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa, n (%)</td>
<td>10 (15)</td>
<td>44 (7)</td>
<td>2 (1–13)</td>
<td>2</td>
</tr>
<tr>
<td>Asia, n (%)</td>
<td>14 (20)</td>
<td>50 (8)</td>
<td>3 (1–9)</td>
<td>2</td>
</tr>
<tr>
<td>Europe, n (%)</td>
<td>26 (38)</td>
<td>361 (55)</td>
<td>12 (1–104)</td>
<td>8</td>
</tr>
<tr>
<td>North America, n (%)</td>
<td>5 (7)</td>
<td>72 (11)</td>
<td>15 (1–35)</td>
<td>9</td>
</tr>
<tr>
<td>Oceania, n (%)</td>
<td>2 (3)</td>
<td>30 (5)</td>
<td>15 (13–17)</td>
<td>15</td>
</tr>
<tr>
<td>South and Central America, n (%)</td>
<td>12 (17)</td>
<td>103 (16)</td>
<td>7 (1–39)</td>
<td>4</td>
</tr>
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*Russia and Turkey had hospitals in both Europe and Asia.*
reducing costs were the next reasons, with a variation in the order by continent.

The resources available for AMS programmes varied by continent (Table 3). In Asia, Europe, North America and Oceania, the main manpower was antimicrobial or infectious diseases pharmacists, but stewardship was delivered by infection control staff in Africa. The main medical input was by infectious diseases doctors in most continents except for Africa and Europe, where medical microbiologists predominated. When asked about the funding of specific posts within the AMS programmes, 81% (820/1008) of posts were funded from general or hospital department budgets, 15% (150/1008) from dedicated funding [the highest proportion being antimicrobial or infectious diseases pharmacists—21% (61/292 posts)], and 4% (38/1008) of all AMS staff were funded from savings.

Figure 1 shows the top three barriers to delivering a functional and effective AMS programme in hospitals at the current time. These were a lack of funding or personnel and a lack of information technology or ability to get data, followed by prescriber opposition or other higher priorities. This was uniform across all continents except for Africa, which ranked information technology as the primary issue. In the 143/636 hospitals (22%) that planned to develop an AMS programme, the main barrier was lack of funding, except in South America, where a lack of awareness on the part of the hospital administration was the main reason stated.

### AMS strategies

Various strategies were employed to deliver AMS (Table 4). Most hospitals throughout the world had specific guidance on the treatment of infections and on prophylaxis for surgical site infections, but there were marked differences for the authorization of restricted antibiotics—38% (5/13) in Asia compared with up to 88% in Europe (224/255). Advice by telephone was available from infectious disease or microbiology specialists but their advice was less available on ward rounds. The routine follow-up of patients with bacteraemia occurred more commonly in Oceania than the other continents. North America used Day 3 reviews, guidance on intravenous-to-oral switching, automatic stop or review policies and pharmacist pre-authorized to optimize the

### Table 2. Summary of AMS standards and programmes

<table>
<thead>
<tr>
<th>Country AMS standards</th>
<th>Africa, n/N (%)</th>
<th>Asia, n/N (%)</th>
<th>Europe, n/N (%)</th>
<th>North America, n/N (%)</th>
<th>Oceania, n/N (%)</th>
<th>South and Central America, n/N (%)</th>
<th>Total, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country AMS standards in preparation</td>
<td>2/10 (20)</td>
<td>5/12 (42)</td>
<td>21/26 (81)</td>
<td>1/5 (20)</td>
<td>1/2 (50)</td>
<td>5/12 (42)</td>
<td>35/67 (52)</td>
</tr>
<tr>
<td>Regional AMS standards</td>
<td>0/10 (0)</td>
<td>1/12 (8)</td>
<td>1/26 (4)</td>
<td>0/5 (0)</td>
<td>0/2 (0)</td>
<td>1/12 (8)</td>
<td>3/67 (4)</td>
</tr>
<tr>
<td>Hospital AMS standards</td>
<td>3/32 (9)</td>
<td>6/38 (16)</td>
<td>120/279 (43)</td>
<td>8/56 (14)</td>
<td>11/30 (37)</td>
<td>21/69 (30)</td>
<td>169/504 (34)</td>
</tr>
<tr>
<td>AMS programme in place</td>
<td>9/42 (21)</td>
<td>29/46 (63)</td>
<td>246/339 (73)</td>
<td>30/65 (46)</td>
<td>16/33 (48)</td>
<td>46/85 (54)</td>
<td>376/610 (62)</td>
</tr>
<tr>
<td>Median duration of AMS programme (years)</td>
<td>10/43 (23)</td>
<td>14/49 (29)</td>
<td>70/348 (20)</td>
<td>15/67 (22)</td>
<td>10/34 (29)</td>
<td>24/95 (25)</td>
<td>143/636 (22)</td>
</tr>
</tbody>
</table>

### Table 3. Average AMS programme resource hours per week, n = 337

<table>
<thead>
<tr>
<th></th>
<th>Africa, n = 12</th>
<th>Asia, n = 25</th>
<th>Europe, n = 190</th>
<th>North America, n = 49</th>
<th>Oceania, n = 14</th>
<th>South and Central America, n = 44</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial or infectious diseases pharmacist (n = 320)</td>
<td>6</td>
<td>13</td>
<td>18</td>
<td>32</td>
<td>17</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Infectious diseases doctor (n = 284)</td>
<td>3</td>
<td>8</td>
<td>8</td>
<td>15</td>
<td>6</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Medical microbiologist (n = 308)</td>
<td>8</td>
<td>6</td>
<td>11</td>
<td>5</td>
<td>1</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Infection control staff (n = 220)</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>6</td>
<td>1</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Nurse (n = 199)</td>
<td>8</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>14</td>
<td>6</td>
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<tr>
<td>Administrative support (n = 202)</td>
<td>4</td>
<td>6</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Data analyst (n = 201)</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>9</td>
<td>2</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Other pharmacist (n = 199)</td>
<td>8</td>
<td>3</td>
<td>2</td>
<td>7</td>
<td>0</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Doctors in training (n = 188)</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Other medical specialty (n = 199)</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Pharmacy technician (n = 188)</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Scientist or laboratory staff (n = 179)</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Surgeon (n = 201)</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>
dose more often than elsewhere in the world. Care bundles (e.g. for community- or ventilator-acquired pneumonia) were quite frequently used in most hospitals across all continents except Europe and Oceania. Interventions used less often were separate antimicrobial prescriptions, the measurement of inflammatory markers such as procalcitonin to avoid starting antibiotics or facilitate stopping antibiotics earlier, restricting the access of pharmaceutical representatives and the cycling of antibiotics.

AMS rounds existed in 64% (261/408) of hospitals. Intensive care ward rounds were the most common in 74% (290/390) of hospitals and mostly occurred daily, followed by ward rounds on medical wards in 68% (248/366, mainly weekly), surgical wards in 63% (232/370, mainly weekly), paediatric wards in 43% (143/335, less than weekly) and less often emergency departments in 35% (120/345, less than weekly). The content of the antimicrobial guidelines (n = 402) varied considerably. Most of the guidelines contained dosages (89%), alternatives for antimicrobial allergy (88%), preferred route (86%), duration of treatment (79%), guidance on intravenous-to-oral switching (70%), dosing in renal or liver impairment (60%) or diagnosis (60%). Less commonly covered were investigations (46%), guidance on directed therapy or a revision of therapy (43%), costs (24%) and dosing in obesity (23%). Some provided guidelines for antifungal (55%) and antiviral (38%) agents. Few hospitals could monitor guideline use (35%) or allow feedback direct from the guideline (38%). Most treatment guidelines were updated annually (41%) but guidance on surgical prophylaxis was most commonly updated every 2 years (38%). The antimicrobial formulary and restricted lists were usually updated annually.

Most hospitals (81%, 329/406) restricted some antimicrobials: 73% (282/384) restricted carbapenems, 64% (246/385) quinolones and 58% (223/383) cephalosporins. A post-prescription review of restricted antimicrobials by the pharmacy departments was carried out in 64% (219/340) of hospitals. A total of 31% (106/342) restricted before the first dose in all areas, 25% (87/342) restricted outside intensive care and 41% (132/319) restricted after the first dose, and only a few hospitals had no restrictions. Only 20% (102/516) had electronic prescribing for all their patients and a further 16% (80/516) had limited electronic prescribing. In the e-prescribing systems used, 51% (83/163) mandated the duration and 35% (56/160) mandated the indication. Approval for restricted antibiotics was required in 46% (72/158) of systems.

Electronic patient records existed for all or some patients in 43% (213/491). Few hospitals had full or limited automated antimicrobial dispensing (15%, 73/481) or data warehouse surveillance systems that linked prescribing to the laboratory results (17%, 78/458). Full or limited dispensing of antimicrobial agents to individual patients occurred in only 34% (163/480) of hospitals.

![Figure 1. Barriers to delivering a functional and effective AMS programme.](image-url)
Communication

The intranet was the most common method of communication, followed by booklets, email, posters and then newsletters. There were, however, differences across the continents, with Africa and South America preferring booklets and staff meetings rather than an intranet. There was little use of newer technologies such as smartphone applications or screensavers.

Evaluation of interventions: process and outcomes

Antimicrobial audit was undertaken in 80% (312/390) of hospitals. Most reported expenditure (82%, 290/353), DDDS (80%, 251/315) and DDDS/occupied bed days (67%, 215/319) at hospital level but less so at specialty level [65% (206/317), 57% (180/315) and 53% (162/308), respectively]. A total of 55% (170/307) linked usage to resistance rates and 49% (146/299) linked usage to infection rates.

Of the 38% (119/317) of hospitals that formally assessed their AMS programme for return on investment or economic viability, most reported reductions in inappropriate prescribing (96%, 77/80), use of broad-spectrum antibiotics (86%, 83/96), direct expenditure (80%, 70/87) and healthcare-acquired infections (71%, 47/66). A total of 65% (26/40) declared a reduction in length of stay or mortality and 58% (39/67) a reduction in antimicrobial resistance. Of the 270 hospitals that had assessed the impact of AMS ward rounds, 121 (45%) reported a reduction in antimicrobial consumption, and 41 (15%) an increase, with the largest impact on reduction in consumption being seen on surgical wards.

Education

Most hospitals (89%, 356/400) educated their healthcare staff. Overall, 96% of hospitals educated their senior and trainee doctors. Doctors most commonly received face-to-face training

Table 4. AMS strategies—all or some wards (actual or planned AMS programme), n=422

<table>
<thead>
<tr>
<th>AMS strategies</th>
<th>Asia (13%)</th>
<th>Africa (31%)</th>
<th>Europe (258%)</th>
<th>North America (54%)</th>
<th>Oceania (23%)</th>
<th>South America (43%)</th>
<th>Total (422%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment guidelines</td>
<td>85</td>
<td>84</td>
<td>98</td>
<td>89</td>
<td>96</td>
<td>84</td>
<td>94</td>
</tr>
<tr>
<td>Surgical prophylaxis guidelines</td>
<td>77</td>
<td>94</td>
<td>95</td>
<td>87</td>
<td>96</td>
<td>88</td>
<td>93</td>
</tr>
<tr>
<td>Approved antibiotics (formulary)</td>
<td>69</td>
<td>84</td>
<td>95</td>
<td>87</td>
<td>91</td>
<td>77</td>
<td>90</td>
</tr>
<tr>
<td>Reserve antibiotics needing authorization by indication</td>
<td>38</td>
<td>84</td>
<td>88</td>
<td>87</td>
<td>87</td>
<td>77</td>
<td>84</td>
</tr>
<tr>
<td>Infectious diseases/microbiology advice by telephone</td>
<td>85</td>
<td>84</td>
<td>92</td>
<td>81</td>
<td>96</td>
<td>84</td>
<td>89</td>
</tr>
<tr>
<td>Infectious diseases/microbiology advice on ward rounds</td>
<td>69</td>
<td>87</td>
<td>84</td>
<td>63</td>
<td>74</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td>Systematic advice for bacteremia by infectious diseases/microbiology</td>
<td>46</td>
<td>74</td>
<td>78</td>
<td>52</td>
<td>83</td>
<td>74</td>
<td>73</td>
</tr>
<tr>
<td>Dose optimization on request</td>
<td>92</td>
<td>71</td>
<td>80</td>
<td>87</td>
<td>96</td>
<td>67</td>
<td>80</td>
</tr>
<tr>
<td>Intravenous-to-oral switch guidance</td>
<td>62</td>
<td>65</td>
<td>82</td>
<td>91</td>
<td>78</td>
<td>67</td>
<td>80</td>
</tr>
<tr>
<td>Review of intravenous therapy at Day 3</td>
<td>62</td>
<td>61</td>
<td>78</td>
<td>89</td>
<td>61</td>
<td>70</td>
<td>76</td>
</tr>
<tr>
<td>Care bundles (e.g. ventilator)</td>
<td>85</td>
<td>90</td>
<td>59</td>
<td>76</td>
<td>30</td>
<td>72</td>
<td>64</td>
</tr>
<tr>
<td>Automatic stop/review policy</td>
<td>23</td>
<td>58</td>
<td>42</td>
<td>69</td>
<td>43</td>
<td>40</td>
<td>46</td>
</tr>
<tr>
<td>Pre-authorized pharmacy-driven dose optimization (e.g. automatic renal dose adjustments, intravenous-to-oral conversions etc.)</td>
<td>31</td>
<td>48</td>
<td>36</td>
<td>69</td>
<td>35</td>
<td>47</td>
<td>42</td>
</tr>
<tr>
<td>Separate antimicrobial chart or section</td>
<td>62</td>
<td>55</td>
<td>40</td>
<td>33</td>
<td>0</td>
<td>47</td>
<td>39</td>
</tr>
<tr>
<td>Inflammatory markers to prevent initiation of antibiotics, e.g. procalcitonin</td>
<td>69</td>
<td>65</td>
<td>37</td>
<td>22</td>
<td>13</td>
<td>51</td>
<td>39</td>
</tr>
<tr>
<td>Inflammatory markers to stop antibiotics early, e.g. procalcitonin</td>
<td>46</td>
<td>58</td>
<td>35</td>
<td>24</td>
<td>13</td>
<td>51</td>
<td>36</td>
</tr>
<tr>
<td>Restrictions on access by pharmaceutical representatives</td>
<td>31</td>
<td>45</td>
<td>26</td>
<td>56</td>
<td>43</td>
<td>40</td>
<td>33</td>
</tr>
<tr>
<td>Antibiotic cycling programme</td>
<td>23</td>
<td>19</td>
<td>14</td>
<td>11</td>
<td>4</td>
<td>42</td>
<td>17</td>
</tr>
</tbody>
</table>
(trainees, 68%; and seniors, 46%) or written information (45% and 35%, respectively) at induction. Short courses were provided for trainees (31%) and seniors (27%). A small number of hospitals did not educate senior doctors (6%) or trainee doctors (2%). Fewer than 25% had mandatory updates every 1 or 2 years.

Nurses received less education; 27% received face-to-face training and/or 16% were given written information at induction, 21% undertook short courses and 15% received no specific education. Only 12% received mandatory updates.

Most pharmacists (94%) were educated, mainly at induction: 43% by face-to-face training and/or 25% by written information and 22% by short courses. Few centres (17% or fewer) used e-learning across the different staff groups.

**Discussion**

We present here data describing AMS practice in 660 hospitals in 67 countries across six continents. Our findings show a significant diversity and variation across the continents in relation to the organizational structures, range of interventions and impact of AMS programmes in hospitals. There were, however, some consistent approaches to AMS, especially across more developed countries.

Our survey has several limitations. First, respondents were self-selecting and there was no method of validating their data entry. Additionally, recruitment often occurred through contact sources of the authors or through their professional associations, thereby further contributing to a potential recruitment bias. Second, the interpretation of the questions and definitions used may not always have been clear or consistent between countries. For example, some may have no relevance or meaning in a local context, although help was available by email to minimize this bias. Third, there was an imbalance between the continents in terms of reporting results. The number of returns from Oceania and North America is clearly low and under-representative of significant and in some cases mature stewardship activity in these continents. Although the number of returns from Oceania and North America was low, these sorts of difference are inherent in this type of survey, especially where there is a country-wide invitation. A comparison to recently published AMS surveys from these countries demonstrated some consistencies and variation. An Australian state-wide survey of 155 hospitals undertaken in 2011 showed similar results for the existence of treatment guidelines but significantly lower rates for restriction and formularies. A 2009 survey of 406 USA hospitals reported a lower rate of AMS programmes in place, antimicrobial restriction and guidelines for intravenous-to-oral switching but reported similar results for the type of staff delivering their AMS programmes and access to an infectious diseases specialist to review the patient. Europe accounted for more than half of the returns, and England for 15% of hospital returns. The impact of the data from England on those from Europe did not, however, cause significant changes in our results. For example, if the English data were removed from our analyses, the most important modifications would be a 7% reduction in AMS programmes in place but no difference in duration. Similarly, antimicrobial pharmacist time would decrease from 17 to 8 hours per week, and medical microbiologist input from 11 to 7 hours. We would observe a reduction in antimicrobial audit activity (from 82% to 71%) and a restriction of cephalosporins (from 66% to 46%) and to a lesser degree fluoroquinolones (from 72% to 61%). Therefore, we do not consider that the high participation of English hospitals represents a significant bias.

Finally, this was a large-scale survey of institutions and we were unable to unravel or explore local circumstances, e.g. whether hospital policies had been adapted for the local setting or reflected regional or national antimicrobial resistance patterns. Prescribing will depend upon the hospital case mix and local experience with pathogens, which will be reflected in recommendations for empirical and definitive therapies. Another limitation is the proportion of respondents that completed the questionnaire to the end. Most continents achieved a 78%–83% completion rate. The outliers were Africa (89%, 39/44) and South America (59%, 61/103).

Regardless of these caveats, the study provides us with some important findings on standard approaches to AMS that are worth highlighting. While 52% of the countries had national AMS standards, there was a large variation across the continents: from 81% in Europe down to 20% in Africa and North America. There were also few countries that were planning to introduce AMS standards—mainly those in Asia. This may reflect the continental approach to antimicrobial resistance and the size of the countries involved. To achieve more effective clinical engagement for stewardship in countries where national stewardship standards already exist, the recent development of national clinical stewardship standards for Australian hospitals signifies possibly a mature and natural evolutionary process for the implementation of more effective stewardship in daily routine clinical care. These data suggest that there is still much to do to deliver the WHO Antibacterial Resistance (AMR) strategy from 2001 and in which national AMS standards or guidelines are a core recommendation. As for AMS standards within hospitals, Europe again had the highest proportion, at 73%, followed by Asia and South America, whereas Africa had the lowest. This presumably reflects the relatively early stages of development of stewardship as a core activity for combating AMR within African hospitals.

There is, however, evidence of emerging activity to address this in Africa through a collaborative approach with infection prevention teams. Such an approach has been commended in other systems as well.

Two-thirds of the hospitals in North America and Europe had AMS programmes. This probably reflects strong and historical leadership on AMS from infectious diseases or microbiology organizations in the USA and Europe. The low- or middle-income countries (Africa and South America) had lower levels of AMS programmes, which may reflect the lack of infrastructure in these continents and a more recent political commitment. Despite this variation, it is encouraging that stewardship programmes are being developed, and are successful, as in Vietnam, or are being promoted as a key policy recommendation as in India: ‘The Chennai Declaration’ recommendations of ‘A roadmap to tackle the challenge of antimicrobial resistance’.

There has been little investigation in the literature into the barriers to the provision of AMS programmes. A review of barriers to AMS programmes, an Australian study and two American studies have concurred that lack of finance is the major obstacle, and the reported drivers matched those found in our global study.

Most hospitals had a drug and therapeutics committee, but it was mainly European and North American hospitals that had AMS committees. AMS policies and strategies were in place in fewer than half of all hospitals, and even fewer published an annual...
AMS report. Currently, the WHO has a Strategic and Technical Advisory Group on antimicrobial resistance aiming to provide stronger leadership to improve this situation. The type of staff delivering AMS activities seems to reflect the staffing within the healthcare system of that country. North America and Oceania primarily deliver their AMS service with specialist pharmacists and infectious disease specialist doctors whereas in Europe the delivery is mixed, mainly with pharmacists and either medical microbiologists (UK and Ireland) or infectious disease specialists on mainland Europe. The skill mix of the stewardship team also reflects in the AMS strategies being delivered. For example, pharmacist skills are often deployed to optimize dosing, implement intravenous-to-oral switching or support post-prescription review, while infectious disease specialists are pivotal for ward rounds and diagnostic input. The role of the microbiology laboratory and the medical microbiologist is fundamental to AMS, particularly through the interpretation, selective processing and reporting of culture and susceptibility results. As laboratories move towards centralization and increasing efficiency, there is a real danger that specimens and culture results will no longer be interpreted by experts and that data will simply be reported without qualification to inexperienced clinicians, leading to overtreatment. There appears to be infrequent use of certain diagnostic or prescribing interventions that have been shown to reduce the volume of antimicrobial prescribing or improve patient outcomes, for example measurement of procalcitonin, electronic prescribing with decision support or data warehousing. On the other hand, AMS ward rounds were frequently used, particularly in low- or middle-income countries. Where their impact had been evaluated, there was about a 40% reduction in antimicrobial use.

A restriction of broad-spectrum antibiotics was reported to occur routinely, often combined with a post-prescription review. The latter is generally regarded as a resource-intensive intervention but a key clinical and cost-effective intervention, particularly when linked to audit and feedback. The focus on optimizing the use of certain antibiotic classes has been especially appealing, with a significant impact on resistance and C. difficile infection rates. Formal antibiotic diversity strategies were infrequently reported despite emerging evidence of their effectiveness in units with high levels of antimicrobial resistance. Antibiotic cycling strategies were also infrequently reported, possibly reflecting the practical difficulties in doing this, including heavy resource use and a scarcity of evidence to support cycling as an effective means of controlling resistance.

Audit and feedback is a core intervention in AMS. There is growing evidence that a regional or country-wide standardized approach can show sustained improvements in acute medical admission units in terms of both compliance with guidelines as well as prophylaxis for surgical site infections. Outside measuring compliance with antibiotic treatment, however, or the duration and indication of treatment for inpatients or prophylaxis bundles, this approach did not frequently occur. Surprisingly, over half of all specialties never audited their own practice. This suggests that the significant impact of audit and feedback as a stewardship and educational tool is underestimated. A recent Cochrane review supported its value, particularly in the context of a low baseline performance, when the source of feedback is a supervisor or colleague, when it is provided more than once, when it is delivered in both verbal and written formats, and when it includes both explicit targets and an action plan. Therefore, this more focused evidence-based approach to feedback should be more widely commended. Additionally, the collection and feedback of consumption data is recommended, as the engagement of prescribers is essential for antimicrobial management teams to make any impact. Consumption metrics are a commonly used indicator of stewardship activity. Antimicrobial usage was monitored by most hospitals with an AMS programme as DDDS or expenditure, but fewer than half linked it to infection or resistance rates. In order to demonstrate positive outcomes of AMS programmes, there need to be improvements in the reporting of antimicrobial usage, and preferably benchmarking between similar hospitals. Using such data for benchmarking is, however, subject to many difficulties.

While most hospitals provided AMS education, it was generally to doctors in training or to pharmacists at induction and with written materials. Nurses, however, appeared to receive little training despite their critical role in the monitoring and administration of treatment. The potential beneficial role of nurses in stewardship is underestimated. A competency- and outcomes-based educational framework for stewardship is useful in planning such an implementation of stewardship education. Few hospitals reported using e-learning and most did not mandate updates. Without a change in our education of prescribers and those who administer or monitor antibiotics, AMS will remain challenging.

Overall, those hospitals that had carried out a formal evaluation of their AMS programme reported significant reductions in inappropriate prescribing, primarily the use of broad-spectrum agents, and a reduction in direct expenditure and healthcare-acquired infections, as well as to a lesser extent in the length of stay or mortality, and antimicrobial resistance. Respondents were not, however, asked to provide references to published reports and we acknowledge the limitations of self-reporting. These findings are nevertheless consistent with the literature and argue for mandatory AMS programmes to be implemented worldwide. The model for AMS programmes and their implementation should offer flexibility to account for the local healthcare structure, geography, culture and resources, and could use published validated quality indicators. The importance of measuring the impact of stewardship on outcomes has recently been emphasized with the competition for scarce financial resources, a key barrier identified in the survey. We did not collect such outcome data, but large multicentre surveys exploring the relationships between different stewardship activities and outcomes (mostly antibiotic use and resistance data) are urgently needed. This could potentially facilitate prioritization from a menu of stewardship activities in resource-limited settings.

The results of this survey showed the depth of AMS across the world and the benefits that hospitals have reported from running an AMS programme. It also demonstrated that there has been some improvement in the implementation of AMS strategies compared with some of the more recent AMS surveys carried out in Europe in 2003, Australia in 2012 and the USA in 2009, 2012 and 1998. We are unaware of published continent-wide surveys in Asia, Africa or South America but one is currently being undertaken in Asia. We hope that this work will inform local and international policy-makers about current stewardship activity and challenges with a view to fostering broader international collaboration as recommended by the recent WHO report on resistance.
Practical impact of our findings and recommendations

Based on our findings, we would advocate: (i) an international AMS framework; (ii) international evidence-based AMS interventions/programmes; and (iii) mandatory public reporting of AMS process and outcome measures.

In summary, the development and implementation of AMS programmes varies considerably across the world. The study highlights the need to better understand current practices globally, not only in hospitals, but across all healthcare systems; this should include ambulatory care, for which such data are scarce. Our results should inform and encourage a further evaluation of this with a view to promoting a worldwide stewardship framework that is relevant to the context of the healthcare system, culturally pertinent and, above all, flexible and dynamic to meet the needs of the population. The prospective measurement of clear, well-defined outcomes of the impact of these programmes clearly remains a significant challenge if we are to persuade policy-makers and funders of the added and long-term clinical effectiveness and cost-effectiveness of these interventions aimed at combating antimicrobial resistance.

Acknowledgements

The summary data were presented at ECCMID, 2013 as an oral abstract (0475). Continental-level data have been presented as follows: interim European data have been presented as a poster at the European Society of Clinical Pharmacy, Leuven, 2012; South American data have been presented as an oral presentation at the Argentinian Association of Hospital Pharmacy Conference, 2013; the Oceanic data have been presented as an oral presentation at the New Zealand Association of Hospital Pharmacy Conference, 2013; and some of the Asian data have been presented as an oral presentation at the Gulf States AMS Conference, 2013. Country-level data for the UK were presented as a poster (2087) at the Federation of Infection Societies, 2012.

We acknowledge Karin Thursky, Amani Alnimr, Wendy Lawson, Shaheen Mehtar, Wattal Chand, Jim Hutchinson, Barry Cookson and Jason Newlands for reviewing the pilot questionnaire, and Tracey Guise, Chris Jay, Sean Egan, Antony Zorzi and Diane Jacobsen for distribution of the survey to their local networks.

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Transparency declarations

None to declare.

Author contributions


Supplementary data

The questionnaire is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

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Antimicrobial stewardship worldwide survey


50 Pope SD, Dellit TH, Owens RC et al. Results of survey on implementation of Infectious Diseases Society of America and Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Infect Control Hosp Epidemiol 2009; 30: 97–8.


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Treatment Recommendations For Adult Inpatients

Also available online at insidehopkinsmedicine.org/amp
1. Introduction ........................................................................................................... 3

2. Johns Hopkins Hospital formulary and restriction status ................................ 6
   2.1 Obtaining ID approval .................................................................................. 6
   2.2 Formulary ................................................................................................. 7

3. Agent-specific guidelines .................................................................................. 8
   3.1 Antibiotics .................................................................................................. 8
       Ceftaroline .................................................................................................. 8
       Ceftolozane/tazobactam ............................................................................. 8
       Colistin ....................................................................................................... 9
       Daptomycin ............................................................................................. 10
       Ertapenem .................................................................................................. 11
       Fosfomycin .............................................................................................. 11
       Linezolid ................................................................................................. 12
       Tigecycline .............................................................................................. 13
       Trimethoprim/sulfamethoxazole ................................................................ 14
   3.2 Antifungals ............................................................................................... 16
       AmBisome® .............................................................................................. 16
       Micafungin ............................................................................................... 17
       Posaconazole .......................................................................................... 18
       Voriconazole ............................................................................................ 19
       Azole drug interactions ............................................................................ 20
   3.3 Vaccines ..................................................................................................... 23
       Pneumococcal vaccines .......................................................................... 23

4. Organism-specific guidelines ........................................................................... 24
   4.1 Anaerobes ................................................................................................. 24
   4.2 Propionibacterium acnes ........................................................................... 25
   4.3 Streptococci ............................................................................................. 27
   4.4 Multi-drug resistant Gram-negative rods .................................................. 28

5. Microbiology information .................................................................................. 31
   5.1 Interpreting the microbiology report .......................................................... 31
   5.2 Spectrum of antibiotic activity .................................................................... 32
   5.3 Interpretation of rapid diagnostic tests ...................................................... 34
   5.4 Johns Hopkins Hospital antibiogram ........................................................ 36

6. Guidelines for the treatment of various infections ........................................... 39
   6.1 Abdominal infections ............................................................................... 39
       Biliary tract infections .............................................................................. 39
       Diverticulitis ............................................................................................ 40
       Pancreatitis .............................................................................................. 41
       Peritonitis (including SBP, GI perforation and peritonitis related to peritoneal dialysis) ................................................................................................................................. 42
   6.2 Clostridium difficile infection (CDI) ............................................................ 47
   6.3 Infectious diarrhea ...................................................................................... 51
   6.4 H. pylori infection ..................................................................................... 54
   6.5 Gynecologic and sexually transmitted infections ..................................... 56
       Pelvic inflammatory disease ...................................................................... 56
       Endomyometritis ...................................................................................... 56
       Bacterial vaginosis ................................................................................... 57
       Trichomoniasis ........................................................................................ 57
       Uncomplicated gonococcal urethritis, cervicitis, proctitis ....................... 57
       Syphilis .................................................................................................... 58
   6.6 Catheter-related bloodstream infections ................................................... 60

(continued on next page)
**Introduction**

Antibiotic resistance is now a major issue confronting healthcare providers and their patients. Changing antibiotic resistance patterns, rising antibiotic costs and the introduction of new antibiotics have made selecting optimal antibiotic regimens more difficult now than ever before. Furthermore, history has taught us that if we do not use antibiotics carefully, they will lose their efficacy. As a response to these challenges, the Johns Hopkins Antimicrobial Stewardship Program was created in July 2001. Headed by an Infectious Disease physician (Sara Cosgrove, M.D., M.S.) and an Infectious Disease pharmacist (Edina Avdic, Pharm.D., M.B.A), the mission of the program is to ensure that every patient at Hopkins on antibiotics gets optimal therapy. These guidelines are a step in that direction. The guidelines were initially developed by Arjun Srinivasan, M.D., and Alpa Patel, Pharm.D., in 2002 and have been revised and expanded annually.

These guidelines are based on current literature reviews, including national guidelines and consensus statements, current microbiologic data from the Hopkins lab, and Hopkins' faculty expert opinion. Faculty from various departments have reviewed and approved these guidelines. As you will see, in addition to antibiotic recommendations, the guidelines also contain information about diagnosis and other useful management tips.

As the name implies, these are only **guidelines**, and we anticipate that occasionally, departures from them will be necessary. When these cases arise, we will be interested in knowing why the departure is necessary. We want to learn about new approaches and new data as they become available so that we may update the guidelines as needed. You should also document the reasons for the departure in the patient's chart.

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Frank Witter, M.D. (OB-GYN)

How to use this guide

• Each section begins by giving recommendations for the choice and dose of antibiotics for the particular infection.

• ALL DOSES IN THE TEXT ARE FOR ADULTS WITH NORMAL RENAL AND HEPATIC FUNCTION.
  • If your patient does NOT have normal renal or hepatic function, please refer to the sections on antibiotic dosing to determine the correct dose.

• Following the antibiotic recommendations, we have tried to include some important treatment notes that explain a bit about WHY the particular antibiotics were chosen and that provide some important tips on diagnosis and management. PLEASE glance at these notes.
when you are treating infections, as we think the information will prove helpful. All references are on file in the office of the Antimicrobial Stewardship Program (7-4570).

**Contacting us**
- **Antibiotic approval:** Use PING; search “antibiotic,” then select “Antibiotic Approval Pager”
  - Please do not send numeric pages
  - Please complete the form as accurately as possible.
  - **ALL** orders for restricted antibiotics MUST be approved unless they are part of an approved order.
  - Please see page 6 for more information about obtaining approval.
- Antimicrobial Stewardship Program: 7-4570
- Infectious Diseases Consults: 3-8026
- Critical Care and Surgery Pharmacy (Zayed 3121): 5-6505
- Adult Inpatient Pharmacy (Zayed 7000): 5-6150
- Weinberg pharmacy: 5-8998
- Bayview Inpatient Pharmacy: 0-0958
- Microbiology lab: 5-6510

**A word from our lawyers**
The recommendations given in this guide are meant to serve as treatment guidelines. They should NOT supplant clinical judgment or Infectious Diseases consultation when indicated. The recommendations were developed for use at The Johns Hopkins Hospital and thus may not be appropriate for other settings. We have attempted to verify that all information is correct but because of ongoing research, things may change. If there is any doubt, please verify the information in the guide by calling the antibiotics pager using PING (search “antibiotic”) or Infectious Diseases.

**Also, please note that these guidelines contain cost information that is confidential. Copies of the book should not be distributed outside of the institution without permission.**
## Obtaining ID approval

The use of restricted and non-formulary antimicrobials requires pre-approval from Infectious Diseases. This approval can be obtained by any of the following methods.

<table>
<thead>
<tr>
<th>Approval method</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PING: “antibiotic”</td>
<td>The pager is answered between 8 a.m. and 10 p.m. PING the ID consult pager if you fail to get a response from the ID approval pager within 10 minutes.</td>
</tr>
<tr>
<td>Overnight Approval</td>
<td>Restricted antibiotics ordered between 10 p.m. and 8 a.m. must be approved by noon the following morning. <em>Please remember to sign out the need for approval if you go off shift before 8 a.m.</em></td>
</tr>
<tr>
<td>Ordersets (e.g. neutropenic fever, etc.)</td>
<td>These forms are P&amp;T-approved for specific agents and specific indications.</td>
</tr>
</tbody>
</table>
## Selected formulary antimicrobials and restriction status

The following list applies to ALL adult floors and includes the status of both oral and injectable dosage forms, unless otherwise noted.

<table>
<thead>
<tr>
<th>Unrestricted</th>
<th>Restricted (requires ID approval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>Amikacin</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>Aztreonam</td>
</tr>
<tr>
<td>Ampicillin/sublactam (Unasyn®)</td>
<td>Cefepime</td>
</tr>
<tr>
<td>Ampicillin IV</td>
<td>Ceftaroline&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Ceftazidime</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Ceftolozane/tazobactam&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>Ciprofloxacin</td>
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<tr>
<td>Cefotetan</td>
<td>Colistin IV</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>Cytomegalovirus Immune Globulin (Cytogam®)&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>Ceftriaxone</td>
<td>Daptomycin&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>Cefuroxime</td>
<td>Fosfomycin&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
<td>Cephalexin</td>
<td>Linezolid</td>
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<tr>
<td>Clarithromycin</td>
<td>Meropenem</td>
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<tr>
<td>Clindamycin</td>
<td>Moxifloxacin</td>
</tr>
<tr>
<td>Dicloxacillin</td>
<td>Nitazoxanide&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Doxycline</td>
<td>Palivizumab (Synagis®)&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>Piperacillin/tazobactam (Zosyn®)&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Quinupristin/ dalfopristin (Synercid®)&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Ribavirin inhaled&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Telavancin&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Tigecycline</td>
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<tr>
<td>Nitrofurantoin</td>
<td>Vancomycin</td>
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<tr>
<td>Oxacillin</td>
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<tr>
<td>Penicillin V/G</td>
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<tr>
<td>Ribavirin oral</td>
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<tr>
<td>Rifampin</td>
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<td>Streptomycin</td>
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<tr>
<td>Tobramycin</td>
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<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B deoxycholate (Fungizone®)</td>
<td>Liposomal amphotericin B (AmBisome®)&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>Micafungin</td>
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<tr>
<td>Itraconazole oral solution</td>
<td>Fluconazole&lt;sup&gt;6&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Posaconazole</td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
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</tbody>
</table>

<sup>1</sup> Approval must be obtained from Antimicrobial Stewardship Program 24h/7 days a week

<sup>2</sup> Approval required, except for solid organ transplant patients

<sup>3</sup> Approval must be obtained 24h/7 days a week

<sup>4</sup> Approval must be obtained from Polk Service or ID Consult

<sup>5</sup> Approval must be obtained from ID attending physician 24h/7 days a week

<sup>6</sup> Oral Fluconazole, when used as a single-dose treatment for vulvovaginal candidiasis or when used in compliance with the SICU/WICU protocol, does not require ID approval

Restricted antimicrobials that are ordered as part of a P&T-approved critical pathway or order set do NOT require ID approval.

**REMINDER:** the use of non-formulary antimicrobials is strongly discouraged. ID approval **MUST** be obtained for ALL non-formulary antimicrobials.

**NOTE:** Formulary antivirals (e.g. Acyclovir, Ganciclovir) do NOT require ID approval.
Antibiotics

Ceftaroline

Ceftaroline is a cephalosporin with in vitro activity against staphylococci (including MRSA), most streptococci, and many Gram-negative bacteria. It does NOT have activity against Pseudomonas spp. or Acinetobacter spp. or Gram negative anaerobes.

Acceptable uses (Cases must be discussed with Infectious Diseases and Antimicrobial Stewardship Program)
- Select cases of MRSA pneumonia or other severe infections when Gram negative coverage is also needed
- Bacteremia or endocarditis caused by MRSA in a patient failing Vancomycin therapy as defined by:
  - Clinical decompensation after 3–4 days
  - Failure to clear blood cultures after 7 days despite Vancomycin troughs of 15–20 mcg/mL
  - MIC of Vancomycin is 2 mcg/mL

Unacceptable uses
- Treatment of community-acquired bacterial pneumonia (CAP) or skin and soft tissue infections (SSTI) where other more established and less expensive options are available
- Initial therapy for Gram-positive or Gram-negative infections

Dose
- 600 mg IV Q12H has been studied for CAP and SSTI
- 600 mg IV Q8H for MRSA bacteremia salvage therapy or other serious infections
- Must adjust for worsening renal function and dialysis (see p. 155 for dose adjustment recommendation).

Laboratory interactions
- Ceftaroline may result in positive direct Coombs’ test without hemolytic anemia. However, if drug-induced hemolytic anemia is suspected, discontinue Ceftaroline.

Ceftolozane/tazobactam

Ceftolozane/tazobactam is a novel cephalosporin and β-lactamase-inhibitor combination. It has activity against Gram-negative organisms and some strains of multi-resistant Pseudomonas spp. It does NOT have activity against carbapenemase-producing Enterobacteriaceae. It also has in vitro activity against some streptococci and some Gram-negative anaerobes, but it does not have reliable Staphylococcus spp. activity.
Acceptable uses (Cases must be discussed with Infectious Diseases and Antimicrobial Stewardship Program)
- Management of infections due to multi-drug resistant *Pseudomonas* spp. infections on a case by case basis

Unacceptable uses
- Empiric treatment of complicated intra-abdominal infections (cIAI) or complicated urinary tract infections (cUTI) as current standard regimens are sufficient for coverage of the typical pathogens involved in these infections and less expensive options are available

Dose
- 1.5 g IV Q8H has been studied for cUTI and in combination with metronidazole for cIAI
- Serious infections including pneumonia: 3 g IV Q8H
- Must adjust dose for worsening renal function and dialysis (see p.155 for dose adjustment recommendation).

**Colistin (Colistimethate)**

Colistin is a polymixin antibiotic. It has *in vitro* activity against *Acinetobacter* spp. and *Pseudomonas* spp. but does NOT have activity against *Proteus, Serratia, Providentia, Burkholderia, Stenotrophomonas, Gram-negative cocci, Gram-positive organisms, or anaerobes.*

Acceptable uses
- Management of infections due to multi-drug resistant *Acinetobacter* and *Pseudomonas* on a case by case basis.

Unacceptable uses
- Monotherapy for empiric treatment of suspected Gram-negative infections

Dose
- Loading dose: 5 mg/kg once
- Maintenance dose: 2.5 mg/kg Q12H; must adjust for worsening renal function and dialysis (see p. 155 for dose adjustment recommendation).

Toxicity
- Renal impairment, neuromuscular blockade, neurotoxicity
- Monitoring: BUN, creatinine twice-weekly
Daptomycin

Daptomycin is a lipopeptide antibiotic. It has activity against most strains of staphylococci and streptococci (including MRSA and VRE). It does NOT have activity against Gram-negative organisms.

**Acceptable uses** (Cases must be discussed with Infectious Diseases and Antimicrobial Stewardship Program)

- Bacteremia or endocarditis caused by MRSA or Methicillin-resistant coagulase-negative staphylococci in a patient with serious allergy to Vancomycin
- Bacteremia or endocarditis caused by MRSA in a patient failing Vancomycin therapy as defined by:
  - Clinical decompensation after 3–4 days
  - Failure to clear blood cultures after 7 days despite Vancomycin troughs of 15–20 mcg/mL (high risk of Daptomycin resistance; check Daptomycin MIC and obtain follow up blood cultures)
  - MIC of Vancomycin is 2 mcg/mL
- Therapy for VRE infections other than pneumonia, on a case by case basis

**Unacceptable uses**

- Daptomycin should NOT be used for treatment of pneumonia due to its inactivation by pulmonary surfactant.
- Initial therapy for Gram-positive infections
- VRE colonization of the urine, respiratory tract, wounds, or drains

**Dose**

- Bacteremia: 6–12 mg/kg IV Q 24H
- Endocarditis: 6–12 mg/kg IV Q 24H
- Dose adjustment is necessary for CrCl < 30 ml/min (see p. 155 for dose adjustment recommendation).

Reference:
Toxicity
- Myopathy (defined as CK $\geq$ 10 times the upper limit of normal without symptoms or $\geq$ 5 times the upper limit of normal with symptoms).
- Eosinophilic pneumonia
- Monitoring: CK weekly, more frequently during initial therapy.

Reference:

**Ertapenem**

Ertapenem is a carbapenem antibiotic. It has *in vitro* activity against many Gram-negative organisms including those that produce extended spectrum beta-lactamases (ESBL), but it does not have activity against *Pseudomonas spp.* or *Acinetobacter spp.* Its anaerobic and Gram-positive activity is similar to that of other carbapenems, except it does not have activity against *Enterococcus spp.*

**Acceptable uses**
- Mild to moderate intra-abdominal infections (biliary tract infections, diverticulitis, secondary peritonitis/GI perforation)
- Moderate diabetic foot infections without osteomyelitis
- Moderate surgical-site infections following contaminated procedure
- Pelvic inflammatory disease
- Urinary tract infections caused by ESBL-producing organisms
- Pyelonephritis in a patient who is not severely ill

**Unacceptable uses**
- Severe infections in which *Pseudomonas spp.* are suspected.

**Dose**
- 1 g IV or IM Q24H, must adjust for worsening renal function and dialysis (see p. 155 for dose adjustment recommendation)

**Toxicity**
- Diarrhea, nausea, headache, phlebitis/thrombophlebitis

**Fosfomycin**

Fosfomycin is a synthetic, broad-spectrum, bactericidal antibiotic with *in vitro* activity against large number of Gram-negative and Gram-positive organisms including *E. coli, Klebsiella spp., Proteus spp., Pseudomonas spp.*, and VRE. It does not have activity against *Acinetobacter spp.* Fosfomycin is available in an oral formulation only in the U.S. and its pharmacokinetics allow for one-time dosing.

**Acceptable uses**
- Management of uncomplicated UTI in patients with multiple antibiotic allergies and/or when no other oral therapy options are available.
Uncomplicated UTI due to VRE
Salvage therapy for UTI due to multi-drug resistant Gram-negative organisms (e.g. *Pseudomonas spp.*) on case by case basis.

**NOTE:** Susceptibility to Fosfomycin should be confirmed prior to initiation of therapy.

**Unacceptable uses**
- Fosfomycin should NOT be used for management of any infections outside of the urinary tract because it does not achieve adequate concentrations at other sites.
- Treatment of asymptomatic bacteriuria (see p. 110)

**Dose**
- Uncomplicated UTI: 3 g (1 sachet) PO once.
- Complicated UTI: 3 g (1 sachet) PO every 1-3 days (up to 21 days of treatment)
- Frequency adjustment may be necessary in patients with CrCl < 50 mL/min. Contact the ID Pharmacist for dosing recommendations.
- Powder should be mixed with 90–120 mL of cool water, stirred to dissolve and administered immediately.

**Toxicity**
- Diarrhea, nausea, headache, dizziness, asthenia and dyspepsia

---

### Linezolid

**Acceptable uses**
- Documented Vancomycin intermediate *Staphylococcus aureus* (VISA) or Vancomycin resistant *Staphylococcus aureus* (VRSA) infection
- Documented MRSA or Methicillin-resistant coagulase-negative staphylococcal infection in a patient with serious allergy to Vancomycin
- Documented MRSA or Methicillin-resistant coagulase-negative staphylococcal infection in a patient failing Vancomycin therapy (as defined below):
  - Bacteremia/endocarditis: failure to clear blood cultures after 7 days despite Vancomycin troughs of 15–20 mcg/mL. Should be used in combination with another agent
  - Pneumonia: worsening infiltrate or pulmonary status in a patient with documented MRSA pneumonia after 2 to 3 days or if the MIC of Vancomycin is 2 mcg/mL, or if achieving appropriate vancomycin trough is unlikely (e.g., obesity)
  - Cases should be discussed with Infectious Diseases or Antimicrobial stewardship
  - High suspicion of CA-MRSA necrotizing pneumonia in a seriously ill patient
• Documented VRE infection
• Gram-positive cocci in chains in blood cultures in an ICU, or oncology transplant patient known to be colonized with VRE

Unacceptable uses
• Prophylaxis
• Initial therapy for staphylococcal infection
• VRE colonization of the stool, urine, respiratory tract, wounds, or drains

Dose
• 600 mg IV/PO Q12H
• Skin and skin-structure infections: 400 mg IV/PO Q12H

Toxicity
• Bone marrow suppression (usually occurs within first 2 weeks of therapy)
• Optic neuritis and irreversible sensory motor polyneuropathy (usually occurs with prolonged therapy > 28 days)
• Case reports of lactic acidosis
• Case reports of serotonin syndrome when co-administered with serotonergic agents (SSRIs, TCAs, MAOIs, etc.)
• Monitoring: CBC weekly

Tigecycline
Tigecycline is a tetracycline derivative called a glycylcycline. It has in vitro activity against most strains of staphylococci and streptococci (including MRSA and VRE), anaerobes, and many Gram-negative organisms with the exception of Proteus spp. and Pseudomonas aeruginosa. It is FDA approved for skin and skin-structure infections and intra-abdominal infections.

NOTE: Peak serum concentrations of Tigecycline do not exceed 1 mcg/mL which limits its use for treatment of bacteremia

Acceptable uses
• Management of intra-abdominal infections in patients with contraindications to both beta-lactams and fluoroquinolones
• Management of infections due to multi-drug resistant Gram-negative organisms including Acinetobacter spp. and Stenotrophomonas maltophilia on a case by case basis
• Salvage therapy for MRSA/VRE infections on a case by case basis

Dose
• 100 mg IV once, then 50 mg IV Q12H
• 100 mg IV once, then 25 mg IV Q12H if severe hepatic impairment (Child - Pugh 10–15)

Toxicity
• Nausea and vomiting
**Trimethoprim/sulfamethoxazole (Bactrim®, TMP/SMX)**

Trimethoprim/sulfamethoxazole is a sulfonamide antibiotic. It has *in vitro* activity against *Enterobacteriaceae* spp., *B. cepacia*, *S. maltophilia*, *Acinetobacter* spp., *Achromobacter* spp., *Nocardia* spp., *Listeria*, *Pneumocystis jirovecii* (PCP), staphylococci (including *S. aureus* and Coagulase-negative staph), but does NOT cover *Pseudomonas* spp. It has variable activity against streptococci and no activity against anaerobes.

**Acceptable uses**
- Urinary tract infections (UTI)
- *S. aureus* skin and soft-tissue infections (SSTI)
- *Pneumocystis jirovecii* pneumonia (PCP) treatment and prophylaxis
- *S. maltophilia* infections
- Nocardia infections
- Gram-negative bacteremia when organism is susceptible
- Salvage therapy for MRSA bacteremia in combination with another agent
- Empiric coverage of *Listeria* meningitis in patients with penicillin allergies
- Suppressive therapy and in some cases treatment for bone and joint infections

**Unacceptable uses**
- Monotherapy for *S. aureus* bacteremia

**Dose**
- Trimethoprim/sulfamethoxazole dosing is based on trimethoprim component
- TMP/SMX has excellent bioavailability, thus conversion from IV to PO is 1:1 (80/400 mg IV = 1 SS tab; 160/800 mg IV = 1 DS tab)
- Use adjusted BW = [IBW + 0.4 (ABW - IBW)] in obese patients (>30% over IBW)

**Treatment**
- UTI: 1 DS tab Q12H
- SSTI: 1-2 DS tab Q12H
- PCP: 15-20 mg/kg/day (in divided doses, Q6-Q8H)
- MRSA bacteremia: 10-15 mg/kg/day (in divided doses, Q6-Q8H)
- *S. maltophilia* infections: 15 mg/kg/day (in divided doses, Q6-Q8H)
• Nocardia infections: 15 mg/kg/day (in divided doses, Q6-Q8H); lower doses (5-10 mg/kg/day) can be used after several weeks of therapy or cutaneous infections
• Meningitis: 20 mg/kg/day (in divided doses, Q6H)
• Other infections: 8-10 mg/kg/day (in divided doses, Q6-12H)
• Must adjust dose for worsening renal function and dialysis (see p.155 for dose adjustment recommendation).

Prophylaxis
• PCP: 1 SS daily or 1 DS 3 times/week
• Toxoplasmosis: 1 DS daily

Toxicity
• Common: hypersensitivity (1.6-8%), G-uptset, pseudo elevation in creatinine (18%)
• Common with higher doses: hyperkalemia, myelosuppression
• Occasional: nephrotoxicity, photosensitivity, methemoglobinemia (with severe G6PD deficiency)
• Rare: aseptic meningitis, hepatotoxicity, toxic epidermal necrolysis (TEN), SJS, Sweet’s syndrome

Drug Interaction
• Warfarin, methotrexate, phenytoin, digoxin, sulfonylureas, procainamide, oral contraceptives
Antifungals

Liposomal Amphotericin B (AmBisome®)

NOTES:
• Dosing of AmBisome and Amphotericin B deoxycholate is significantly different. Do not use AmBisome doses when ordering Amphotericin B deoxycholate and vice versa.
• Amphotericin B deoxycholate is preferred in patients with end-stage renal disease on dialysis who are anuric.

AmBisome, like all Amphotericin B products, has broad spectrum antifungal activity with in vitro activity against Candida, Aspergillus, Zygomycosis and Fusarium.

Acceptable uses
• Candidal endophthalmitis, endocarditis, CNS infection—first line therapy
• Cryptococcus meningitis—first line therapy
• Zygomycoses (Mucor, Rhizopus, Cunninghamella)—first line therapy
• Neutropenic fever if receiving Voriconazole or Posaconazole prophylaxis
• Alternative treatment of invasive aspergillosis
• Alternative treatment of candidemia, candida peritonitis

Dose
• Candidemia, histoplasmosis, other non-invasive candida infections: 3 mg/kg/day
• Candidal endophthalmitis, endocarditis, CNS infection, C. krusei candidemia: 5 mg/kg/day
• Invasive filamentous fungi: 5 mg/kg/day
• Neutropenic fever, candidemia in neutropenic patient: 3–5 mg/kg/day
• Cryptococcal meningitis: 3–4 mg/kg/day

Toxicity
• Infusion-related reactions: fever, chills, rigors, hypotension
• Renal impairment (enhanced in patients with concomitant nephrotoxic drugs)
• Electrolyte imbalances
• Pulmonary toxicity (chest pain, hypoxia, dyspnea), anemia, elevation in hepatic enzymes—rare
• Monitoring: BUN/creatinine, K, Mg, Phos at baseline and daily in hospitalized patients; AST/ALT at baseline and every 1-2 weeks
NOTE: Micafungin does not have activity against Cryptococcus.

Aspergillosis

• **Acceptable uses**
  - In combination with Voriconazole for confirmed invasive aspergillosis (see p. 133)
  - Refractory disease- for use in combination with Voriconazole, Posaconazole or AmBisome® for confirmed invasive aspergillosis.

• **Unacceptable uses**
  - Micafungin alone or in combination with other antifungal agents is not recommended for empiric therapy in patients with CT findings suggestive of aspergillosis (e.g., possible aspergillosis) without plans for diagnostic studies.
  - Micafungin does not have good *in vitro* activity against zygomycoses (*Mucor, Rhizopus, Cunninghamamella, etc.*).

Candidiasis

• **Acceptable uses**
  - Treatment of invasive candidiasis due to *C. glabrata* or *C. krusei*.
  - Treatment of invasive candidiasis in patients who are NOT clinically stable due to candidemia or have received prior long-term azole therapy.
  - Alternative treatment of recurrent esophageal candidiasis.
  - Alternative treatment of endocarditis.

• **Unacceptable uses**
  - Micafungin has poor penetration into the CNS and urinary tract. It should be avoided for infections involving those sites.

Neutropenic fever

• Micafungin can be used for neutropenic fever in patients who are not suspected to have aspergillosis or zygomycosis.

Dose

• Candidemia, invasive candidiasis, neutropenic fever: 100 mg IV Q24H
• Candidal endocarditis: 150 mg IV Q24H
• Recurrent esophageal candidiasis: 150 mg IV Q24H
• Invasive aspergillosis: 100–150 mg IV Q24H
• Obese patients
  - 100–150 kg: 150 mg IV Q24
  - > 150 kg: Consult ID Pharmacist

Drug Interactions

• Close monitoring is recommended when Micafungin is used with the following agents concomitantly:
3.2 Agent-specific guidelines: Antifungals

- Sirolimus – levels of Sirolimus may be increased, monitor for Sirolimus toxicity
- Nifedipine – levels of Nifedipine may be increased, monitor for Nifedipine toxicity
- Itraconazole – levels of Itraconazole may be increased, monitor for Itraconazole toxicity

Toxicity
- Infusion-related reactions (rash, pruritis), phlebitis, headache, nausea and vomiting, and elevations in hepatic enzymes.
- Monitoring: AST/ALT/bilirubin at baseline and every 1–2 weeks after.

Posaconazole

Posaconazole is a broad spectrum azole anti-fungal agent. It has in vitro activity against Candida, Aspergillus, Zygomycosis and Fusarium spp.

Acceptable uses
- Treatment of invasive zygomycosis in combination with Amphotericin B
- Monotherapy for zygomycosis after 7 days of combination therapy with Amphotericin B
- Prophylaxis in patients with hematologic malignancy
- Treatment of aspergillosis in patients with Voriconazole intolerance

Unacceptable uses
- Candidiasis/Neutropenic fever
- First-line treatment of aspergillosis

Dose
NOTES:
- Each dose of suspension should be given with a full meal or with liquid nutritional supplements if patients cannot tolerate full meals. Can also be given with an acidic beverage (e.g. ginger ale).
- Delayed release tablets and oral suspension cannot be used interchangeably due to differences in the dosing of each formulation.

Prophylaxis
- Oral Suspension: 200 mg PO Q8H
- Extended Release Tablet: 300 mg PO daily

Treatment
- Oral Suspension: 200 mg PO Q6H for 7 days, then 400 mg PO Q8-Q12H
- Extended Release Tablet: 300 mg PO Q12H for 1 day, then 300 mg PO daily
Therapeutic monitoring:
- Posaconazole trough levels should be considered in patients who are:
  - Not responding to therapy for at least 7 days
  - Being treated for uncommon or less susceptible organisms
  - Experiencing mucositis or malabsorption syndrome
  - Unable to consume high fat meals (if receiving the suspension)

Drug Interactions: See Table on p. 21

Toxicity
- GI upset (~40%), headaches, elevation in hepatic enzymes. Rare but serious effects include QTc prolongation.
- Monitoring: AST/ALT/bilirubin at baseline and every 1–2 weeks after

References:

Voriconazole

NOTE: Voriconazole does not cover zygomycoses (Mucor, Rhizopus, Cunninghamella, etc.).

Acceptable uses
- Aspergillosis
- Scedosporium apiospermum
- Prophylaxis in patients with hematologic malignancy

Unacceptable uses
- Candidiasis / Neutropenic fever
  Voriconazole should not be used as first-line therapy for the treatment of candidiasis or for empiric therapy in patients with neutropenic fever.

Dose
- Loading dose: 6 mg/kg IV/PO Q12H x 2 doses
- Maintenance dose: 4 mg/kg IV/PO Q12H
  - Dose adjustment is necessary for hepatic insufficiency:
    - Child - Pugh (A or B): ↓ maintenance dose by 50%
    - Child - Pugh (C): Use only if benefits outweigh risks. Consult ID pharmacist for dose adjustment recommendations.
  - Dose escalation may be necessary for some patients due to subtherapeutic levels.
  - Dose based on actual body weight unless patient >30% over IBW; then use adjusted body weight. (Adj. BW).

\[
\text{Adj. BW} = [\text{IBW} + 0.4 (\text{ABW} - \text{IBW})]
\]

IBW - Ideal Body Weight
ABW - Actual Body Weight
3.2 Agent-specific guidelines: Antifungals

Therapeutic monitoring
- Voriconazole trough levels should be considered in patients who are:
  - Not responding to therapy after at least 5 days of therapy using a mg/kg dosing strategy
  - Receiving concomitant drugs that may increase or decrease Voriconazole levels
  - Experiencing adverse events due to Voriconazole
  - Experiencing GI dysfunction
- Voriconazole trough levels should be obtained 5–7 days after start of therapy (performed M–F).
- Goal trough: 2–5.5 mcg/mL. Levels < 1 mcg/mL have been associated with clinical failures and levels >5.5 mcg/mL with toxicity.

Drug Interactions: See Table on p. 21

Toxicity
- Visual disturbances (~30%) usually self-limited, rash, fever, elevations in hepatic enzymes.
- Monitoring: AST/ALT/bilirubin at baseline and every 1–2 weeks after

References:

Azole drug interactions

The following list contains major drug interactions involving drug metabolism and absorption. This list is not comprehensive and is intended as a guide only. You must check for other drug interactions when initiating azole therapy or starting new medication in patients already receiving azole therapy.

Drug metabolism:
Cytochrome (CYP) P450 inhibitors: decrease the metabolism of certain drugs (CYP450 substrates) resulting in increased drug concentrations in the body (occurs immediately)
Cytochrome (CYP) P450 inducers: increase the metabolism of certain drugs (CYP450 substrates) resulting in decreased drug concentrations in the body (may take up to 2 weeks for upregulation of enzymes to occur)

Drug absorption/penetration:
P-glycoprotein (P-gp) inhibitor: decrease the function of the efflux pump, resulting in increased absorption/penetration of P-gp substrates
P-glycoprotein inducer: increase the function of the efflux pump, resulting in decreased absorption/penetration of P-gp substrates

Potency of Cytochrome P450 inhibition: Voriconazole > Itraconazole > Posaconazole > Fluconazole
### 3.2 Agent-specific guidelines: Antifungals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POSOACONAZOLE</strong> (substrate and inhibitor for P-gp efflux, inhibitor of CYP3A4)</td>
<td><strong>Contraindicated</strong></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Do not use</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Consider dose reducing</td>
</tr>
<tr>
<td>Metoclopramide, proton pump inhibitors</td>
<td>↓ cyclosporine dose to 1/3 and monitor levels</td>
</tr>
<tr>
<td>Itraconazole, hydroxyitraconazole</td>
<td>Monitor effect of drugs and consider decreasing dose when posaconazole is added</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITRACONAZOLE</strong> and major metabolite hydroxyitraconazole (substrate and inhibitor of CYP3A4 and P-gp efflux)</td>
<td><strong>Contraindicated</strong></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Do not use</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>↓ tacrolimus dose to 1/3 and monitor levels</td>
</tr>
<tr>
<td>Lovastatin, simvastatin</td>
<td>Avoid concomitant use unless benefit outweighs risk</td>
</tr>
<tr>
<td>Statins, dofetilide, erythromycin, all calcium channel blockers, vinca alkaloids</td>
<td>↓ plasma concentration of the interacting drug, monitor levels when possible, monitor for drug toxicity and consider dose reduction</td>
</tr>
<tr>
<td>Efavirenz, phenytoin, rifabutin, rifampin</td>
<td>If used together, monitor effects of drugs and consider decreasing dose when posaconazole is added</td>
</tr>
</tbody>
</table>

**Drug Recommendations**

- **Contraindicated**
- **Warning/precaution**

**Cyclosporine**

- ↓ cyclosporine dose to 1/3 and monitor levels

**Tacrolimus**

- Consider dose reducing

**Italgidine, efavirenz, phenytoin, rifampin**

**Metoclopramide, proton pump inhibitors**

- ↓ cyclosporine dose to 1/3 and monitor levels

**Posaconazole**

- Do not use

**Cisapride, ergot alkaloids, pimozide, quinidine, triazolam**

**Cimetidine, efavirenz, phenytoin, rifabutin, rifampin**

**Amiodarone, azithromycin, digoxin, erythromycin, all calcium channel blockers, vinca alkaloids, rituximab, statins (lovastatin and simvastatin), vinca alkaloids**

**Metoclopramide, proton pump inhibitors**

- ↓ posaconazole concentrations when using suspension

**Midazolam**

- Consider dose reducing

**Cyclosporine**

- ↓ tacrolimus dose to 1/3 and monitor levels

**Metoclopramide, proton pump inhibitors**

- ↓ posaconazole concentrations when using suspension

**Midazolam**

- Consider dose reducing

**Cyclosporine**

- ↓ tacrolimus dose to 1/3 and monitor levels

**Metoclopramide, proton pump inhibitors**

- ↓ posaconazole concentrations when using suspension

**Midazolam**

- Consider dose reducing

**Cyclosporine**

- ↓ tacrolimus dose to 1/3 and monitor levels

**Metoclopramide, proton pump inhibitors**

- ↓ posaconazole concentrations when using suspension

**Midazolam**

- Consider dose reducing
3.2 Agent-specific guidelines: Antifungals

### Voriconazole (substrate and inhibitor of CYP2C19, CYP2C9, and CYP3A4)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| **Contraindicated**   | Commonly prescribed: carbamazepine, rifabutin, rifampin, ritonavir 400 mg Q12H
|                       | Less commonly prescribed: long-acting barbiturates, cisapride, ergot alkaloids, pimozide, quinidine, St. John’s Wort |
|                       | Do not use                                           |
| **Warning/precaution**| Cyclosporine                                         |
|                       | ↓ cyclosporine dose to ½ and monitor levels          |
|                       | Efavirenz                                            |
|                       | ↑ voriconazole dose to 5 mg/kg IV/PO Q12H and ↓ efavirenz to 300 mg PO daily |
|                       | Tacrolimus                                           |
|                       | ↓ tacrolimus dose to ½ and monitor levels            |
|                       | Sirolimus                                            |
|                       | ↓ sirolimus dose by 75% and monitor levels           |
|                       | Omeprazole                                           |
|                       | ↓ omeprazole dose to ½                               |
|                       | Maraviroc                                            |
|                       | ↓ maraviroc dose to 150 mg twice daily               |
|                       | Methadone                                            |
|                       | Monitor effect of the interacting drug and consider decreasing dose |
|                       | Phenytoin                                            |
|                       | ↓ voriconazole to 5 mg/kg IV/PO Q12H and monitor levels |
|                       | Ritonavir low dose (100 mg Q12H)                     |
|                       | Avoid this combination unless benefits outweigh risks |
|                       | Warfarin                                             |
|                       | Monitor INR levels                                   |
|                       | Commonly prescribed: all benzodiazepines (avoid midazolam and triazolam), all calcium channel blockers, fentanyl, oxycodone & other long acting opioids, is added NSAI ds, oral contraceptives, statins (avoid lovastatin and simvastatin), sulfonlureas, vinca alkaloids, pomalidomide, simeprevir, boceprevir, telaprevir |
|                       | Less commonly prescribed: alfentanil                  |

### Fluconazole (substrate of CYP3A4 and inhibitor of CYP3A4, CYP2C9, and CYP2C19, interactions are often dose dependent)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contraindicated</strong></td>
<td>Cisapride</td>
</tr>
<tr>
<td></td>
<td>Do not use</td>
</tr>
<tr>
<td><strong>Warning/precaution</strong></td>
<td>Commonly prescribed: cyclosporine, glipizide, glyburide, phenytoin, rifabutin, tacrolimus, warfarin</td>
</tr>
<tr>
<td></td>
<td>Less commonly prescribed: oral midazolam, theophylline, tolbutamide</td>
</tr>
<tr>
<td></td>
<td>↑ plasma concentration of the interacting drug, monitor levels when possible, monitor for drug toxicity and consider dose reduction</td>
</tr>
<tr>
<td></td>
<td>Rifampin</td>
</tr>
<tr>
<td></td>
<td>↓ plasma concentration of fluconazole, consider increasing fluconazole dose</td>
</tr>
</tbody>
</table>
**Pneumococcal vaccination**

There are two types of pneumococcal vaccines that are recommended by ACIP guidelines for adult patients: Pneumococcal polysaccharide (Pneumovax 23®, PPV23) and Pneumococcal conjugate vaccine (Prevnar 13®, PCV13). Most patients should receive both vaccines in sequential order, but NEVER together. See table below for indications for each vaccine.

### Indications for pneumococcal vaccines for adults ≥ 19 years of age

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Prevnar 13®</th>
<th>Pneumovax 23®</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adults ≥ 65 years of age</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CSF leak or cochlear implants</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Functional or anatomic asplenia</td>
<td>Yes</td>
<td>Yes, revaccinate 5 years after first dose</td>
</tr>
<tr>
<td>Immunocompetent persons with certain chronic medical conditions (e.g. heart disease*, lung disease†, liver disease, DM), alcoholism, cigarette smoking</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Immunocompromised host: congenital/ acquired immunodeficiencies, HIV, chronic renal failure, nephrotic syndrome, hematologic malignancies, organ transplant, long-term immunosuppressive therapy (e.g. steroids, active chemotherapy, radiation)</td>
<td>Yes</td>
<td>Yes, revaccinate 5 years after first dose</td>
</tr>
</tbody>
</table>

*Including CHF, cardiomyopathies, excluding hypertension; †Including COPD, emphysema, asthma

### Timing and sequential administration of pneumococcal vaccines

- No history or unknown history of pneumococcal vaccination and both vaccines are indicated, patient should receive Prevnar 13® first followed by Pneumovax 23® at a minimum of 8 weeks later (ideally 6-12 months)
- If patient has received Pneumovax 23® and both vaccines are indicated, the patient should receive Prevnar 13® (minimum 1 year separation)
- If patient has received Prevnar 13® ≥ 8 weeks ago, and both vaccines are indicated, the patient should receive Pneumovax 23® (minimum 8 weeks separation)
- If patient has received both vaccines ≥ 5 years ago and revaccination is needed with Pneumovax 23®, a second dose should be administered (minimum 5 years apart)
- Patients who are severely immunocompromised (e.g. BMT, solid organ transplant) should follow institutional policy when available or consult ID for optimal timing of vaccine administration

Reference:
Organism-specific guidelines

Anaerobes

Although anaerobic bacteria dominate the human intestinal microbiome only a few species seem to play an important role in human infections. Infections caused by anaerobes are often polymicrobial.

- Gram-negative cocci - Veillonella spp.
- Gram-positive bacilli - Propionibacterium spp., Lactobacillus spp., Actinomyces spp., Clostridium spp.
- Gram-positive cocci - Peptostreptococcus spp. and related genera

Clinical diagnosis of anaerobic infections should be suspected in the presence of foul smelling discharge, infection in proximity to a mucosal surface, gas in tissues or negative aerobic cultures. Proper specimen collection is critical; refer to specimen collection guidelines at http://www.hopkinsmedicine.org/microbiology/specimen/index.html

Treatment Notes

- Surgical debridement of anaerobic infections is important because anaerobic organisms can cause severe tissue damage.
- Ampicillin/subactam and Clindamycin are considered to be effective empiric therapy against Gram-positive anaerobes seen in infections
above the diaphragm. Metronidazole is not active against microaerophilic streptococci (e.g. S. anginosus group) and should not be used for these infections.

- Vancomycin is also active against many Gram-positive anaerobes (e.g. Clostridium spp., Peptostreptococcus spp., P. acnes).
- Empiric double coverage with Metronidazole AND carbapenems (Meropenem, Ertapenem) or beta-lactam/beta-lactamase inhibitors (Ampicillin/Sulbactam, Piperacillin/Tazobactam, Amoxicillin/Clavulanic acid) is NOT recommended given the excellent anaerobic activity of these agents.
- B. fragilis group resistance to Clindamycin, Cefotetan, Cefoxitin, and Moxifloxacin has increased and these agents should not be used empirically for treatment of severe infections where B. fragilis is suspected (e.g. intra-abdominal infections).
- Most resistance in the B. fragilis group is caused by beta-lactamase production, which is screened for by the JHH micro lab.
- Bacteroides thetaiotaomicron is less likely to be susceptible to Piperacillin/Tazobactam; therefore, when this organism is isolated or strongly suspected (e.g. Gram negative rods in anaerobic blood cultures in a patient on Piperacillin/tazobactam) alternative agents with anaerobic coverage should be used until susceptibilities are confirmed.
- Tigecycline is active against a wide spectrum of gram-positive and gram-negative anaerobic bacteria in vitro but clinical experience with this agent is limited.

**Propionibacterium acnes**

**Indications for consideration of testing for P. acnes:**

- CNS shunt infections
- Prosthetic shoulder joint infections
- Other implantable device infections

**Diagnosis**

- Cultures should be held for 10-14 days if high suspicion for P. acnes as growth is slow
- Collection of tissue and fluid specimens for culture is preferred. Do not send swabs for culture
- Multiple representative specimens (preferably 3) should be sent for shoulder joint infections to assist in distinguishing contaminants from pathogenic isolates — these could include synovial fluid, any inflammatory tissue, and synovium
- Tissue specimens should also be sent for histopathology
4.2 Organism-specific guidelines: P. acnes

Treatment
- Penicillin G 2-3 million units IV Q4H (preferred)
  - OR
- PCN allergy: Vancomycin (see dosing section, p. 150)

NOTES
- ID consult recommended for assistance with choice and duration of antibiotic therapy
- P. acnes is usually a contaminant in blood culture specimens. Draw repeat cultures and consider clinical context before treatment
- Rare reports of spinal infections have been noted for P. acnes
- All P. acnes isolates at JHH are susceptible to Penicillin (see anaerobic antibiogram p. 24)
- Metronidazole does not have activity against P. acnes. Tetracyclines are not routinely tested and resistance rates are variable.
- Broader spectrum agents such as Meropenem and Piperacillin/tazobactam would be expected to be active for Penicillin susceptible isolates, but these are not first-line therapy
- Susceptibility data should be used to help guide therapeutic decisions
- Consider removal of associated hardware
**Streptococci**

**Viridans group Streptococci (alpha-hemolytic streptococci)**

Normal microbiota of the oral cavity and GI tract; single blood cultures growing these organisms often represent contamination or transient bacteremia.

Five groups

- **S. anginosus** group (contains *S. intermedius*, *anginosus*, and *constellatus*): commonly cause abscesses; majority are Penicillin susceptible.
- **S. bovis** group [contains *S. gallolyticus* subspecies *gallolyticus* (associated with colon cancer—colonoscopy mandatory, endocarditis also present in > 50% of cases) and subspecies *pasteurinus* (associated with hepatobiliary disease, endocarditis less common)]; majority are Penicillin susceptible.
- **S. mitis** group (contains *S. mitis*, *oralis*, *gordonii*, and *sanguinous*): commonly cause bacteremia in neutropenic patients and endocarditis; many have Penicillin resistance.
- **S. salivarius** group: less common cause of endocarditis; majority are Penicillin susceptible.
- **S. mutans** group: common cause of dental caries; uncommon cause of endocarditis; majority are Penicillin susceptible.

**Beta-hemolytic Streptococci**

All are susceptible to Penicillin.

Variable rates of resistance to Clindamycin; ask the microbiology laboratory to perform susceptibility testing if you plan to use Clindamycin or macrolides for moderate to severe infections.

While anti-staphylococcal penicillins (Oxacillin and Nafcillin) are the agents of first choice for susceptible *S. aureus* infections, their activity against streptococci is sub-optimal.

High rates of resistance to tetracyclines and TMP/SMX preclude their empiric use for infections suspected to be caused by beta-hemolytic streptococci.

- **S. pyogenes** (group A strep): pharyngitis, skin and soft tissue infections including erysipelas, cellulitis, necrotizing fasciitis; Clindamycin resistance in 1.5-5.2%; macrolide resistance in 4-7%.
- **S. agalactiae** (group B strep): neonatal infections, infections of the female genital tract, skin and soft tissue infections, bacteremia; Clindamycin resistance in 16-26%; macrolide resistance in 7-32%.
• Group C and G streptococci: infections similar to *S. pyogenes* and *S. agalactiae*; associated with underlying diseases (e.g. diabetes, malignancy, cardiovascular disease); Clindamycin resistance in ~16% of group C and ~33% of group G isolates; macrolide resistance in ~25% of group C and ~28% of group G isolates.

**Streptococcus pneumoniae**

• Common cause of respiratory tract infections including otitis media, sinusitis, pneumonia via local spread from the nasopharynx; infections involving the CNS, bones/joints and endocarditis via hematogenous spread

• Genetically, *S. pneumoniae* is in the *S. mitis* group of viridans group streptococci; consequently, rapid molecular tests may not be able to distinguish *S. pneumoniae* and streptococci in the *S. mitis* group.

• Penicillin is the agent of first choice for serious *S. pneumoniae* infections when it is susceptible

• Penicillin and Ceftriaxone susceptibility breakpoints are different for CNS and non-CNS sites

**MIC breakpoints for Penicillin and Ceftriaxone against *S. pneumoniae***

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin (oral)</td>
<td>≤ 0.06</td>
<td>0.12-1</td>
<td>≥ 2</td>
</tr>
<tr>
<td>Penicillin (parenteral)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-CNS</td>
<td>≤ 2</td>
<td>4</td>
<td>≥ 8</td>
</tr>
<tr>
<td>CNS</td>
<td>≤ 0.06</td>
<td></td>
<td>≥ 0.12</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-CNS</td>
<td>≤ 1</td>
<td>2</td>
<td>≥ 4</td>
</tr>
<tr>
<td>CNS</td>
<td>≤ 0.5</td>
<td>1</td>
<td>≥ 2</td>
</tr>
</tbody>
</table>

• Addition of Vancomycin to Ceftriaxone is not indicated in the empiric treatment of non-CNS infections caused by *S. pneumoniae* due to low rates of resistance

**Multi-drug resistant Gram-negative rods**

Patients with infection or colonization with the resistant organisms listed below should be placed on CONTACT precautions (see isolation chart on p. 141)

**Extended spectrum beta-lactamase (ESBL)-producing organisms**

• ESBLs are enzymes that confer resistance to all penicillins, cephalosporins, and Aztreonam.

• They are most commonly seen in *K. pneumoniae* and *K. oxytoca*, *E. coli*, and *P. mirabilis*, and these organisms are automatically screened by the JHH microbiology lab for the presence of ESBLs.
• Risk factors for infection or colonization: recent hospitalization at an institution with a high rate of ESBLs, residence in a long-term care facility and prolonged use of broad spectrum antibiotics.

Treatment:
• Meropenem 1 g IV Q8H (2 g IV Q8H for CNS infections) should be used for ALL severe infections if the organism is susceptible.
• Ertapenem 1 g IV Q24H can be used for uncomplicated UTI or soft tissue infection with adequate source control if the organism is susceptible.
• Ciprofloxacin or TMP/SMX can be used as alternatives to Ertapenem for uncomplicated UTI or soft tissue infection with adequate source control if the organism is susceptible. Nitrofurantoin may also be used for uncomplicated UTI if the organism is susceptible.

Carbapenemase-producing Enterobacteriaceae (CRE)
• Carbapenemases are enzymes that confer resistance to all penicillins, cephalosporins, carbapenems and Aztreonam.
• JHH microbiology lab is no longer performing the modified Hodge test
• If carbapenem is resistant JHH microbiology lab will report organism as “carbapenem resistant”; however, the exact mechanism of resistance is not tested for at this time.

Treatment:
• Meropenem 2 g IV Q8H infused over 3 hours should be included in most regimens based on data from small, retrospective studies showing benefit even when the isolate is intermediate or resistant.
• At least one additional agent should be added based on susceptibilities (e.g. Amikacin, Tigecycline, Colistin) except for UTI.

Multi-drug resistant (MDR) gram-negative organisms: defined as organisms susceptible to NO MORE than ONE of the following antibiotic classes: carbapenems, aminoglycosides, fluoroquinolones, penicillins, or cephalosporins. Note: susceptibility to sulfonamides, tetracyclines, polymixins, and Sulbactam are NOT considered in this definition.

Treatment

<table>
<thead>
<tr>
<th>MDR Pseudomonas aeruginosa</th>
<th>MDR Acinetobacter baumannii/calcoaceticus complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Ceftolozane/tazobactam</td>
<td>- β-lactam PLUS aminoglycoside if synergy expected</td>
</tr>
<tr>
<td>(if susceptible)</td>
<td>OR</td>
</tr>
<tr>
<td>OR</td>
<td>Colistin (if susceptible)</td>
</tr>
<tr>
<td>Anti-pseudomonal β-lactam PLUS aminoglycoside if synergy predicted or confirmed</td>
<td>Ampicillin/sulbactam (if susceptible) PLUS aminoglycoside (Sulbactam component has in vitro activity against Acinetobacter spp.)</td>
</tr>
<tr>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td>Colistin (if susceptible)</td>
<td>Tigecycline (if susceptible; for infections other than bacteremia)</td>
</tr>
</tbody>
</table>

*Combination therapy should be considered in severe infections.
Synergy:
- If the organism is intermediate to a beta-lactam and susceptible to aminoglycosides, synergy can be assumed.
- The microbiology lab does not perform synergy testing.

**Antibiotic doses for MDR and carbapenemase-producing infections – normal renal and hepatic function**

- Meropenem: 2 g IV Q8H, infuse over 3 hours
- Cefepime: 2 g IV Q8H, infuse over 3 hours
- Ceftazidime/Cefepime: 2 g IV bolus loading dose over 30 minutes, then 6 g IV as continuous infusion over 24 hours
- Piperacillin/tazobactam: 3.375 g IV bolus loading dose over 30 minutes, then continuous infusion 3.375 g IV Q4H infused over 4 hours OR 4.5 g IV Q6H, infuse over 4 hours
- Colistin: 5 mg/kg once, then 2.5 mg/kg IV Q12H (for additional information, see p. 9)
- Ampicillin/subactam: 3 g IV Q4H (for MDR A. baumannii only)
- Aminoglycosides (for dosing, see p. 146)
- Tigecycline: 100-150 mg IV Q12H
- Ceftolozane/tazobactam 1.5-3 g IV Q8H

References:
Combination therapy for CRE. Clin Microbiol Infec 2014;20: 862-72.
Interpreting the microbiology report

Interpretation of preliminary microbiology data

<table>
<thead>
<tr>
<th>Gram-positive cocci</th>
<th>Gram-negative cocci</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobic</strong></td>
<td><strong>Aerobic</strong></td>
</tr>
<tr>
<td>In clusters</td>
<td>Diplococcus: N. meningitidis, N.</td>
</tr>
<tr>
<td>• Coagulase (+): S. aureus</td>
<td>gonorrhoeae, Moraxella catarrhalis</td>
</tr>
<tr>
<td>• Coagulase (-): S. epidermidis,</td>
<td>Cocco-bacillus: H. flu, Acinetobacter</td>
</tr>
<tr>
<td>S. lugdunensis</td>
<td>spp., HACEK organisms</td>
</tr>
<tr>
<td>In pairs/chains</td>
<td></td>
</tr>
<tr>
<td>• Diplococcus, Quellung positive:</td>
<td></td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td></td>
</tr>
<tr>
<td>• Alpha-hemolytic: Viridans group</td>
<td></td>
</tr>
<tr>
<td>Streptococci, Enterococcus</td>
<td></td>
</tr>
<tr>
<td>(faecalis and faecium)</td>
<td></td>
</tr>
<tr>
<td>• Beta-hemolytic:</td>
<td></td>
</tr>
<tr>
<td>Group A strep (S. pyogenes),</td>
<td></td>
</tr>
<tr>
<td>Group B strep (S. agalactiae),</td>
<td></td>
</tr>
<tr>
<td>Group C, D, G strep</td>
<td></td>
</tr>
<tr>
<td><strong>Anaerobic: Peptostreptococcus spp.</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram-positive rods</th>
<th>Gram-negative rods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobic</strong></td>
<td><strong>Aerobic</strong></td>
</tr>
<tr>
<td>Large: Bacillus spp.</td>
<td>Lactose fermenting: Citrobacter spp.,</td>
</tr>
<tr>
<td>Cocco-bacillus: Listeria monocyto genes,</td>
<td>Enterobacter spp., E. coli, Klebsiella</td>
</tr>
<tr>
<td>Lactobacillus spp.</td>
<td>spp., Serratia spp.*</td>
</tr>
<tr>
<td>Small, pleomorphic: Corynebacterium spp.</td>
<td>Non-lactose fermenting</td>
</tr>
<tr>
<td>Branching filaments: Nocardia spp.,</td>
<td>• Oxidase (–): Acinetobacter spp.,</td>
</tr>
<tr>
<td>Streptomyces spp.</td>
<td>Burkholderia spp., E. coli (rare),</td>
</tr>
<tr>
<td><strong>Anaerobic</strong></td>
<td>Proteus spp., Salmonella spp.,</td>
</tr>
<tr>
<td>Large: Clostridium spp.</td>
<td>Shigella spp., Serratia spp.*</td>
</tr>
<tr>
<td>Small, pleomorphic: P. acnes, Actinomyces</td>
<td>Stenotrophomonas maltophilia</td>
</tr>
<tr>
<td>spp.</td>
<td>• Oxidase (+): P. aeruginosa, Aeromonas</td>
</tr>
<tr>
<td></td>
<td>spp., Vibrio spp., Campylobacter spp.</td>
</tr>
<tr>
<td></td>
<td>(curved)</td>
</tr>
<tr>
<td></td>
<td>**Anaerobic: Bacteroides spp.,</td>
</tr>
<tr>
<td></td>
<td>Fusobacterium spp., Prevotella spp.</td>
</tr>
</tbody>
</table>

* Serratia spp. can appear initially as non-lactose fermenting due to slow fermentation.

The Johns Hopkins microbiology laboratory utilizes standard reference methods for determining susceptibility. The majority of isolates are tested by the automated system.

The minimum inhibitory concentration (MIC) value represents the concentration of the antimicrobial agent required at the site of infection for inhibition of the organism.

The MIC of each antibiotic tested against the organism is reported with one of three interpretations S (susceptible), I (intermediate), or R (resistant). The highest MIC which is still considered susceptible represents the breakpoint concentration. This is the highest MIC which is usually associated with clinical efficacy. MICs which are $\frac{1}{2}-\frac{1}{8}$ the
breakpoint MIC are more frequently utilized to treat infections where antibiotic penetration is variable or poor (endocarditis, meningitis, osteomyelitis, pneumonia, etc.). Similarly, organisms yielding antibiotic MICs at the breakpoint frequently possess or have acquired a low-level resistance determinant with the potential for selection of high-level expression and resistance. This is most notable with cephalosporins and Enterobacter spp., Serratia spp., Morganella spp., Providencia spp., Citrobacter spp. and Pseudomonas aeruginosa. These organisms all possess a chromosomal beta-lactamase which frequently will be over-expressed during therapy despite initial in vitro susceptibility. The intermediate (I) category includes isolates with MICs that approach attainable blood and tissue levels, but response rates may be lower than fully susceptible isolates. Clinical efficacy can potentially be expected in body sites where the drug is concentrated (e.g., aminoglycosides and beta-lactams in urine) or when a higher dose of the drug can be used (e.g., beta-lactams). The resistant (R) category indicates the organism will not be inhibited by usually achievable systemic concentrations of the antibiotic of normal doses.

**NOTE:** MIC values vary from one drug to another and from one bacterium to another, and thus MIC values are NOT comparable between antibiotics or between organisms.

### Spectrum of antibiotic activity

The spectrum of activity table is an approximate guide of the activity of commonly used antibiotics against frequently isolated bacteria. It takes into consideration JHH specific resistance rates, in vitro susceptibilities and expert opinion on clinically appropriate use of agents. For antibiotic recommendations for specific infections refer to relevant sections of the JHH Antibiotic Guidelines.
5.2 Spectrum of antibiotic activity

<table>
<thead>
<tr>
<th>GRAM-POSITIVE</th>
<th>GRAM-NEGATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G</td>
<td>VRE</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>MRSA</td>
</tr>
<tr>
<td>Ampicillin/sulbactam</td>
<td>MSSA</td>
</tr>
<tr>
<td>Oxacillin/Nafcillin</td>
<td>Coag. reg. staph.</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>βhemolytic strep.</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>S. pneumoniae</td>
</tr>
<tr>
<td>Cefotetan</td>
<td>Viridans strep.</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>E. coli</td>
</tr>
<tr>
<td>Cefepime</td>
<td>E. faecalis</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>K. pneumoniae</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>H. influenzae</td>
</tr>
<tr>
<td>Meropenem</td>
<td>K. pneumoniae</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>H. influenzae</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>K. pneumoniae</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>P. aeruginosa</td>
</tr>
<tr>
<td>Gent/Tobra/Amkacin</td>
<td>S. pneumoniae</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>S. pneumoniae</td>
</tr>
<tr>
<td>Linezolid</td>
<td>S. pneumoniae</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>S. pneumoniae</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>S. pneumoniae</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>S. pneumoniae</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>S. pneumoniae</td>
</tr>
<tr>
<td>Colistin</td>
<td>S. pneumoniae</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>S. pneumoniae</td>
</tr>
</tbody>
</table>

- Not active
- Less active or potential resistance
- Active

**Adjunctions:**
- Pseudomonas spp.
- Enterobacter spp.
- Oral anaerobes
- Abicals

**Atypicals:**
- Abdominal anaerobes

**GRAM-POSITIVE (Examples):**
- E. faecalis
- MRSA
- MSSA
- Coag. reg. staph.
- βhemolytic strep.
- S. pneumoniae
- Viridans strep.
- E. coli
- K. pneumoniae
- H. influenzae
- S. pneumoniae

**GRAM-NEGATIVE (Examples):**
- VRE
- MRSA
- MSSA
- Coag. reg. staph.
Interpretation of rapid diagnostic tests

The JHH microbiology lab performs rapid nucleic acid microarray testing on blood cultures growing Gram-positive organisms and peptide nucleic acid fluorescence in situ hybridization (PNA-FISH) testing on blood cultures growing yeast.

Nucleic acid microarray testing (Verigene®) for Gram-positive cocci in blood cultures

- Detects and identifies the nucleic acids of 12 Gram-positive bacterial genera/species and 3 resistance markers.
- Bacteria species: *S. aureus*, Coagulase-negative staphylococci, *S. lugdunensis*, Staphylococcus spp. *E. faecalis*, *E. faecium*, *S. pyogenes* (group A streptococci), *S. agalactiae* (group B streptococci), *S. pneumoniae*, *S. anginosus*, *Streptococcus* spp. (e.g., group C and G streptococci, viridans group streptococci, etc.), *Listeria* spp.
- Resistance markers: mecA, vanA, vanB
  - If *S. aureus* is mecA positive the organism is resistant to Methicillin and is reported as MRSA
  - If *S. aureus* is mecA negative the organism is susceptible to Methicillin and is reported as MSSA
  - If *E. faecalis/faecium* is vanA/B positive the organism is resistant to Vancomycin and is reported as VRE; note that all Vancomycin-resistant *E. faecalis* are susceptible to Ampicillin at JHH
- Results of the test are reported within 3-4 hours after the blood cultures turn positive
- Testing is performed only on the first positive blood culture
- Testing is NOT performed on blood cultures growing more than one Gram positive organism but is performed on blood cultures growing both Gram positive and negative organisms
- If the test is negative it will be reported as negative for the following organisms: Staphylococcus spp, *Streptococcus* spp., *E. faecalis*, *E. faecium*, *Listeria* spp.
5.3 Interpretation of rapid diagnostic tests

<table>
<thead>
<tr>
<th>Organism</th>
<th>Preferred empiric therapy (% susceptible in blood at JHH)</th>
<th>Alternative empiric therapy if PCN allergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA</td>
<td>Oxacillin (100%)</td>
<td>Non-severe PCN allergy: Cefazolin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe PCN allergy: Vancomycin¹</td>
</tr>
<tr>
<td>MRSA</td>
<td>Vancomycin (100%)</td>
<td>Daptomycin</td>
</tr>
<tr>
<td>Coagulase-negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>staphylococci</td>
<td>Single positive cultures are often a contaminant; no treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>recommended. See p. 60 of the JHH Antibiotic Guidelines for information and indications for treatment. Call the microbiology lab for more information and further work up if infection suspected (5-6510).</td>
<td></td>
</tr>
<tr>
<td>S. lugdunensis</td>
<td>Vancomycin (100%)²</td>
<td>Oxacillin (96%) or Daptomycin</td>
</tr>
<tr>
<td>E. faecalis</td>
<td>Ampicillin (98%)</td>
<td>Vancomycin (95%)¹</td>
</tr>
<tr>
<td>E. faecium (VRE)</td>
<td>Linezolid (87%)³</td>
<td>Daptomycin (97%)</td>
</tr>
<tr>
<td>E. faecium (not VRE)</td>
<td>Vancomycin (100%)³</td>
<td>Linezolid</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>Non-oncology patient: Ceftriaxone⁴</td>
<td>Severe PCN allergy: Vancomycin¹</td>
</tr>
<tr>
<td></td>
<td>Oncology patient: Vancomycin⁴</td>
<td></td>
</tr>
<tr>
<td>S. anginosus (group A strep)</td>
<td>Penicillin G (100%)</td>
<td>Non-severe PCN allergy: Ceftriaxone¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe PCN allergy: Vancomycin¹</td>
</tr>
<tr>
<td>S. pyogenes</td>
<td>Penicillin G (100%)</td>
<td>Non-severe PCN allergy: Cefazolin</td>
</tr>
<tr>
<td>(group A strep)</td>
<td></td>
<td>Severe PCN allergy: Vancomycin¹</td>
</tr>
<tr>
<td>S. agalactiae (group B strep)</td>
<td>Penicillin G (100%)</td>
<td>Non-severe PCN allergy: Cefazolin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe PCN allergy: Vancomycin¹</td>
</tr>
<tr>
<td>S. pneumoniae (not meningitis)</td>
<td>Ceftriaxone (100%)⁴</td>
<td>Severe PCN allergy: Vancomycin¹</td>
</tr>
<tr>
<td>S. pneumoniae (meningitis)</td>
<td>Ceftriaxone + Vancomycin</td>
<td></td>
</tr>
<tr>
<td>Listeria spp.</td>
<td>Ampicillin (100%)</td>
<td>Trimethoprim/sulfamethoxazole</td>
</tr>
</tbody>
</table>

¹Consult allergy for skin testing / desensitization  
²Narrow to Oxacillin if found to be susceptible  
³Narrow to Ampicillin if found to be susceptible  
⁴Narrow to Penicillin G if found to be susceptible

PNA-FISH for yeast
- If PNA-FISH shows *C. albicans*, most non-oncology patients without prior azole exposure can be treated with fluconazole. For more information see p. 117 and 134.
- If PNA-FISH shows *C. glabrata*, treat with Micafungin until susceptibilities available. For more information see p. 117 and 134.
- If PNA-FISH negative for *C. albicans* or *C. glabrata*, most cases can be treated as unspeciated candidemia, unless cryptococcus is suspected (send serum cryptococcal antigen). For more information see p. 117 and 134.
Biliary tract infections – cholecystitis and cholangitis

EMPIRIC TREATMENT
Community-acquired infections in patients without previous biliary procedures AND who are not severely ill
• Ceftriaxone 1 g IV Q24H
  OR
• Ertapenem 1 g IV Q24H
  OR
• Severe PCN allergy: Ciprofloxacin 400 mg IV Q12H

Hospital-acquired infections OR patients with multiple therapeutic biliary manipulations (e.g. stent placement/exchange, bilio-enteric anastomosis of any severity) OR patients who are severely ill
• Piperaclillin/tazobactam 3.375 g IV Q6H
  OR
• Non-severe PCN allergy: Cefepime 1 g IV Q8H PLUS Metronidazole 500 mg IV Q8H
  OR
• Severe PCN allergy: Aztreonam 1 g IV Q8H PLUS Metronidazole 500 mg IV Q8H ± Vancomycin (see dosing section, p. 150)

In severely ill patients with cholangitis and complicated cholecystitis, adequate biliary drainage is crucial as antibiotics will not enter bile in the presence of obstruction.

Duration
• Uncomplicated cholecystitis: treat only until obstruction is relieved. NO post-procedure antibiotics are necessary if the obstruction is successfully relieved.
• Complicated cholecystitis: 4 days, unless adequate source control is not achieved.
• Biliary sepsis: 4-7 days, unless adequate source control is not achieved.

TREATMENT NOTES

Microbiology
• Gram-negative rods – *E. coli*, *Klebsiella spp.*, *Proteus spp.*, *P. aeruginosa* (mainly in patients already on broad-spectrum antibiotics or those who have undergone prior procedures)
• Anaerobes – *Bacteroides spp.*, generally in more serious infections, or in patients with a history of biliary manipulations; rare in uncomplicated and community-acquired infections
• *Enterococcus spp.* – treatment not always indicated; use clinical judgment
• Yeast – rare
6.1 Abdominal infections

Management

- In cases of uncomplicated acute cholecystitis, antibiotics should be given until the biliary obstruction is relieved (either by surgery, ERCP, or percutaneous drain).
- Treatment of enterococci is usually not needed in mild/moderate disease.
- Yeast generally should be treated only if they are recovered from biliary cultures, not empirically.

References:

Diverticulitis

EMPIRIC TREATMENT

NOTE: Patients with uncomplicated diverticulitis (defined as CT confirmed left-sided disease without abscess; free air or fistula ± fever and elevated inflammatory markers), can be treated conservatively without antibiotics based on a RCT.

Mild/moderate infections – can be oral if patient can take PO

- Amoxicillin/clavulanate 875 mg PO Q12H
  OR
- Ceftriaxone 1 g IV Q24H PLUS Metronidazole 500 mg IV/PO Q8H
  OR
- Ertapenem 1 g IV Q24H
  OR
- Severe PCN allergy: [Ciprofloxacin 400 mg IV Q12H OR Ciprofloxacin 500 mg PO Q12H] PLUS Metronidazole 500 mg IV/PO Q8H

Severe infections

- Piperacillin/tazobactam 3.375 g IV Q6H
  OR
- Non-severe PCN allergy: Cefepime 1 g IV Q8H PLUS Metronidazole 500 mg IV Q8H
  OR
- Severe PCN allergy: [Ciprofloxacin 400 mg IV Q12H OR Aztreonam 1 g IV Q8H] PLUS Metronidazole 500 mg IV Q8H

Duration

- 4 days, unless adequate source control is not achieved.
**Microbiology**
- Almost all infections are polymicrobial
- Most commonly isolated anaerobic organisms – *B. fragilis, Prevotella, Peptostreptococci*

**Other considerations**
- Antimicrobial treatment for acute uncomplicated diverticulitis may not accelerate recovery or prevent complications/recurrence.
- CT scan is important in assessing need for drainage in severe disease.

Reference:

**Pancreatitis**

**TREATMENT**
- Antibiotic prophylaxis is NOT indicated in patients with severe acute pancreatitis (SAP), including those with sterile pancreatic necrosis.
- Antimicrobial therapy has no effect on morbidity and mortality, and prophylactic antibiotics have been associated with a change in the spectrum of pancreatic isolates from enteric Gram-negatives to Gram-positive organisms and fungi.
- Infected pancreatic necrosis is defined by CT scan with gas in the pancreas and/or percutaneous or surgical specimen with organisms evident on gram stain or culture. Therapy should be directed based on culture results.
- In patients presenting with suspected abdominal sepsis, consider empiric therapy:
  - Piperacillin-tazobactam 4.5 g IV Q6H
  - Non-severe PCN allergy: Cefepime 1 g IV Q8H PLUS Metronidazole 500 mg IV Q8H
  - Severe PCN allergy: Ciprofloxacin 400 mg IV Q12H PLUS Metronidazole 500 mg IV Q8H
Pancreatic penetration of selected antibiotics

**Good (>40%; MIC exceeded for most relevant organisms):** fluoroquinolones, carbapenems, Ceftazidime, Cefepime, Metronidazole, Piperacillin-tazobactam

**Poor (<40%):** aminoglycosides, first-generation cephalosporins, Ampicillin

**Duration**

For infected pancreatic necrosis, continue antibiotics for 14 days after source control is obtained. Continuation of antibiotics beyond this time places the patient at risk for colonization or infection with resistant organisms and drug toxicity.

**TREATMENT NOTES**

- Infection develops in 30–50% of patients with necrosis documented by CT scan or at the time of surgery.
- Peak incidence of infection occurs in the 3rd week of disease
- There is insufficient evidence to recommend selective gut decontamination in management of pancreatitis.

References:

### Peritonitis

**DEFINITIONS**

**Primary peritonitis** is spontaneous infection of the peritoneal cavity, usually associated with liver disease and ascites (spontaneous bacterial peritonitis (SBP)).

**Secondary peritonitis** is infection of the peritoneal cavity due to spillage of organisms into the peritoneum, usually associated with GI perforation.

**Tertiary peritonitis** is a recurrent infection of the peritoneal cavity following an episode of secondary peritonitis.

**Primary peritonitis/Spontaneous bacterial peritonitis (SBP)**

**EMPIRIC TREATMENT**

- Ceftriaxone 1 g IV Q12H
  - OR
  - Severe PCN allergy: Moxifloxacin 400 mg IV/PO Q24H (call ID or Antimicrobrial Stewardship to discuss regimens for patients who have been taking fluoroquinolones for SBP prophylaxis).
• Patients with serum creatinine >1 mg/dL, BUN >30 mg/dL or total bilirubin >4 mg/dL should also receive Albumin (25%) 1.5 g/kg on day 1 and 1 g/kg on day 3 (round to the nearest 12.5 g).

Duration
• Treat for 5 days

PROPHYLAXIS

Cirrhotic patients with gastrointestinal hemorrhage
• Ciprofloxacin 500 mg PO BID for 7 days
• Ceftriaxone 1 g IV Q24H can be used only if patient is NPO, then switch to Ciprofloxacin 500 mg PO BID once bleeding is controlled

Non-bleeding cirrhotic patients with ascites
• TMP/SMX 1 DS PO once daily
  OR
• If sulfa allergic, Ciprofloxacin 500 mg PO daily

TREATMENT NOTES

Microbiology
• Gram-negative rods (Enterobacteriaceae, esp. E. coli and K. pneumoniae), S. pneumoniae, enterococci, and other streptococci.
• Polymicrobial infection should prompt suspicion of GI perforation.

Diagnostic criteria
• 250 PMN per mm$^3$ of ascitic fluid.
• Positive culture with < 250 PMN should prompt repeat tap. If PMN > 250 OR culture remains positive, patient should be treated.

Follow-up
• Consider repeat paracentesis after 48 hours of therapy.
• Consider changing antibiotics if ascites fluid PMN has not dropped by 25% after 48 hours and/or patient is not clinically responding.

Notes on prophylaxis against SBP
• All patients with cirrhosis and upper GI bleed should receive prophylaxis for 7 days (50% develop SBP after bleed).
• Patients who get SBP should get lifelong prophylaxis to prevent future episodes (40–70% risk of recurrence in 1 year).
• Prophylaxis should be considered for those with low protein concentrations in ascites (< 10 g/L) or immunosuppression while patient is in hospital.

References:
Diagnosis, treatment and prophylaxis of SBP: J Hepatol 2000;32:142.
**Secondary peritonitis/GI perforation**

**EMPIRIC TREATMENT**

Perforation of esophagus, stomach, small bowel, colon, or appendix

**Patient mild to moderately ill**
- Ertapenem 1 g IV Q24H
  
  OR
- Severe PCN allergy: Ciprofloxacin 400 mg IV Q12H PLUS Metronidazole 500 mg IV Q8H

**Patient severely ill or immunosuppressed**
- Piperacillin/tazobactam 3.375 g IV Q6H
  
  OR
- Non-severe PCN allergy: Cefepime 1 g IV Q8H PLUS Metronidazole 500 mg IV Q8H
  
  OR
- Severe PCN allergy: Vancomycin (see dosing section, p. 150) PLUS [Aztreonam 1 g IV Q8H OR Ciprofloxacin 400 mg IV Q8H] PLUS Metronidazole 500 mg IV Q8H

**Empiric antifungal therapy is generally not indicated for GI perforation unless patient has one of the following risk factors:**

Esophageal perforation, immunosuppression, prolonged antacid or antibiotic therapy, prolonged hospitalization, persistent GI leak.

**Recommendations for patients who are clinically stable and have not received prior long-term azole therapy:**
- Fluconazole 400-800 mg IV/PO Q24H

**Recommendations for patients who are NOT clinically stable or have received prior long-term azole therapy:**
- Micafungin 100 mg IV Q24H

### Duration of therapy for secondary peritonitis/GI perforation

<table>
<thead>
<tr>
<th>Uncomplicated</th>
<th>Stomach</th>
<th>Small Bowel</th>
<th>Colon</th>
<th>Appendix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Operated on within 24 hours</td>
<td>Operated on within 12 hours</td>
<td>Operated on within 12 hours</td>
<td>Non-necrotic or gangrenous appendix</td>
</tr>
<tr>
<td>Duration</td>
<td>24–48 hours</td>
<td>24–48 hours</td>
<td>24–48 hours</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complicated</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Late operation or no operation; or necrotic/gangrenous appendix</td>
</tr>
<tr>
<td>Duration</td>
<td>4 days unless adequate source control is not achieved</td>
</tr>
</tbody>
</table>
TREATMENT NOTES

- Pathogens causing tertiary peritonitis are variable and are often resistant to or not covered by the initial antimicrobial regimen; thus, a change in antimicrobials is advised.
- A change in antimicrobials therapy should be considered in patients with hospital-acquired infections who are already on antimicrobials.
- Treatment of enterococci remains controversial but should be considered in critically ill or immunocompromised patients or when they are a dominant organism in the peritoneal culture.
- Treatment of *Candida spp.* is generally indicated only when they are recovered from blood or are a dominant organism in the peritoneal culture in critically ill or immunocompromised patients.
- Postoperative antibiotics for appendicitis are unnecessary unless there is clinical evidence of peritonitis, abscess, or gangrene.
- Antibiotics are adjunctive to source control, which is an absolute necessity.
- Lack of source control is defined as on-going contamination and/or an undrained collection of infection.

Reference:

**Peritonitis related to peritoneal dialysis**

**EMPIRIC TREATMENT**

**Mild to moderate illness:** intraperitoneal therapy is preferred in most cases.

**Anuric patient**
- Cefazolin 15 mg/kg in one bag Q24H (1 g if patient < 65 kg) PLUS
- Gentamicin 2 mg/kg in one bag loading dose, then Gentamicin 0.6 mg/kg in one bag Q24H

**Patient with urine output > 100 mL/day**
- Ceftazidime 1 g in one bag Q24H

**Severe illness:** systemic therapy is preferred.
- FIRST DOSE: Vancomycin (see dosing section, p. 150) IV PLUS ONE of the following:
  [Gentamicin 2 mg/kg IV OR Ceftazidime 1 g IV OR Ciprofloxacin 400 mg IV]
MAINTENANCE DOSE: Dose per drug levels and/or renal function; consult pharmacy for recommendations for redosing and monitoring

**Duration:** 10–14 days

**TREATMENT NOTES**

**Microbiology**
- Most cases caused by contamination of the catheter
- Cultures may be negative in 5–20%
- Gram-positive coci (S. aureus, coagulase-negative staphylococci, Enterococcus spp.), Gram-negative rods, yeast (much less common)

**Diagnosis**
- All patients with suspected PD-related peritonitis should have PD fluid sampled for cell count, differential, gram stain, culture AND amylase. WBC > 100/mm³ with > 50% PMN suggests infection.
- Elevated amylase suggests pancreatitis or bowel perforation.
- In symptomatic patients with cloudy fluid accompanied by abdominal pain and/or fever, empiric treatment should be started given the high likelihood of infection.
- In symptomatic patients with clear fluid, another PD fluid exchange, with a dwell time of at least 2 hours, should be sampled. The decision to start empiric therapy in these cases will depend on how sick the patient appears.
- In asymptomatic patients with cloudy fluid, it is reasonable to delay therapy pending the results of cell count, gram stain, and culture.

Reference:
**Clostridium difficile infection (CDI)**

**Diagnosis and testing**
- Case definition of *C. difficile* diarrhea: passage of ≥ 3 unformed stools in ≤ 24 hours AND either a positive stool test for *C. difficile* or colonoscopic/histopathologic finding of pseudomembranous colitis.
- The microbiology lab uses a real-time PCR assay to detect the toxin B gene, the toxin responsible for CDI. Thus, patients who are colonized with toxigenic strains will test positive even if they do not have active infection and clinical correlation with positive test results is important. The sensitivity of real time PCR is > 90% compared to toxigenic culture.
- Do NOT send stool for *C. difficile* testing if patients do not have diarrhea or ileus. Hard stool, fluid obtained from colonoscopy and rectal swabs will be rejected by the microbiology lab.
- In patients receiving laxatives, it is recommended to discontinue laxatives for 24-48 hours prior to *C. difficile* stool test to see if diarrhea improves, unless the patient is clinically unstable.
- Because of enhanced sensitivity of PCR, duplicate testing is not necessary or recommended. Testing is restricted to one specimen within 7 days. Call the Laboratory Medicine resident or faculty member on call for those rare instances when a second specimen is required.
- Stool for *C. difficile* testing should be collected prior to starting treatment for *C. difficile*.
- Specimens should be hand carried to the lab as soon as possible after collection. If they cannot be transported promptly, the samples should be refrigerated.
- Do NOT send follow-up *C. difficile* PCR during treatment or to document resolution of disease, as utility of the results has not been demonstrated.

**TREATMENT**
- **STOP ALL ANTIMICROBIAL AGENTS WHENEVER POSSIBLE.**
- Oral therapy must be used whenever possible as the efficacy of IV Metronidazole is poorly established for CDI and **there is no efficacy of IV Vancomycin for CDI.**
6.2 Clostridium difficile infection (CDI)

Treatment depends on clinical severity

<table>
<thead>
<tr>
<th>Infection severity</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic carriage*</td>
<td>C. difficile PCR positive without diarrhea, ileus, or colitis</td>
</tr>
<tr>
<td>Mild or moderate</td>
<td>C. difficile PCR positive with diarrhea but no manifestations of severe disease</td>
</tr>
<tr>
<td>Severe</td>
<td>C. difficile PCR positive with diarrhea and one or more of the following attributable to CDI:</td>
</tr>
<tr>
<td></td>
<td>• WBC ≥ 15,000</td>
</tr>
<tr>
<td></td>
<td>• Increase in serum creatinine &gt; 50% from baseline</td>
</tr>
<tr>
<td>Severe Complicated</td>
<td>Criteria as above plus one or more of the following attributable to CDI:</td>
</tr>
<tr>
<td></td>
<td>• Hypotension</td>
</tr>
<tr>
<td></td>
<td>• Ileus</td>
</tr>
<tr>
<td></td>
<td>• Toxic megacolon or pancolitis on CT</td>
</tr>
<tr>
<td></td>
<td>• Perforation</td>
</tr>
<tr>
<td></td>
<td>• Need for colectomy</td>
</tr>
<tr>
<td></td>
<td>• ICU admission for severe disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infection severity</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic carriage</td>
<td>Do NOT treat; treatment can promote relapsing disease</td>
</tr>
<tr>
<td>Mild or moderate</td>
<td>• Metronidazole 500 mg PO/NGT Q8H</td>
</tr>
<tr>
<td></td>
<td>Unable to tolerate oral therapy</td>
</tr>
<tr>
<td></td>
<td>• Metronidazole 500 mg IV Q8H (suboptimal; see note at start of CDI section above)</td>
</tr>
<tr>
<td>Severe</td>
<td>• Vancomycin solution 125 mg PO/NGT Q6H</td>
</tr>
<tr>
<td>Severe Complicated</td>
<td>• Consult surgery for evaluation for colectomy and ID</td>
</tr>
<tr>
<td></td>
<td>• Vancomycin solution 500 mg by NGT Q6H PLUS</td>
</tr>
<tr>
<td></td>
<td>Metronidazole 500 mg IV Q8H†</td>
</tr>
<tr>
<td></td>
<td>Unable to tolerate oral therapy or complete ileus</td>
</tr>
<tr>
<td></td>
<td>• Vancomycin 500 mg in 500 ml NS Q6H as retention enema via Foley catheter in rectum +</td>
</tr>
<tr>
<td></td>
<td>Metronidazole 500 mg IV Q8H‡</td>
</tr>
</tbody>
</table>

*15-25% of hospitalized patients are colonized with C. difficile.
† Vancomycin dose can be decreased to 125 mg PO Q6H and Metronidazole can be stopped once the patient has stabilized.

Other indications for oral Vancomycin use
• No response to oral Metronidazole after 5 days of therapy
• Second episode of recurrent disease
• Patients with significant side effects to Metronidazole
• Patients who are pregnant
• Consider in patients > 65 years given reports of increased morbidity from CDI.
Duration
• 10–14 days

Approach to patients who need to continue broad spectrum antibiotic therapy
• Determine the shortest possible course of antibiotic therapy.
• Replace the antibiotic that induced CDI, particularly cephalosporins, Clindamycin, and fluoroquinolones.
• If the inducing agent is replaced and the CDI resolves, complete a standard 10-14 day course of CDI therapy; there is no need to extend CDI therapy until the end of the course of antibiotic therapy.
• If the inducing agent cannot be stopped or replaced, consider continuing CDI therapy until the end of the course of antibiotic therapy (data are limited); CDI therapy should not be continued beyond the end of antibiotic therapy if the patient remains asymptomatic.

Recurrent disease
• Resistance to Metronidazole or Vancomycin has not been documented conclusively.
• Recurrent disease after a complete course of therapy occurs in ~25% of patients. Relapse is due to failure to eradicate spores (60%) or acquisition of a new strain (40%). Document recurrent disease with repeat stool testing.
• First recurrence should be treated the same as the initial episode; severe disease should be treated with Vancomycin.
• Second recurrence should be treated with Vancomycin taper followed by pulse dosing or fecal microbiota transplant (consult GI).
• If serious or multiple recurrences, consult ID.

Vancomycin taper regimen
125 mg 4 times daily × 10–14 days
125 mg BID × 7 days
125 mg daily × 7 days
125 mg every 2–3 days for 2–8 weeks (pulse dosing)

NOTES

Management
• Surgical intervention for colectomy should be considered early if the patient is clinically unstable secondary to CDI.
• Treatment of CDI should be continued in patients who have a subtotal colectomy with preservation of the rectum.
• Most patients with severe CDI should undergo abdominal CT to rule out toxic megacolon or pancolitis.
- Do NOT send follow-up *C. difficile* PCR to document resolution of disease.
- Do not use antimitility agents.
- Stop proton pump inhibitors (PPIs) whenever possible as data suggest PPIs increase the risk of CDI.
- The offending antimicrobial agents should be discontinued. If antimicrobials are still required, it is best to avoid cephalosporins, Clindamycin, and fluoroquinolones.
- Prophylactic use of oral Metronidazole or Vancomycin in patients receiving antimicrobial therapy for treatment of underlying infection (other than CDI) is not recommended and may increase the patient’s risk for CDI.

**Infection control**
- Patients with CDI should be placed in contact precautions and single rooms for the duration of hospitalization.
- Use soap and water rather than alcohol-based hand gel upon exiting the room of a patient with CDI.

References:
Infectious diarrhea

- For treatment of *C. difficile* infection, see p. 47.
- Carefully assess the patient before prescribing antimicrobials.
- Most infectious diarrhea is self-limited and only requires supportive management.
- Treatment with antibiotics is not recommended for most mild-moderate disease; see specific indications in table below.
- Viral pathogens, such as Norovirus and Rotavirus commonly cause diarrhea and do not require antibiotics.
- Antibiotic use may lead to adverse outcomes (e.g. hemolytic uremic syndrome with Shiga toxin-producing *E. coli*).
- Antimotility agents should not be used in patients with bloody diarrhea, fever, or elevated WBC.

Microbiology

- Common non-viral pathogens in acute community-acquired diarrhea: *Salmonella, Shigella, Shiga toxin-producing E. coli, Campylobacter, C. difficile* (usually with antibiotic exposure).
- Nosocomial diarrhea: *C. difficile*
- Persistent diarrhea if immunocompromised (most likely causes vary depending on type of immunocompromise): *Giardia, Cryptosporidium, Cyclospora, Isospora, Microsporidia, Cytomegalovirus (CMV)*.

Diagnosis

- Not every diarrheal illness requires stool culture. Decision to test should be based on suspicion for specific pathogens and/or clinical judgment of illness severity.
- Patients with febrile diarrheal illnesses with clinical features of moderate to severe disease should receive empiric therapy only after a fecal specimen is obtained for appropriate testing.
- Fecal specimens from patients hospitalized for > 3 days should not be submitted for routine stool culture unless a high suspicion for specific pathogen exists and/or if the patient is immunocompromised.
- Multiple stool examinations for ova and parasites (O&P) are of low yield.
- Fecal leukocyte/lactoferrin assessments should not be used to determine the therapeutic approach.
## Treatment of infectious diarrhea

<table>
<thead>
<tr>
<th>Organism/Indications for treatment</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Campylobacter spp.</strong></td>
<td>• Azithromycin 500 mg PO daily for 1–3 days</td>
</tr>
<tr>
<td>Treatment recommended for:</td>
<td></td>
</tr>
<tr>
<td>• Severe illness</td>
<td></td>
</tr>
<tr>
<td>• Age &lt; 6 months or &gt; 50 years</td>
<td></td>
</tr>
<tr>
<td>• Gross blood in stool</td>
<td></td>
</tr>
<tr>
<td>• High fever</td>
<td></td>
</tr>
<tr>
<td>• Worsening or relapsing symptoms</td>
<td></td>
</tr>
<tr>
<td>• Pregnancy</td>
<td></td>
</tr>
<tr>
<td>• Immunocompromised host</td>
<td></td>
</tr>
<tr>
<td><strong>E. coli</strong> (enterotoxigenic, enteropathogenic, entero invasive) or <strong>empiric therapy of traveler’s diarrhea</strong></td>
<td>• Ciprofloxacin 500 mg PO BID</td>
</tr>
<tr>
<td><strong>Duration:</strong> 1–3 days</td>
<td></td>
</tr>
<tr>
<td><strong>Shiga toxin producing E. coli</strong> (including E. coli 0157:H7)</td>
<td>Treatment not recommended. Antibiotic use associated with development of hemorrhagic uremic syndrome.</td>
</tr>
<tr>
<td><strong>Non-typhoid Salmonella spp.</strong></td>
<td>• Ciprofloxacin 500 mg PO BID</td>
</tr>
<tr>
<td>Treatment recommended for:</td>
<td>OR</td>
</tr>
<tr>
<td>• Severe illness requiring hospitalization</td>
<td>TMP/SMX 160/800 mg PO BID</td>
</tr>
<tr>
<td>• Age &lt; 6 months or &gt; 50 years</td>
<td>(if susceptible)</td>
</tr>
<tr>
<td>• Bacteremia</td>
<td>OR</td>
</tr>
<tr>
<td>• Presence of prostheses</td>
<td>Ceftriaxone 1 g IV Q24H</td>
</tr>
<tr>
<td>• Valvular heart disease</td>
<td><strong>Duration:</strong> 5–7 days; 14 days for immunocompromised host</td>
</tr>
<tr>
<td>• Severe atherosclerosis</td>
<td></td>
</tr>
<tr>
<td>• Malignancy or other immunocompromise</td>
<td></td>
</tr>
<tr>
<td><strong>Shigella spp.</strong></td>
<td>• TMP/SMX 160/800 mg PO BID (if susceptible)</td>
</tr>
<tr>
<td>Treatment always recommended even if result returns when patient is asymptomatic.</td>
<td>OR</td>
</tr>
<tr>
<td>• Immunocompromised host</td>
<td>Ciprofloxacin 500 mg PO BID</td>
</tr>
<tr>
<td><strong>Vibrio parahaemolyticus</strong></td>
<td><strong>Duration:</strong> 3 days; 7 days for immunocompromised host</td>
</tr>
<tr>
<td>Note: Associated with shellfish consumption</td>
<td>• Ciprofloxacin 500 mg PO BID x 3 days</td>
</tr>
<tr>
<td>Treatment recommended for severe illness</td>
<td></td>
</tr>
<tr>
<td><strong>Yersinia spp.</strong></td>
<td>• TMP/SMX 160/800 mg PO BID x 3–5 days (if susceptible)</td>
</tr>
<tr>
<td>Treatment recommended for:</td>
<td>OR</td>
</tr>
<tr>
<td>• Immunocompromised host</td>
<td>Ciprofloxacin 500 mg PO BID x 3 days</td>
</tr>
<tr>
<td>• Bacteremia</td>
<td>OR</td>
</tr>
<tr>
<td>• Pseudoappendicitis syndrome</td>
<td>Doxycycline 100 mg PO BID x 3 days (not for bacteremia)</td>
</tr>
</tbody>
</table>
### Parasites

| **Entamoeba histolytica** | • Metronidazole 750 mg PO TID x 5–10 days  
OR  
• Tinidazole 1 g PO Q12H x 3 days  

**PLUS** all patients should receive  
Paromomycin 500 mg PO TID x 7 days  
after the course of 1st agent complete  

**Asymptomatic patients**  
• Paromomycin 500 mg PO TID x 7 days |
|-------------------------|------------------------------------------|
| Treat all (even asymptomatic)  
*E. dispar & E. moshkovskii* infections do not require treatment  

**Giardia spp.** | • Metronidazole 250-500 mg PO TID x 7–10 days  
OR  
• Tinidazole 2 g PO once |
<table>
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</tbody>
</table>

References:  
**Helicobacter pylori infection**

**NOTE:** CONSIDER WITHHOLDING THERAPY INITIATION UNTIL PATIENT DISCHARGED FROM HOSPITAL UNLESS ACUTE ULCER IS PRESENT

Established indications for testing for *H. pylori* and treating positive patients
- Active peptic ulcer disease (PUD) – gastric or duodenal
- Confirmed history of PUD (not previously treated for *H. pylori*)
- Gastric MALT lymphoma (low grade)
- Following resection of gastric cancer
- Family history of gastric cancer in a 1st degree relative
- Atrophic gastritis

Other indications where testing for *H. pylori* and treating positive patients can be considered: nonulcer dyspepsia, long term PPI use, persons using NSAID/ASA, unexplained iron deficiency anemia or vitamin B12 deficiency, family members of patients with *H. pylori* with mild dyspepsia.

**First-line treatment**
- Amoxicillin 1 g PO Q12H **PLUS** Clarithromycin 500 mg PO Q12H **PLUS** Pantoprazole 40 mg PO Q12H
- OR
- PCN allergy
  - Clarithromycin 500 mg PO Q12H **PLUS** Metronidazole 500 mg PO Q12H **PLUS** Pantoprazole 40 mg PO Q12H
  - OR
  - Tetracycline 500 mg PO Q6H **PLUS** Metronidazole 500 mg PO Q8H **PLUS** Bismuth subsalicylate 525 mg PO Q6H **PLUS** Pantoprazole 40 mg PO Q12H

**Duration:** 10–14 days

**Documented recurrence of *H. pylori* disease**
- If possible, avoid antibiotics previously used to treat *H. pylori*
- Tetracycline 500 mg PO Q6H **PLUS** Metronidazole 500 mg PO Q8H **PLUS** Bismuth subsalicylate 525 mg PO Q6H **PLUS** Pantoprazole 40 mg PO Q12H

**Duration:** 14 days

**TREATMENT NOTES**

**Diagnosis**
- PPIs, *H₂*RA, Bismuth, and antibiotics with activity against *H. pylori* should be withheld for at least 4 weeks prior to testing.
• *H. pylori* stool antigen is the only FDA approved test (>90% sensitivity and specificity).
• Urea breath test may be optimal but not commonly available.
• Endoscopy PLUS rapid urease test (80–95% sensitivity; 92–100% specificity).
• *H. pylori* serology does not document current infection and should not be used for clinical diagnosis.

**Management**
• First line treatment eradication rates estimated between 50–75%. Failure most often due to Clarithromycin resistance (10–15%) and/or non-adherence.
• H2-receptor antagonists (e.g. Ranitidine) can be substituted for the PPI if patients are unable to tolerate PPIs or if drug interactions are a concern.
• Amoxicillin PLUS Tetracycline can NOT be used together in treatment due to low response rates.
• Do not substitute Doxycycline/Minocycline for Tetracycline or Azithromycin for Clarithromycin.
• In patients with positive test results endoscopy is mandatory for age > 45-50 years, presence of mass GI bleeding, anemia, weight loss, or family history of gastric cancer.
• Test of cure is recommended > 4–8 weeks post treatment.

References:
Pelvic inflammatory disease

- Includes salpingitis, tubo-ovarian abscess and pelvic peritonitis.
- For treatment of post-operative peritonitis or wound infection, see p. 44 and p. 105.

TREATMENT

NOTE: Avoid use of fluoroquinolones for *N. gonorrhoeae* due to resistance (~10% in Baltimore City)

- Cefotetan 2 g IV Q12H PLUS Doxycycline* 100 mg PO BID for 14 days
  OR
- Ertapenem 1 g IV Q24H PLUS Doxycycline* 100 mg PO BID for 14 days
  OR
- PCN allergy: Clindamycin 600-900 mg IV Q8H PLUS Gentamicin (see dosing section, p. 146)

Step-down therapy once patient is afebrile

- Preferred: Doxycycline 100 mg PO BID ± [Clindamycin 450 mg PO QID OR Metronidazole 500 mg PO BID] to complete 14 days total

*Azithromycin 1 g PO once weekly for 2 weeks can be used in the case of Doxycycline contraindication or intolerance.

TREATMENT NOTES

Microbiology: *N. gonorrhoeae, C. trachomatis, Gardnerella spp, Ureaplasma urealyticum, anaerobes (Prevotella spp., B. fragilis), Gram-negative rods, Streptococci*

Treatment of partners

- All women diagnosed with acute PID should be offered HIV testing.
- Male partners of women who have PID often are asymptomatic.
- Sex partners (male or female) of patients who have PID should be examined and treated empirically for *C. trachomatis* and *N. gonorrhoeae* if they have had sexual contact with the patient during the 60 days preceding onset of symptoms in the patient, regardless of the pathogens isolated from the patient.

Endomyometritis

TREATMENT

- Same as for PID but no need for addition of Doxycycline/Azithromycin

Duration

- Treat until patient afebrile for 24–48 hours
Bacterial vaginosis

TREATMENT
• Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once daily for 5 days (preferred)
  OR
• Metronidazole 500 mg PO BID for 7 days
  OR
• Clindamycin 300 mg PO BID for 7 days

TREATMENT NOTES
Microbiology: anaerobic bacteria (Prevotella spp, Mobiluncus spp.), G. vaginalis, Ureaplasma, Mycoplasma.

• Treatment is recommended in all symptomatic women and high risk asymptomatic pregnant women.

Trichomoniasis (T. vaginalis)

NOTE: Treatment of partner recommended.

TREATMENT
• Metronidazole 2 g PO once
  OR
• Metronidazole 500 mg PO BID for 7 days

Uncomplicated gonococcal urethritis, cervicitis, proctitis

TREATMENT (includes treatment for C. trachomatis):
• Ceftriaxone 250 mg IM once PLUS Azithromycin 1 g orally (preferred)
  OR
• Ceftriaxone 250 mg IM once PLUS Doxycycline 100 mg PO BID for 7 days
  OR
• Severe PCN allergy: Azithromycin 2 g PO once (premedicate with antiemetic or give snack before administration)

TREATMENT NOTES
• HIV testing recommended
• The use of Ceftriaxone is preferred over Cefixime and Cefpodoxime due to increasing MICs for oral cephalosporins.
Dual therapy recommended for *N. gonorrhoeae* even if *C. trachomatis* is excluded.

Send gonorrhea culture (not nucleic acid amplification test) if you suspect a treatment failure.

### Syphilis

**SCREENING**

- Screening algorithm at JHH: a treponemal-specific antibody test (CIA) if positive, followed by RPR. A confirmatory FTA-ABS is provided if RPR is negative.
- A positive CIA, a negative RPR and a positive FTA may be due to: (1) old treated syphilis (2) old untreated syphilis (3) early syphilis.
- Get history and call Baltimore City Health Department 410-396-4448 for prior history of syphilis treatment in Maryland
- If penicillin allergic, ID consults is recommended to guide therapy

| Algorithm for reverse sequence syphilis screening |
|---------------------------------|---------------------------------|---------------------------------|
| CIA                              | CIA positive                   | CIA negative                    |
| RPR positive                    | RPR negative                   |                                 |
| Consistent with syphilis infection (past or present) | Treponemal test that uses a different antigen (FTA-ABS or TPPA) | • If incubating or primary syphilis is suspected, treat for early syphilis |
| Requires historical and clinical evaluation to determine prior treatment history | • Possible syphilis infection | • Syphilis unlikely |
| FTA-ABS positive                | FTA-ABS negative               | • If patient at high risk for syphilis, retest in one month |
| • Requires historical and clinical evaluation | 

### Neurosyphilis diagnosis

- Requires both clinical (neurological symptoms) and laboratory criteria.
- Laboratory criteria (any combination of): serological evidence of syphilis, positive CSF VDRL (50% sensitivity; high specificity), CSF pleocytosis (>5 WBC/ml if HIV; >10-20 WBC/ml if HIV+), CSF elevated protein concentration (>50 mg/dl)
- Lumbar puncture (LP) should be obtained in patients with positive serological tests for syphilis plus neurological symptoms, serological treatment failure (lack of four-fold decline in RPR titer), evidence of tertiary syphilis
- Consider LP in asymptomatic HIV+ patients with a CD4 count ≤350 cells/ml or RPR titer ≥1:32
TREATMENT

**Early syphilis** (primary, secondary, and early latent syphilis within one year after infection)
- Penicillin G Benzathine (Bicillin® L-A) 2.4 million units IM once
- Severe PCN allergies: Doxycycline 100 mg PO BID for 2 weeks

*Note:* due to increased resistance (~45% of strains in Baltimore are resistant), Azithromycin is not recommended.

**Late latent syphilis** (asymptomatic infection with positive serology >1 year after infection or latent syphilis of unknown duration)
- Penicillin G Benzathine (Bicillin® L-A) 2.4 million units IM weekly for 3 weeks (total of 3 doses)

**Neurosyphilis** (can occur during any stage of syphilis)
- Penicillin G 3–4 million units IV Q4H for 10–14 days

**Syphilis in pregnancy**
- Penicillin is the only recommended therapy in pregnant patients with any kind of syphilis. Allergy consult for penicillin desensitization is recommended.

References:
Sexually transmitted diseases CDC treatment guidelines. MMWR 2010/59 (RR12); 1–110.
Discordant Results from Reverse Sequence Syphilis Screening. MMWR 2011/60 (05);133–137
**Management of catheter-related bloodstream infections (CR-BSI)**

**Diagnosis**
- If there is more than minimal erythema or ANY purulence at the exit site, the catheter is likely infected. It should be removed and replaced at a different site.
- When CR-BSI is suspected, 2–3 sets of blood cultures should be drawn with AT LEAST one (and preferably > 1) from peripheral sites. Blood cultures drawn through non-tunneled catheters are more likely to yield contaminants.
- The utility of cultures of the catheter tip itself is not well defined, and should ONLY be sent when there is a clinical suspicion of infection, NOT routinely when lines are removed. They MUST be accompanied by two sets of blood cultures obtained as detailed above.
  - Technique: The exit site should be cleaned with alcohol. The catheter should be grasped a few centimeters proximal to the exit site. A 5 cm segment of catheter including the tip should be cut off with sterile scissors and placed in a sterile container.
  - In instances where the blood and catheter tip are cultured at the same time and the blood cultures are negative but the catheter tip culture is positive, antibiotics are generally not recommended, even for patients with valvular heart disease or immunosuppression.
    - The exception is patients whose catheter tips grow *S. aureus* and have negative blood cultures. These patients should receive 5–7 days of antibiotics.
    - All patients should be followed closely, and repeat cultures should be sent if clinically indicated.
- When a catheter-related BSI is associated with catheter dysfunction, consider the possibility of suppurative thrombophlebitis.

**EMPIRIC TREATMENT**
- Vancomycin (see dosing section, p. 150) ± Cefepime 1–2 g IV Q8H (use higher dose if pseudomonas suspected)
  - OR
- Severe PCN allergy: Vancomycin (see dosing section, p. 150) ± [Ciprofloxacin 400 mg IV Q8H OR Aztreonam 2 g IV Q8H] ± Tobramycin (see dosing section, p. 146)

**Empiric treatment – Gram-positive cocci in clusters in 2 or more sets of blood cultures**
- Vancomycin (see dosing section, p. 150)
Coagulase-negative staphylococci (CoNS)

NOTE: Single positive cultures of CoNS should NOT be treated unless they are confirmed by follow-up cultures, the patient is immunosuppressed and/or critically ill, or the patient has implanted hardware. In these cases, treatment can be started but repeat cultures should be sent PRIOR to initiation of therapy to confirm the diagnosis.

- Vancomycin (see dosing section, p. 150)
  Change to
  - Oxacillin 2 g IV Q4H if susceptible (preferred to Vancomycin)

Duration:
- 3–7 days if catheter removed (preferred)
- 10–14 days if catheter salvage attempt

Methicillin-susceptible Staphylococcus aureus

- Oxacillin 2 g IV Q4H if susceptible
  OR
- Non-anaphylactic PCN allergy: Cefazolin 2 g IV Q8H
  OR
- Anaphylactic PCN allergy: Vancomycin (see dosing section, p. 150)

Methicillin-resistant Staphylococcus aureus

- Vancomycin (see dosing section, p. 150)
- Vancomycin allergy or intolerance (not red man syndrome)
  - Daptomycin 8-10 mg/kg IV Q 24H
    OR
  - Ceftaroline 600 mg IV Q 8H
- Vancomycin failure: consult ID

TREATMENT NOTES

- Remove catheter. High relapse rates if catheter is not removed.
- Vancomycin is inferior to Oxacillin for treatment of MSSA.
- Patients with S. aureus bacteremia should have an echocardiogram to rule out endocarditis. Transthoracic echo is acceptable only if the study adequately views the left-sided valves; most experts recommend TEE.
- Linezolid should not be used routinely for treatment of S. aureus bacteremia
- Criteria for a 14 day course of therapy
  - Endocarditis excluded with TEE (preferred); high quality TTE may be adequate in select patients
- No implanted prostheses
- Follow-up blood cultures drawn 2-4 days after the initial cultures are negative for S. aureus
• The patient defervesces with 72 hours of initiation of effective antistaphylococcal therapy
• The patient has no localizing signs or symptoms of metastatic staphylococcal infection
• Source control has been obtained
• Absence of other conditions that may affect ability to clear infection based on clinical judgment (e.g. poorly controlled diabetes)
• All other patients should receive 4-6 weeks of therapy based on extent of infection

**Enterococcus faecalis**

**NOTE:** Can be contaminants. Draw repeat cultures to confirm before starting treatment. 100% of *E. faecalis* blood isolates at JHH are susceptible to Ampicillin, which should be used unless the patient has a PCN allergy.

- Ampicillin 2 g IV Q4H

**OR**

- PCN allergy: Vancomycin (see dosing section p. 150)

**Duration:** 7–14 days

**Enterococcus faecium**

**NOTE:** Can be contaminants. Draw repeat cultures to confirm before starting treatment. The majority (78%) of *E. faecium* blood isolates at JHH are resistant to Vancomycin. If the isolate is susceptible to Ampicillin or Vancomycin, these agents should be used preferentially at the doses listed above for *E. faecalis* bacteremia.

- Linezolid 600 mg IV/PO Q12H

**OR**

- Daptomycin 8–12 mg/kg IV Q24H

**TREATMENT NOTES**

- Consider echocardiogram if there is persistent bacteremia (> 3 days) on antibiotics.
- The addition of Gentamicin does not appear to change outcomes in CR-BSI caused by Enterococcus in the absence of endocarditis.

**Gram-negative bacilli**

Antibiotic selection based on organism and susceptibilities.

**Duration:** 7–10 days
TREATMENT NOTES
• Catheters are less commonly the source of the infection; however, most advocate catheter removal if the catheter is the source.

*Candida spp.*
• Refer to p. 117 for treatment of candidemia

CATHETER SALVAGE
• Catheter removal is STRONGLY recommended for infections with *S. aureus*, yeast and *Pseudomonas*, as the chance of catheter salvage is low and the risk of recurrent infection is high.
• Catheters associated with tunnel infections CANNOT be salvaged and should be removed.
• When catheter salvage is attempted, systemic antibiotics should be given through the infected line.
• Antibiotic used as lock therapy should preferentially match antibiotic used for systemic therapy.

Anti*biotic Lock Therapy (ALT)*
• Antibiotic lock therapy can be used for catheter salvage in addition to systemic antibiotics when feasible.
• Catheter removal should be performed if cultures remain positive after 72 hours of appropriate antibiotic lock therapy

Acceptable uses:
• Salvage of long-term catheters that cannot be removed (e.g. dialysis catheters, implantable permanent ports or central venous catheters for chemotherapy) when there are NO systemic complications (hemodynamic instability, tissue hypoperfusion, septic thrombosis, infectious endocarditis or distant septic metastases) or signs of local infection.

Unacceptable uses:
• Short-term venous catheters
• Complicated CRBSI (e.g. tunnel or port-pocket infection, severe sepsis, septic shock, endocarditis, osteomyelitis and hematogenous seeding at other sites)
• Catheter salvage with *S. aureus* infection.

Duration: 7–14 days
### Standardized Concentrations of Antibiotics for ALT

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Heparin (optional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin 5 mg/mL in 0.9% NS</td>
<td>0 or 5000 units</td>
</tr>
<tr>
<td>Gentamicin 5 mg/mL in 0.9% NS</td>
<td>2500 units</td>
</tr>
</tbody>
</table>

- ALT should be instilled in the lumen of the catheter when not in use.
- Dwell times should be at minimum of 8–12 hours per day (up to 24–48 h)
- ALT volume needed will vary by type of catheter and available number of lumens. In general, 2–5 mL should be sufficient.

References:
Treatment of native valve endocarditis

NOTES:
- Beta-lactams are **highly preferable** to Vancomycin if the organism is susceptible and if the patient is not severely allergic. Strongly consider PCN desensitization for allergic patients.
- Infectious Diseases consultation is advised for cases of left-sided infective endocarditis and prosthetic valve endocarditis, particularly in those in which the preferred antibiotic cannot be used or in which the organism is resistant to usual therapy.
- Therapeutic monitoring:
  - Vancomycin
    - Goal trough level: 15–20 mcg/mL
  - Gentamicin for Gram-positive synergy
    - Daily dosing
      - Goal trough level: <1 mcg/mL
    - Traditional dosing (Q8H)
      - Goal peak level: 3–4 mcg/mL
      - Goal trough level: <1 mcg/mL
  - See p. 148 and p. 150 for details

**Viridans streptococci or S. bovis with PCN MIC \(\leq\) 0.12 mcg/mL**
- Penicillin G 3 million units IV Q4H for 4 weeks
  OR
- Non-severe PCN allergy: Ceftriaxone 2 g IV/IM Q24H for 4 weeks
  OR
  - [Penicillin G 3 million units IV Q4H OR Ceftriaxone 2 g IV/IM Q24H for 2 weeks] **PLUS** Gentamicin 3 mg/kg IV Q24H for 2 weeks
  OR
- Severe PCN allergy: Vancomycin (see dosing section, p. 150) for 4 weeks

**Criteria for 2 week treatment:**
- Patient does not have cardiac or extracardiac abscess
- CrCl >20 mL/min
- Patient does not have impaired 8th cranial nerve function
- Patient does not have Abiotrophia, Granulicatella, or Gemella spp.

**Viridans streptococci or S. bovis with PCN MIC > 0.12 mcg/mL and \(\leq\) 0.5 mcg/mL**
- [Penicillin G 4 million units IV Q4H OR Ceftriaxone 2 g IV/IM Q24H for 4 weeks] **PLUS** Gentamicin 3 mg/kg IV Q24H for the first 2 weeks of therapy
6.7 Endocarditis

**OR**
- Severe PCN allergy: Vancomycin (see dosing section, p. 150) for 4 weeks

**Viridans streptococci or S. bovis with PCN MIC > 0.5 mcg/mL and Abiotrophia defectiva, Granulicatella spp. and Gemella spp.**
- Consult ID

**TREATMENT NOTES**
- All patients with S. bovis biotype I endocarditis should undergo GI work-up to rule out underlying cancer.

**Staphylococcus aureus – Methicillin susceptible, native valve, right-sided involvement only**
- Oxacillin 2 g IV Q4H
  - Use Nafcillin for Oxacillin-induced hepatitis

Criteria for 2-week treatment:
- Patient is an injecting drug user with minimal other comorbidities
- Left-sided endocarditis is ruled out with TEE (preferred) or high quality TTE
- Treatment is with Oxacillin or Nafcillin
- Patient does not have AIDS (CD4 < 200)
- Patient does not have an implanted prosthesis (dialysis graft, etc)
- Blood cultures are negative within 4 days after starting therapy
- There is no evidence of embolic disease OTHER than septic pulmonary emboli
- Vegetations are all < 2 cm in size
- If patient does not meet criteria for 2-week treatment, treat for 4 weeks

**Staphylococcus aureus – Methicillin susceptible, native valve, left-sided involvement**
- Oxacillin 2 g IV Q4H
  **OR**
- Non-severe PCN allergy: Cefazolin 2 g IV Q8H
  **OR**
- Severe PCN allergy: Strongly consider PCN desensitization or Vancomycin (see dosing section, p. 150)
- The addition of Gentamicin to a beta-lactam may help clear blood cultures faster but does not appear to affect mortality. It particularly should be avoided in the elderly and in those with baseline renal impairment.

**Staphylococcus aureus – Methicillin resistant, native valve**
- Vancomycin (see dosing section, p. 150)
**Duration**
- Uncomplicated: 6 weeks
- Complicated (perivalvular abscess formation, metastatic complication, poor controlled diabetes mellitus): 6 or more weeks based on clinical picture and response to therapy
- ID and cardiac surgery consults recommended for complicated diseases

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**S. pneumoniae, and Group A streptococci**
- Penicillin G 3 million units IV Q4H for 4 weeks
  OR
- Non-severe PCN allergy: Ceftriaxone 2 g IV Q24H for 4 weeks OR Cefazolin 2 g IV Q8H for 4 weeks
  OR
- Severe PCN allergy: Vancomycin (see dosing section, p. 150) for 4 weeks
- For *S. pneumoniae*, if PCN MIC $\geq 0.1$, consult ID

---

**Groups B, C and G streptococci**
- Penicillin G 3 million units IV Q4H for 4–6 weeks ± Gentamicin 3 mg/kg IV Q24H for the first 2 weeks of therapy
  OR
- Non-severe PCN allergy: Ceftriaxone 2 g IV Q8H for 4–6 weeks ± Gentamicin 3 mg/kg IV Q24H for the first 2 weeks of therapy
  OR
- Severe PCN allergy: Vancomycin (see dosing section, p. 146) for 4–6 weeks ± Gentamicin 3 mg/kg IV Q24H for the first 2 weeks of therapy
- Consider an ID Consult

---

**Enterococcus faecalis**
- Ampicillin and Gentamicin susceptible: Ampicillin 2 g IV Q4H OR Penicillin G 4 million units IV Q4H PLUS Gentamicin 1 mg/kg IV Q8H BOTH for 4-6 weeks
- Ampicillin susceptible with contraindications for aminoglycosides or Gentamicin resistant: Ampicillin 2 g IV Q4H OR Penicillin G 4 million units IV Q4H PLUS Ceftriaxone 2 g IV Q12H BOTH for 4-6 weeks
OR
• Severe PCN allergy: Strongly consider PCN desensitization if PCN allergy is anaphylactic or Vancomycin (see dosing section, p. 146) PLUS Gentamicin 1 mg/kg IV Q8H BOTH for 4–6 weeks
• Treat for 4 weeks only when symptoms have been present for < 3 months AND there is a prompt response to therapy

**Enterococcus faecium**
• Consult ID

Reference:

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**HACEK organisms (Haemophilus parainfluenzae, H. aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominus, Eikenella corrodens, Kingella kingae)**

• Ceftriaxone 2 g IV/IM Q24H for 4 weeks
• Severe PCN allergy: Consult ID

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**Gram-negative organisms, culture negative endocarditis, or fungal endocarditis**
• Consult ID

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**Treatment of prosthetic valve endocarditis**

• Generally caused by staphylococci in the first 1–2 years following valve replacement (both S. aureus and coagulase-negative staph). Etiologies are similar to native valve infections 2 or more years post-op.
• Medical treatment alone is often NOT effective.
• All patients should have a TEE.

**EMPIRIC TREATMENT**

• Vancomycin (see dosing section, p. 150) PLUS Gentamicin 1 mg/kg IV Q8H

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**Viridans streptococci or S. bovis with PCN MIC ≤ 0.12 mcg/mL**

• [Penicillin G 4 million units IV Q4H OR Ceftriaxone 2 g IV/IM Q24H] for 6 weeks ± Gentamicin 3 mg/kg IV Q24H for first 2 weeks of therapy
• Severe PCN allergy: Vancomycin (see dosing section, p. 150) for 6 weeks
Viridans streptococci or _S. bovis_ with PCN MIC > 0.12 mcg/mL
- [Penicillin G 4 million units IV Q4H OR Ceftriaxone 2 g IV/IM Q24H] 
  PLUS Gentamicin 3 mg/kg IV Q24H for 6 weeks 
  OR
- Severe PCN allergy: Vancomycin (see dosing section, p. 150) for 6 weeks

### Staphylococcus aureus—Methicillin susceptible
- Oxacillin 2 g IV Q4H for 6 weeks PLUS Gentamicin 1 mg/kg IV Q8H for first 2 weeks of therapy
  AND
- Rifampin 300 mg PO Q8H for 6 weeks _after blood cultures have cleared_
  - ID and cardiac surgery consults recommended

### Staphylococcus aureus—Methicillin resistant or Coagulase-negative staphylococci
- Vancomycin (see dosing section, p. 150) for 6 weeks PLUS Gentamicin 1 mg/kg IV Q8H for the first 2 weeks of therapy
  AND
- Rifampin 300 mg PO Q8H for 6 weeks _after blood cultures have cleared_
  - If coagulase-negative staphylococci is susceptible to Oxacillin then treat as _S. aureus_ – Methicillin susceptible.
  - ID and cardiac surgery consults recommended

### Gram-negative organisms or culture negative endocarditis
- Consult ID

### DUKE CRITERIA FOR INFECTIVE ENDOCARDITIS

**Diagnostic criteria (Modified Duke criteria)**
- **Definite endocarditis**
  - Presence of 2 major criteria OR 1 major AND 3 minor OR 5 minor
- **Possible endocarditis**
  - Presence of 1 major AND 1 minor OR 3 minor criteria
- **Rejected endocarditis**
  - Firm alternate diagnosis that explains ALL manifestations of IE
  (**NOTE:** simply having another infection does NOT exclude endocarditis)
**Major criteria**

**Microbiologic**
- Persistent bacteremia with any organism as evidenced by: 2 positive blood cultures drawn at least 12 hours apart OR 3/3 positive blood cultures with at least 1 hour between the first and last OR the majority of more than 4 cultures positive from any time period.
- Positive *Coxiella burnetti* (Q fever) culture or serology.

**Echocardiographic (TEE strongly recommended for prosthetic valve)**
- Vegetation (on valve or supporting structure OR in path of regurgitant jet)
- Abscess
- New dehiscence of prosthetic valve

**Physical exam**
- NEW regurgitant murmur (worsening of old murmur is NOT sufficient)

**Minor criteria**
- Predisposing condition: previous endocarditis, injection drug use, prosthetic valve, ventricular septal defect, coarctation of the aorta, calcified valve, patent ductus, mitral valve prolapse with regurgitation, IHSS or other valvular heart disease
- Fever \( \geq 38.0^\circ C (100.4^\circ F) \)
- Embolic events: arterial or pulmonary emboli, conjunctival hemorrhage, retinal hemorrhage, splinter hemorrhage, intracranial hemorrhage, mycotic aneurysm
- Immunologic phenomenon: Osler nodes, glomerulonephritis, positive rheumatoid factor
- Positive blood cultures that don’t meet criteria above OR serologic evidence of active infection with an organism known to cause endocarditis BUT single positive cultures for coagulase-negative staphylococci are NOT considered even a minor criterion

References:
Permanent pacemaker (PPM) and implantable cardioverter-defibrillator (ICD) infections

NOTE: Obtain at least 2 sets of blood cultures before initiation of antibiotic therapy

EMPIRIC TREATMENT
• Vancomycin (see dosing section, p. 150). Narrow therapy based on culture results.

TREATMENT NOTES

Microbiology—staphylococci in 70-80% of cases (~50% coagulase-negative staphylococci and ~50% S. aureus)

Management
• If blood cultures are positive or endocarditis is suspected patients should undergo transesophageal echocardiography (TEE)
• Complete extraction recommended for patients with pocket infection and/or valvular or lead endocarditis
• At the time of extraction, tissue (rather than swabs) from the generator pocket should be sent for Gram-stain and culture and lead tips should be sent for culture.
• Note that because leads are extracted through an open generator pocket, they may become contaminated by the infected pocket; therefore, positive lead cultures are not always indicative of lead endocarditis in patient with negative blood cultures.
• Blood cultures should be obtained after device removal.
• Device reimplantation should be on the contra-lateral side whenever possible.
• Complete extraction is strongly recommended in all patients presenting with S. aureus bacteremia and no other source
• Complete extraction should be considered in patients with persistent positive blood cultures with other organisms (e.g. coagulase-negative staphylococci, enterococci, Gram-negative bacilli) on a case-by-case basis.
• Complete device and lead removal is recommended for patients with valvular endocarditis.
• Antimicrobial prophylaxis is NOT recommended for dental or other invasive procedures following placement

Reference:
## Reimplantation timing and duration of therapy

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Timing of reimplantation</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pocket site infection</td>
<td>Blood cultures negative for 72 hours and surgical site healing</td>
<td>7-10 days if device erosion without inflammation 10-14 days all others Oral therapy can be considered</td>
</tr>
</tbody>
</table>
| Positive blood cultures with rapid clearance AND TEE with either no vegetation or uncomplicated lead vegetation | Post-explantation blood cultures negative for 72 hours     | Non-S. aureus: 2 weeks IV therapy  
S. aureus: 4 weeks IV therapy |
| Sustained positive blood cultures AND TEE with no vegetation or uncomplicated lead vegetation | Post-explantation blood cultures negative for 72 hours     | 4 weeks IV therapy                                       |
| Valve endocarditis                             | Blood cultures negative for 14 days                          | 4-6 weeks IV therapy                                      |

Reference:
Meningitis – Empiric treatment

TREATMENT

• **ANTIBIOTICS SHOULD BE STARTED AS SOON AS THE POSSIBILITY OF BACTERIAL MENINGITIS BECOMES EVIDENT, IDEALLY WITHIN 30 MINUTES.**

• **DO NOT WAIT FOR CT SCAN OR LP RESULTS. IF LP MUST BE DELAYED, GET BLOOD CULTURES AND START THERAPY.**

• Adjust therapy once pathogen and susceptibilities are known.

• Some advocate penicillin desensitization for pathogen-specific therapy in patients with severe allergies (p. 137).

• **Antibiotic doses are higher for CNS infections (p. 77).**

• Infectious Diseases consultation is advised for all CNS infections, particularly those in which the preferred antibiotic cannot be used or in which the organism is resistant to usual therapy.

Empiric therapy

<table>
<thead>
<tr>
<th>Host</th>
<th>Pathogens</th>
<th>Preferred Abx</th>
<th>Alternative for serious PCN allergy (ID consult recommended)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocompetent* age &lt; 50</td>
<td>S. pneumo, N. mening, H. influenzae</td>
<td>Vancomycin PLUS Ceftriaxone</td>
<td>Moxifloxacin‡ PLUS Vancomycin</td>
</tr>
<tr>
<td>Immunocompetent* age &gt; 50</td>
<td>S. pneumo, Listeria, H. influenzae, N. mening, Group B streptococci</td>
<td>Vancomycin PLUS Ceftriaxone PLUS Ampicillin</td>
<td>Moxifloxacin‡ PLUS Vancomycin PLUS TMP/SMX</td>
</tr>
<tr>
<td>Immunocompromised†</td>
<td>S. pneumo, N. mening, H. influenzae, Listeria, (Gram-negatives)</td>
<td>Vancomycin PLUS Cefepime PLUS Ampicillin</td>
<td>Vancomycin PLUS TMP/SMX PLUS Ciprofloxacin</td>
</tr>
<tr>
<td>Post neurosurgery or penetrating head trauma</td>
<td>S. pneumo (if CSF leak), H. influenzae, Staphylococci, (Gram-negatives)</td>
<td>Vancomycin PLUS Cefepime</td>
<td>Vancomycin PLUS Ciprofloxacin</td>
</tr>
<tr>
<td>Infected shunt</td>
<td>S. aureus, coagulase-negative staphylococci, (Gram-negatives (rare))</td>
<td>Vancomycin PLUS Cefepime</td>
<td>Vancomycin PLUS Ciprofloxacin</td>
</tr>
</tbody>
</table>

† Immунocompromised is defined as solid organ transplant, BMT in the past year, leukemia undergoing treatment, or neutropenia

‡ Allergy consult for beta-lactam desensitization

* **Use of Dexamethasone**

• Addition of dexamethasone is recommended in all adult patients with suspected pneumococcal meningitis (note that this will be most adult patients).

• Dose: 0.15 mg/kg IV Q6H for 2–4 days

• The first dose must be administered 10–20 minutes before or concomitant with the first dose of antibiotics.
- Administration of antibiotics should not be delayed to give dexamethasone.
- Dexamethasone should not be given to patients who have already started antibiotics.
- Continue dexamethasone only if the CSF Gram stain shows Gram-positive diplococci or if blood or CSF grows *S. pneumoniae*

### Pathogen-specific therapy (ID consult recommended)

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Preferred</th>
<th>Alternative for serious PCN allergy (Consult allergy for PCN skin testing ± desensitization)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pneumonia</em> PCN MIC ≤ 0.06 μg/ml AND/OR Ceftriaxone MIC &lt;0.5 μg/ml</td>
<td>Penicillin OR Ceftriaxone</td>
<td>Vancomycin OR Moxifloxacin OR Linezolid</td>
</tr>
<tr>
<td><em>S. pneumonia</em> PCN MIC &gt;0.1–1 μg/ml AND Ceftriaxone MIC &lt;1 μg/ml (ID consult recommended)</td>
<td>Ceftriaxone</td>
<td>Moxifloxacin OR Linezolid</td>
</tr>
<tr>
<td><em>S. pneumonia</em> PCN MIC &gt; 1 μg/ml AND Ceftriaxone MIC ≥1 μg/ml (ID consult recommended)</td>
<td>Ceftriaxone PLUS Vancomycin PLUS Rifampin</td>
<td>Moxifloxacin OR Linezolid</td>
</tr>
<tr>
<td><em>N. meningitidis</em> PCN susceptible (MIC &lt; 0.1)</td>
<td>Penicillin OR Ceftriaxone</td>
<td>Consult ID</td>
</tr>
<tr>
<td><em>H. influenzae</em> Non β-lactamase producer</td>
<td>Ampicillin OR Ceftriaxone</td>
<td>Ciprofloxacin *</td>
</tr>
<tr>
<td><em>H. influenzae</em> β-lactamase producer</td>
<td>Ceftriaxone</td>
<td>Ciprofloxacin *</td>
</tr>
<tr>
<td><em>Listeria</em></td>
<td>Ampicillin ± Gentamicin‡</td>
<td>TMP/SMX</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>Cefepime OR Meropenem</td>
<td>Ciprofloxacin PLUS Aztreonam</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>Ceftriaxone</td>
<td>Aztreonam OR Ciprofloxacin OR TMP/SMX</td>
</tr>
<tr>
<td><em>Enterobacter</em> spp.</td>
<td>Meropenem</td>
<td>TMP/SMX OR Ciprofloxacin</td>
</tr>
<tr>
<td><em>S. aureus</em>–MSSA</td>
<td>Oxacillin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td><em>S. aureus</em>–MRSA</td>
<td>Vancomycin</td>
<td></td>
</tr>
<tr>
<td>Coagulase-negative staphylococci if Oxacillin MIC ≤ 0.25</td>
<td>Oxacillin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci Oxacillin MIC &gt; 0.25</td>
<td>Vancomycin</td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>Ampicillin PLUS Gentamicin‡</td>
<td>Vancomycin PLUS Gentamicin‡</td>
</tr>
<tr>
<td>Candida species</td>
<td>Amphotericin B</td>
<td></td>
</tr>
<tr>
<td><em>Cryptococcus</em></td>
<td>Amphotericin B PLUS Flucytosine</td>
<td></td>
</tr>
</tbody>
</table>

* Consider beta-lactam desensitization
+ Must give Ciprofloxacin 500 mg once to eradicate carrier state if PCN used as treatment
‡ Administer aminoglycosides systemically, not intrathecally
TREATMENT NOTES

Indications for head CT prior to LP
• History of CNS diseases (mass lesion, CVA)
• New-onset seizure (≤ 1 week)
• Papilledema
• Altered consciousness
• Focal neurologic deficit

Duration
• STOP treatment if LP culture obtained prior to antibiotic therapy is negative at 48 hours OR no PMNs on cell count
• *S. pneumoniae*: 10–14 days
• *N. meningitidis*: 7 days
• *Listeria*: 21 days
• *H. influenzae*: 7 days
• Gram-negative bacilli: 21 days

Adjunctive therapy
• Consider intracranial pressure monitoring in patients with impaired mental status.

Encephalitis

• Herpes viruses (HSV, VZV) remain the predominant causes of treatable encephalitis.
• CSF PCRs are rapid diagnostic tests and appear quite sensitive and specific.
• Have low threshold to treat if suspected as untreated mortality exceeds 70%.
• Treatment: Acyclovir 10 mg/kg IV Q8H for 14–21 days
Brain abscess

- Empiric treatment is guided by suspected source and underlying condition. While therapy should be adjusted based on culture results, anaerobic coverage should ALWAYS continue even if none are grown.

<table>
<thead>
<tr>
<th>Source/Condition</th>
<th>Pathogens</th>
<th>Preferred</th>
<th>Alternative for serious PCN allergy (ID consult recommended)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>S. aureus, Streptococci, Gram-negatives, Anaerobes</td>
<td>Vancomycin PLUS Ceftriaxone PLUS Metronidazole</td>
<td>Vancomycin PLUS Ciprofloxacin PLUS Metronidazole</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>Streptococci (incl. S. pneumoniae), Anaerobes</td>
<td>[Penicillin OR Ceftriaxone] PLUS Metronidazole</td>
<td>Vancomycin PLUS Metronidazole</td>
</tr>
<tr>
<td>Chronic otitis</td>
<td>Gram-negatives, Streptococci Anaerobes</td>
<td>Cefepime PLUS Metronidazole</td>
<td>Aztreonam PLUS Metronidazole PLUS Vancomycin</td>
</tr>
<tr>
<td>Post neurosurgery</td>
<td>Staphylococci, Gram-negatives</td>
<td>Vancomycin PLUS Cefepime</td>
<td>Vancomycin PLUS Ciprofloxacin</td>
</tr>
<tr>
<td>Cyanotic heart disease</td>
<td>Streptococci (esp. S. viridans)</td>
<td>Penicillin OR Ceftriaxone</td>
<td>Vancomycin</td>
</tr>
</tbody>
</table>

References:

CNS shunt infection

Diagnosis
- Culture of cerebrospinal fluid remains the mainstay of diagnosis. Clinical symptoms may be mild and/or non-specific, and CSF chemistries and leukocyte counts may be normal.

Empiric Therapy
- Vancomycin (see dosing section, p. 150) PLUS Cefepime 2 g IV Q8H OR
- PCN Allergy: Vancomycin (see dosing section, p. 150) PLUS Ciprofloxacin 400 mg IV Q8H

TREATMENT NOTES
- ID consult recommended for assistance with timing of shunt replacement and length of antibiotic therapy.
- Removal of all components of the infected shunt with external ventricular drainage or intermittent ventricular taps in combination with the appropriate intravenous antibiotic therapy leads to the highest effective cure rates. Success rates are substantially lower when the infected shunt components are not removed.
• The role of intraventricular antibiotics is controversial, and generally limited to refractory cases or cases in which shunt removal is not possible. Intraventricular injection should be administered only by experienced physicians.

References:

**Antimicrobial doses for CNS infections – normal renal function**

**Antibiotics**

- Aminoglycosides: see p. 145
- Ampicillin: 2 g IV Q4H
- Aztreonam: 2 g IV Q6H
- Ceftriaxone: 2 g IV Q12H
- Cefepime: 2 g IV Q8H
- Ciprofloxacin: 400 mg IV Q8H (based on limited data)
- Moxifloxacin: 400 mg IV Q24H
- Meropenem: 2 g IV Q8H
- Metronidazole: 500 mg IV Q6H
- Oxacillin: 2 g IV Q4H
- Penicillin: 4 million units IV Q4H (24 million units per day)
- Rifampin: 600 mg IV Q12–24H
- TMP/SMX: 5 mg/kg (TMP component) IV Q6H
- Vancomycin: load with 25–35 mg/kg, then 15–20 mg/kg Q8–12H (minimum 1 g Q12H)
  - Vancomycin should be administered to maintain serum trough concentrations close to 20 mcg/mL.

**Antifungals**

- Amphotericin: 0.7–1 mg/kg IV Q24H
- AmBisome®: 3-4 mg/kg IV Q24H for Cryptococcal meningitis
- AmBisome®: 5 mg/kg IV Q24H for Candida meningitis
- Fluconazole: 800–1200 mg IV/PO Q24H (can give in divided doses)
- Flucytosine: 25 mg/kg PO Q6H

**Intraventricular antibiotics (ID consult recommended)**

- Amikacin: 30 mg Q24H (contains preservative)
- Gentamicin: 5 mg Q24H
- Tobramycin: 5 mg Q24H
- Vancomycin: 20 mg Q24H
**Acute bacterial rhinosinusitis (ABRS)**

**NOTE:** Sinusitis in immunocompromised hosts can be caused by fungi and other less-common pathogens; consultation with ID and ENT is recommended to guide management and therapy.

Most rhinosinusitis does not require antibiotic treatment; treatment should be considered in the following scenarios:

- Persistent symptoms of acute rhinosinusitis ≥ 10 days without improvement
- Fever ≥39°C and purulent nasal discharge or facial pain lasting >3-4 days from the beginning of illness
- New onset of fever, headache or increase in nasal discharge following viral URI that lasted 5-6 days and was initially improving

**EMPIRIC TREATMENT**

**Oral regimens**
- Amoxicillin/clavulanate 875 mg PO Q12H  
  **OR**  
  Amoxicillin/clavulanate XR 2 g PO Q12H for patients with severe infection (e.g. systemic toxicity with fever of 39°C), antibiotic use in previous 30 days, immunocompromised
  **OR**  
  Non-severe PCN allergy: Cefpodoxime 200 mg PO Q12H  
  **OR**  
  Severe PCN allergy: Moxifloxacin 400 mg PO daily

**Parenteral regimens**
- Amoxicillin/sulbactam 1.5 g IV Q6H  
  **OR**  
  Non-severe PCN allergy: Ceftriaxone 1 g IV Q24H  
  **OR**  
  Severe PCN allergy: Moxifloxacin 400 mg IV Q24H

**Duration**
- 5-7 days

**TREATMENT NOTES**

**Microbiology**
- Predominantly *S. pneumoniae, H. influenzae, M. catarrhalis*
- Gram-negative enteric bacilli are rare

**Management**
- ABRS is rarely present prior to 7–10 days of symptoms; typical inciting etiologies of acute sinusitis include allergies and viral URI
• Cultures by direct sinus aspiration or endoscopically guided culture of the middle meatus should only be obtained in patients who fail empiric antibiotic therapy. Nasopharyngeal swab is NOT recommended for obtaining culture data.

• Confirmation of diagnosis with imaging is not recommended for uncomplicated ABRS. Consider CT in those with severe disease with possible extension to the orbit or intracranial space.

• Intranasal saline irrigation (physiologic or hypertonic) and intranasal corticosteroids are recommended as adjuncts to antibiotic therapy and can also provide symptomatic relief in patients in whom antibiotic are not indicated.

• Macrolides (Clarithromycin, Azithromycin) are not recommended for initial empiric therapy due to high rates of resistance of *S. pneumoniae* (55% at JHH).

• Despite IDSA guidelines supporting use of Doxycycline as an alternative agent for ABRS, Doxycycline is NOT recommended for initial empiric therapy at JHH due to high rates of resistance of *S. pneumoniae* (27%) and *H. influenzae* (35%).

• Routine coverage for MRSA in initial empiric therapy for ABRS in not recommended.

Reference:
Orbital cellulitis

Preseptal cellulitis (>90% of cases)
- Involves tissues anterior to the orbital septum
- Presents with fever, eyelid erythema and soft tissue swelling but no orbital congestion

Postseptal cellulitis
- Signs of periorbital cellulitis as well as limitation of ocular movements, pain with ocular movement, and/or proptosis
- Severe infection can also involve visual loss, subperiosteal abscess, globe displacement, abscess formation
- Often associated with sinusitis
- Can be associated with cavernous sinus thrombosis

Empiric Treatment
- Ampicillin/sulbactam 3 g IV Q6H
  OR
- Non-severe PCN allergy: Ceftriaxone 2 g IV daily
  OR
- Severe PCN allergy: Moxifloxacin 400 mg IV daily
Add Vancomycin (see dosing section, p. 150) in patients with history of MRSA colonization or infection, evidence of abscess or bone involvement, orbital trauma, recent ophthalmic surgery or severe infection

Oral step down therapy (for patients without culture data to guide therapy and without evidence of bony involvement or cavernous sinus thrombosis)
- Amoxicillin/clavulanate 875 mg PO Q12H
  OR
- Non-severe PCN allergy: Cefpodoxime 400 mg PO Q12H
  OR
- Severe PCN allergy: Moxifloxacin 400 mg PO daily

Duration
- 7 days up to 6 weeks if evidence of bony involvement

Treatment Notes

Microbiology
- S. aureus, beta-hemolytic streptococci, S. pneumoniae, H. influenza, M. catarrhalis (cultures are infrequently positive)

Management
- Imaging is recommended in post-septal cellulitis (CT or MRI)
- Consultation with ID, ENT, and ophthalmology recommended
• Post-septal cellulitis in immunocompromised hosts can be caused by fungi and molds; empiric antifungal therapy is recommended in consultation with ID
• Post-septal cellulitis with abscess formation should prompt immediate surgical intervention
• Response to appropriate antibiotic therapy should occur in 24 – 48 hours
• Poor response to antibiotics, worsening visual acuity or pupillary changes and/or evidence of an abscess are indications for surgery
COPD exacerbations

EMPIRIC TREATMENT

• Doxycycline 100 mg PO BID for 5 days
  OR
• Azithromycin 500 mg PO/IV Q24H for 3 days
  OR
• Amoxicillin/clavulanate 875 mg PO BID for 5 days
  OR
• Cefpodoxime 200 mg PO BID for 5 days
  OR
• Cefdinir 300 mg PO BID for 5 days

TREATMENT NOTES

Microbiology

• Predominantly *H. influenzae*, *M. catarrhalis*, *S. pneumoniae*
• *Pseudomonas, Enterobacteriaceae* are less common and seen in patients with severe COPD and extensive antibiotic exposure.

Management

• Empiric use of fluoroquinolones is discouraged and should only be considered if past or present microbiologic evidence indicates infection with a pathogen(s) that is resistant to standard therapy (e.g. *Pseudomonas, Enterobacteriaceae*).
• IV antibiotics should only be used if the patient cannot tolerate PO antibiotics.
• Antibiotics are not indicated for asthma flares in the absence of pneumonia.

Prophylactic antibiotics for the prevention of COPD exacerbations

• Prophylactic antibiotics have been shown to reduce rates of exacerbations and improve reported quality of life but not to decrease all-cause or respiratory-associated mortality.
• Prolonged Azithromycin use has been associated with hearing loss and QT prolongation; patients with baseline QT-prolongation were not included in clinical trials.
• The decision to initiate prophylactic antibiotics should be made on a case-by-case basis and should take into account patient preferences, financial constraints, risk factors for adverse events and input from the patient’s pulmonologist.
• Recommended regimen: Azithromycin 250 mg PO daily
• Baseline audiometry and EKG is recommended

References:
Community-acquired pneumonia (CAP) in hospitalized patients

NOTE: If patient is coming from a nursing home or long-term care facility, see Healthcare-acquired pneumonia, p. 87.

EMPIRIC TREATMENT

Patient NOT in the ICU

- Ampicillin/sulbactam 1.5 g IV Q6H PLUS Azithromycin 500 mg IV/PO once daily
  
  OR

- Ceftriaxone 1 g IV Q24H PLUS Azithromycin 500 mg IV/PO once daily
  
  OR

- Moxifloxacin 400 mg IV/PO Q24H

In non-critically ill patients, consider switch to oral agents as soon as patient is clinically improving and eating (see next page for oral options and doses).

Patient in the ICU

Not at risk for infection with Pseudomonas (see risks below)

- Ceftriaxone 1 g IV Q24H PLUS Azithromycin 500 mg IV Q24H
  
  OR

- PCN allergy: Moxifloxacin 400 mg IV Q24H

At risk for infection with Pseudomonas (see risks below)

- Cefepime 1-2 g IV Q8H PLUS Azithromycin 500 mg IV Q24H
  
  OR

- Piperacillin/tazobactam 4.5 g IV Q6H PLUS Azithromycin 500 mg IV Q24H
  
  OR

- Severe PCN allergy: Moxifloxacin 400 mg IV Q24H PLUS Aztreonam 2 g IV Q8H

- Sputum gram stain may help determine if Pseudomonas is present.

  • Narrow coverage if Pseudomonas is NOT present on culture at 48 hours.

Risks for Pseudomonas and other resistant Gram-negative organisms:

- bronchiectasis; broad-spectrum antibiotics for > 7 days in the past month; prolonged hospitalization > 7 days; debilitated nursing home resident; recent mechanical ventilation > 48 H; immunocompromised due to solid organ transplant, hematologic malignancy, BMT, active chemotherapy, prednisone > 20 mg daily for > 3 weeks.

DIAGNOSIS

- Immunocompetent patients MUST have a chest X-ray infiltrate to meet diagnostic criteria for pneumonia.

- Sputum and blood cultures should be sent on all patients admitted to the hospital BEFORE antibiotics are given.

- S. pneumoniae urine antigen should be obtained in all patients with CAP. It has specificity of 96% and positive predictive value of 88.8-96.5%. It is particularly useful if antibiotics have already been started or cultures cannot be obtained.
• The legionella urine antigen is the test of choice for diagnosing legionella infection. This test detects only L. pneumophila serogroup 1, which is responsible for 70–80% of infections.

**DURATION**

• Therapy can be stopped after the patient is:
  - Afebrile for 48–72 hours
  - Has no more than one of the following signs and symptoms: HR > 100 beats/min, RR > 24 breaths/min, BP < 90 mmHg, O₂ sat < 90%, altered mental status.

• **Suggested duration of therapy based on patient specific factors:**
  - **3–5 days:** Patient without immunocompromise or structural lung disease
  - **7 days:** Patients with moderate immunocompromise and/or structural lung disease
  - **10–14 days:** Patients with poor clinical response, who received initial inappropriate therapy, or who are significantly immunocompromised

• Uncomplicated bacteremic pneumococcal pneumonia—prolonged course of antibiotic therapy not necessary, treat as pneumonia

• Cough and chest X-ray abnormalities may take 4–6 weeks to improve. There is NO need to extend antibiotics if the patient is doing well otherwise (e.g. no fever).

**Other causes of pneumonia**

• Suspected aspiration: Additional empiric coverage for aspiration is justified only in classic aspiration syndromes suggested by loss of consciousness (overdose, seizure) PLUS gingival disease or esophageal motility disorder. Ceftriaxone, Cefepime, and Moxifloxacin have adequate activity against most oral anaerobes. For classic aspiration, Clindamycin 600 mg IV Q8H can be added to regimens not containing Piperacillin/tazobactam.

• Community-acquired MRSA: Necrotizing pneumonia with cavitation in absence of risk factors for aspiration listed above is concerning for CA-MRSA pneumonia, particularly if associated with a preceding or concomitant influenza-like illness. In these cases, Linezolid 600 mg IV/PO Q12H can be added while awaiting culture data. Infectious Diseases consult is strongly recommended. Use of Linezolid monotherapy for MRSA bacteremia, even if associated with a pulmonary source, is not recommended. In the absence of necrotizing pneumonia with cavitation, empiric coverage for CA-MRSA can be deferred until sputum and blood culture results return given their high diagnostic yield for CA-MRSA.

• Respiratory viruses: Respiratory viruses can cause primary viral pneumonia as well as lead to bacterial superinfection. Strongly consider testing all patients with CAP during respiratory virus season (see p. 93).

References:  
S. pneumo antigen: Arch Intern Med 2011;171(2):166–72  
3 days of therapy for CAP: BMJ 2006;332:1355.
<table>
<thead>
<tr>
<th>Organism</th>
<th>Preferred therapy</th>
<th>PCN allergy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae PCN susceptible</td>
<td>Penicillin G 1 million units IV Q6H OR Amoxicillin 500 mg PO TID</td>
<td><strong>Non-severe reaction:</strong> Cefpodoxime 200 mg PO BID OR Cefdinir 300 mg PO BID</td>
<td><strong>Severe reaction:</strong> Azithromycin* [500 mg PO daily X 3 days OR 500 mg once, then 250 mg PO daily X 4 days] OR Moxifloxacin 400 mg IV/PO daily (if Erythromycin resistant)</td>
</tr>
<tr>
<td>S. pneumoniae PCN intermediate or urine antigen positive</td>
<td>Penicillin G 1 million units IV Q6H OR Amoxicillin 1 g PO TID</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td>S. pneumoniae PCN resistant, cephalosporin susceptible</td>
<td>Ceftriaxone 1 g IV Q24 OR Cefpodoxime 200 mg PO BID OR Cefdinir 300 mg PO BID</td>
<td>Moxifloxacin 400 mg IV/PO Q24H</td>
<td>None of the S. pneumoniae isolates at (excluding oncology) are resistant JHH to PCN</td>
</tr>
<tr>
<td>H. influenzae non-beta-lactamase producing (Ampicillin susceptible)</td>
<td>Ampicillin 1 g IV Q6H OR Amoxicillin 500 mg PO TID</td>
<td>Azithromycin* [500 mg PO daily X 3 days OR 500 mg once, then 250 mg PO daily X 4 days] OR Cefpodoxime 200 mg PO BID OR Cefdinir 300 mg PO BID OR Doxycycline† 100 mg PO BID OR Moxifloxacin 400 mg IV/PO daily (if resistant to other options)</td>
<td>75% of H. influenzae isolates at JHH (excluding oncology) are susceptible to Ampicillin, 100% to Ceftriaxone, 65% to Tetracycline, and 100% to Moxifloxacin</td>
</tr>
<tr>
<td>Organism</td>
<td>Preferred therapy</td>
<td>PCN allergy</td>
<td>Notes</td>
</tr>
<tr>
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</tr>
<tr>
<td><em>H. influenzae</em> beta-lactamase producing (Ampicillin resistant)</td>
<td>Ampicillin/subactam 1.5 g Q6H OR Amoxicillin/clavulanate 875 mg PO BID</td>
<td>Azithromycin* [500 mg PO daily X 3 days OR 500 mg once, then 250 mg PO daily X 4 days] OR Cefpodoxime 200 mg PO BID OR Cefdinir 300 mg PO BID OR Doxycycline† 100 mg PO BID OR Moxifloxacin 400 mg IV/PO Q24H (if resistant to other options)</td>
<td></td>
</tr>
<tr>
<td><em>L. pneumophilia</em></td>
<td>Azithromycin 500 mg IV/PO Q24H OR Moxifloxacin 400 mg IV/PO Q24H</td>
<td>Azithromycin 500 mg IV/PO Q24H x 7-10 days OR Moxifloxacin 400 mg IV/PO Q24H X 10-14 days</td>
<td></td>
</tr>
<tr>
<td>Culture and urine antigen negative</td>
<td>Cefpodoxime 200 mg PO BID OR Cefdinir 300 mg PO BID OR Amoxicillin/clavulanate XR 2 g PO BID</td>
<td>Moxifloxacin 400 mg IV/PO Q24H</td>
<td>45% of <em>S. pneumoniae</em> isolates at JHH (excluding oncology) are susceptible to Erythromycin (Erythromycin susceptibilities predict Azithromycin susceptibilities for <em>S. pneumoniae</em>) and 73% are susceptible to Tetracycline; therefore, these agents are suboptimal for empiric step-down therapy</td>
</tr>
</tbody>
</table>

*if Erythromycin susceptible; † if Tetracycline susceptible*
Healthcare-acquired pneumonia (NOT ventilator-associated)

NOTE: If the patient is on antibiotic therapy or has recently been on antibiotic therapy, choose an agent from a different class.

EMPIRIC TREATMENT

Patient with mild to moderate illness (e.g., not in or transferring to the ICU/intermediate care unit, no or minimal oxygen requirement, no hypotension)

- Ceftriaxone* 1 g IV Q24H

  OR

- Severe PCN allergy: Moxifloxacin 400 mg IV/PO Q24H

Patient with severe illness (e.g., in or transferring to the ICU/intermediate care unit, concern for sepsis, significant oxygen requirement, multi-lobar consolidation)

- Cefepime* 2 g IV Q8H ± Vancomycin† (see dosing section, p. 150)

  OR

- Piperacillin/tazobactam* 4.5 g IV Q6H ± Vancomycin† (see dosing section, p. 150)

  OR

- Severe PCN allergy: Vancomycin (see dosing section, p. 150) PLUS Ciprofloxacin 400 mg IV Q8H ± Gentamicin (see dosing section, p. 146)

*Consider adding Azithromycin 500 mg IV/PO Q24H if the patient is immunosuppressed or coming from a nursing home or long term care facility to cover Legionella

†Add Vancomycin in patients with a history of MRSA colonization or infection, necrotizing pneumonia, pneumonia after a respiratory viral illness, ill patients coming from a nursing home or long term care facility, sepsis

Patient with history of or risk factors for Pseudomonas and other resistant Gram-negative organisms (e.g., bronchiectasis; broad-spectrum antibiotics for > 7 days in the past month; prolonged hospitalization > 7 days; debilitated nursing home resident; recent mechanical ventilation > 48 hours; immunocompromised due to solid organ transplant, hematologic malignancy, BMT, active chemotherapy, prednisone > 20 mg daily for > 3 weeks): treat as severe illness with tailoring of antibiotic based on past culture data

NOTE: Always narrow therapy based on cultures results

Oral step down therapy (if no sputum culture data to guide therapy)

- Cefpodoxime 400 mg PO BID (if on Ceftriaxone) OR Moxifloxacin 400 mg PO daily

Duration: if pneumonia confirmed 5-7 days; if pneumonia diagnosis is questionable and patient improves, can considered stopping therapy after 3 days

TREATMENT NOTES

Microbiology

- Enterococci and candida species are often isolated from the sputum in hospitalized patients. In general, they should be considered to be colonizing organisms and should not be treated with antimicrobials.
Antimicrobial management of “aspiration events”

- Prophylactic antibiotics ARE NOT recommended for patients who are at increased risk for aspiration.
- Immediate treatment is indicated for patients who have small-bowel obstructions or are on acid suppression therapy given the increased risk of gastric colonization.
- Antibiotic treatment of patients who develop fever, leukocytosis and infiltrates in the first 48 hours after an aspiration is likely unnecessary since most aspiration pneumonias are chemical and antibiotic treatment may only select for more resistant organisms.
- Treatment IS recommended for patients who have symptoms for more than 48 hours or who are severely ill.

References:

Ventilator-associated pneumonia (VAP)

- Sputum cultures should be obtained prior to starting antibiotics or if patient is failing therapy by endotracheal suction or invasive techniques. ET suction appears just as sensitive but less specific than invasive methods.
- **Empiric treatment MUST be narrowed as soon as sputum culture results are known.**
- If the patient is on antibiotic therapy or has recently been on antibiotic therapy, choose an agent from a different class.

Optimal treatment can likely be based on severity of illness as determined by the Clinical Pulmonary Infection Score (CPIS).

**Calculating the Clinical Pulmonary Infection Score (CPIS)**

<table>
<thead>
<tr>
<th></th>
<th>0 points</th>
<th>1 point</th>
<th>2 points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Temperature (°C)</strong></td>
<td>36.5 to 38.4</td>
<td>38.5 to 38.9</td>
<td>≤ 36.4 or ≥ 39</td>
</tr>
<tr>
<td><strong>Peripheral WBC</strong></td>
<td>4,000 – 11,000</td>
<td>&lt; 4,000 or &gt; 11,000</td>
<td>&gt; 50% bands: add 1 extra point</td>
</tr>
<tr>
<td><strong>Tracheal secretions</strong></td>
<td>None</td>
<td>Non-purulent</td>
<td>Purulent</td>
</tr>
<tr>
<td><strong>Chest X-ray</strong></td>
<td>No infiltrate</td>
<td>Diffuse or patchy infiltrates</td>
<td>Localized infiltrate</td>
</tr>
<tr>
<td><strong>Progression of infiltrate from prior radiographs</strong></td>
<td>None</td>
<td></td>
<td>Progression (ARDS, CHF thought unlikely)</td>
</tr>
<tr>
<td><strong>Culture of ET suction</strong></td>
<td>No growth/light growth</td>
<td>Heavy growth Same bacteria on gram stain: add 1 extra point</td>
<td></td>
</tr>
<tr>
<td><strong>Oxygenation (PaO2/FiO2)</strong></td>
<td>&gt; 240 or ARDS</td>
<td></td>
<td>≤ 240 and no ARDS</td>
</tr>
</tbody>
</table>
EMPIRIC TREATMENT

If the CPIS is ≤ 6
• VAP is unlikely
• If VAP strongly suspected see treatment recommendations below
• If CPIS remains ≤ 6 after 3 days, antibiotics can be stopped in most cases

If the CPIS is > 6

Early-onset VAP (occurring within 72 hours of hospitalization and patient has not been hospitalized or resided in a nursing home, long-term care or rehabilitation facility in the past 3 months)

Etiology: *S. pneumoniae, H. influenzae, S. aureus*
• Ceftriaxone 1 g IV Q24H
  OR
• Severe PCN allergy: Moxifloxacin 400 mg IV Q24H

Late-onset VAP (all VAP that is not early-onset)

Etiology: *S. aureus, P. aeruginosa, other Gram-negative bacilli*
• Vancomycin (see dosing section, p. 150) PLUS [Piperacillin/tazobactam 4.5 g IV Q6H OR Cefepime 2 g IV OR Q8H] ± Gentamicin (see dosing section, p. 146)
  OR
• Severe PCN allergy: Vancomycin (see dosing section, p. 150) PLUS [Ciprofloxacin 400 mg IV Q8H OR Aztreonam 2 g IV Q8H] PLUS Gentamicin (see dosing section, p. 146)

Enterococci and candida species are often isolated from sputum in hospitalized patients. In general, they should be considered to be colonizing organisms and should not be treated with antimicrobials.

If the patient is immunocompromised, consider adding Azithromycin 500 mg Q24H to Piperacillin/tazobactam, Cefepime or Aztreonam to cover *Legionella*

Duration
• **3 days** if CPIS remains ≤ 6 in patients with initial CPIS ≤ 6; VAP is unlikely
• **7 days** if the patient has clinical improvement
• If symptoms persist at 7 days consider alternative source and/or bronchoscopy with quantitative cultures
• VAP associated with *S. aureus* bacteremia should be treated for at least 14 days
TREATMENT NOTES

- Treatment MUST be narrowed based on culture results
- Tobramycin is recommended as a second agent to broaden empiric coverage rather than fluoroquinolones because of high rates of resistance to fluoroquinolones in the institution.
- Antimicrobial therapy should be tailored once susceptibilities are known. Vancomycin should be stopped if resistant Gram-positive organisms are not recovered. Gram-negative coverage can be reduced to a single susceptible agent in most cases. The benefits of combination therapy in the treatment of Pseudomonas are not well documented; if it is desired, then consider giving it for the first 72 hours of therapy only.

Diagnosis

- VAP is difficult to diagnose.
- Bacteria in endotracheal suction may represent tracheal colonization and NOT infection.
- Quantitative cultures of BAL fluid can help distinguish between colonization and infection; ≥ 10^4 cfu/ml is considered significant growth.

Other considerations

- Tracheal colonization of Gram-negatives and S. aureus is not eradicated even though lower airways are sterilized. Thus, post-treatment cultures in the absence of clinical deterioration (fever, rising WBC, new infiltrates, worsening ventilatory status) are not recommended.
- Inadequate initial treatment of VAP is associated with higher mortality (even if treatment is changed once culture results are known).

References:
Clinical response to VAP: AJRCCM 2001;163:1371-1375.
Antibiotic selection and dosing for cystic fibrosis patients

- Therapy should be based on culture and susceptibility data when available; the agent with the narrowest spectrum of activity should be selected preferentially
- If possible, stop failing antibiotics when initiating new antibiotics
- High doses of antibiotics should be used to maximize lung penetration and reduce the risk of emergence of resistance (see below)

TREATMENT NOTES FOR SPECIFIC ORGANISMS

- **Pseudomonas aeruginosa**
  - Piperacillin, Cefepime, and Ceftazidime should be used preferentially to Meropenem to minimize the induction of resistance to beta-lactams by Meropenem
  - These agents are generally combined with high-dose aminoglycosides based on *in vitro* evidence that there is synergy against *Pseudomonas*
  - For patients with penicillin allergy, Ciprofloxacin or Aztreonam can be combined with an aminoglycoside; desensitization to beta-lactams or carbapenems should be strongly considered
  - In patients intolerant or resistant to aminoglycosides, Colistin can be added
  - Continuous infusion of beta-lactams can be considered in some patients; see p. 28 for more information.
  - Inhaled Tobramycin and Colistin can be used as adjunctive therapy

- **Stenotrophomonas maltophilia**
  - *S. maltophilia* isolated from sputum usually represents colonization.
  - If superinfection is suspected, TMP/SMX is the first line agent.
  - Ticarcillin/clavulanate OR Minocycline may be used if susceptible in patients who are allergic or intolerant or resistant to TMP/SMX.

- **Staphylococcus aureus**
  - *S. aureus* isolated from sputum can indicate colonization or infection.
  - Whether treating colonization with *S. aureus* in CF patients improves outcomes is an area of active research, although historically such colonization has not been successfully eradicated with antimicrobial therapy. If this is attempted, possible agents include Dicloxacillin, Cefazolin or Cephalexin for MSSA and Clindamycin, TMP/SMX, Doxycycline, and Minocycline for MRSA.
  - Oxacillin is the drug of choice for MSSA pneumonia; Vancomycin or Linezolid can be used for MRSA pneumonia.
Antibiotic doses for cystic fibrosis infections – normal renal function

- Ceftazidime: 2 g IV Q8H
- Piperacillin/tazobactam: 3.375 g IV Q4H
- Cefepime: 2 g IV Q8H
- Meropenem: 2 g IV Q8H
- Ciprofloxacin: 750 mg PO Q12H OR 400 mg IV Q8H
- Aztreonam: 2 g IV Q8H
- Ticarcillin/clavulanate: 3.1 g IV Q4H
- TMP/SMX for *S. maltophilia*: 5 mg/kg IV/PO Q8H
- TMP/SMX for *S. aureus*: 2 DS tablets PO BID
- Colistin: 3-6 mg/kg/day IV divided in 3 doses
- Inhaled Tobramycin (*TOBI®*): 300 mg Q12H
- Inhaled Colistin: 75-150 mg Q12H depending on the delivery system

**Intravenous Tobramycin dosing and monitoring:**

- Loading dose: 10 mg/kg/day given over 1 hour.
- Peak is recommended after first dose, 1 hour after the end of infusion with goal of 20-30 and trough at 23 hours with goal < 1 mcg/mL.
- Doses can be increased up to 12 mg/kg/day if adequate peaks are not achieved. If trough is too low or too high, interval should be changed.
Respiratory virus diagnosis and management

Diagnosis

- Respiratory virus testing should be obtained year round on any patient for whom there is a clinical suspicion of respiratory virus infection. In addition, during influenza and RSV season testing should be obtained in patients with:
  - Fever and influenza-like symptoms (sore throat, myalgia, arthralgia, cough, runny nose and/or headache)
  - Suspected bronchiolitis or pneumonia
  - COPD/asthma exacerbation or respiratory failure
  - Unexplained CHF exacerbation
  - Elderly patients with unexplained new onset malaise
  - Pregnant patients with unexplained respiratory symptoms
  - Nonspecific symptoms and a documented exposure to someone with a respiratory illness
  - Respiratory virus testing at JHH (one NP flocked swab should be submitted for either panel)
  - Testing for immunocompetent hosts: rapid nucleic acid test for RSV and influenza A/B
  - Testing for immunocompromised hosts, patients being admitted to the ICU, and patients with structural lung disease: extended panel for RSV, influenza A/B, adenovirus, human metapneumovirus, parainfluenza 1-3, and rhinovirus

Treatment of influenza in inpatients

- Empiric treatment of adult inpatients should be considered in the following situations during influenza season:
  - Patients with fever and influenza-like symptoms, unexplained interstitial pneumonia or new respiratory failure without an obvious non-influenza cause
  - Treatment should be initiated in all patients who are admitted to the hospital and have influenza with symptom onset in the past 48-72 hours
  - The utility of treatment of patients who present late in the course of disease is uncertain and the decision to treat these patients can be made on a case-by-case basis
  - Antiviral choice is dependent on the susceptibility of circulating strains which may vary from season to season (see www.hopkinsmedicine.org/amp for current recommendations)
  - Duration: 5 days except for patients with solid organ transplant, hematologic malignancy, or BMT in whom 10 days can be given because of prolonged viral shedding
Infection control

- All individuals with suspected respiratory virus infection should be placed on droplet precautions. A private room is required, unless patients are cohorted. When outside of their room (i.e. during transport) patients should wear a mask.
- All health care workers must receive the influenza vaccine yearly.
- Personnel with direct patient care or working in clinical areas who have not received the influenza vaccine are required to wear a mask when within 6 feet of a patient. The dates of the mask requirement are determined by HEIC and based on influenza activity in the local community.
- No one with fever may work until at least 24 hours after fever has resolved (without antipyretics). All personnel with respiratory symptoms and fever must call or report to their supervisor and must call Occupational Health Services (OHS).
- Afebrile employees who have respiratory systems must wear a surgical mask during patient contact (≤ 6 ft).
- If an unvaccinated HCW is exposed to a patient with documented influenza who was not on Droplet Precautions, notify HEIC and call Occupational Health Services (OHS) immediately. OHS will decide whether to recommend post-exposure prophylaxis.

Anti-influenza agents

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adult dosing</th>
<th>Side effects</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Oseltamivir | **Treatment:** 75 mg PO twice a day for 5 days  
**Prophylaxis:** 75 mg PO once a day | Common: nausea, vomiting  
Severe: hypersensitivity, neuropsychiatric | Dose adjustment needed for GFR <60 mL/min |
| Zanamivir | **Treatment:** 10 mg (2 oral inhalations) twice daily for 5 days  
**Prophylaxis:** 10 mg (2 oral inhalations) once a day | Common: diarrhea, nausea, cough, headache, and dizziness  
Severe: bronchospasm, hypersensitivity, laryngeal edema, facial swelling | Should NOT be used in patients with chronic underlying airway diseases |
Tuberculosis (TB) infection

Latent TB infection (LTBI)
- Previous infection with *M. tuberculosis* (MTB) that has been contained by the host immune response
- Patient may have a positive test (see below) or suggestive radiographic findings such as calcified granulomata or minimal apical scarring, but do not have symptoms of active TB disease
- Not infectious and does not require isolation

Tests to diagnose latent LTBI
- Both Tuberculin skin test (TST) and Interferon gamma release assay (IGRA) are imperfect, and may offer discordant results (~20%). Sensitivity of TST and IGRA are similar.
- Both tests should be interpreted in the context of epidemiologic risk of TB exposure
- LTBI therapy should not be initiated until active TB is excluded (by symptoms and radiography). Individuals with signs or symptoms of active TB require further diagnostic workup before LTBI therapy.
- LTBI therapy should not be started in the hospital without a clear follow-up plan

Tuberculin skin test (TST)
- Intradermal injection of purified protein derivative (PPD) and measurement of induration diameter in 48-72
- Criteria for a positive test are
  - \( \geq 5 \text{ mm} \) – high risk of developing active TB (e.g., HIV infection, close contact of TB case, immunocompromised)
  - \( \geq 10 \text{ mm} \) – other risk factors for TB infection (HCW, IDU, DM)
  - \( \geq 15 \text{ mm} \) – no risk factors for TB

Interferon gamma release assay (IGRA)
- IGRA measure lymphocyte release of interferon gamma in response to stimulation by MTB antigens.
- IGRA are less affected by BCG vaccination status or infection with most atypical mycobacteria (except *M. marinum* and *M. kansasii*) than TST
- Quantiferon-Gold-In-Tube (QGIT) is used at JHH. Results are reported as positive, negative, or indeterminate. An indeterminate result means that the test result is not valid, which can be due to errors in specimen collection (most common- insufficient/incorrect shaking of tubes after blood draw or processing delays), or associated with certain conditions such as HIV with a low CD4 count, steroid use or other immunosuppression, and malnutrition [albumin <3.5]. Indeterminate results often require a repeat test (ensure proper specimen collection).
- When pre-test probability or prevalence of LTBI is <5% (e.g., US-born without foreign travel), PPV of IGRA is reduced (70-90%, i.e., false-positives) while NPV is high (99%).
- When pre-test probability for infection is high (e.g., foreign-born, ~30% LTBI prevalence), PPV of IGRA increases to ~95-99%, but NPV decreases (80-90%, i.e., false-negatives).
• Quantitative results may be helpful to guide interpretation. Consider ID consultation for results near the threshold for QGIT positive: antigen > 0.35. Serial testing is not advised without ID consultation.

• IGRA do not have good sensitivity or specificity for diagnosis of active TB

**Active TB infection**

• Active replication of MTB causing pulmonary or extrapulmonary signs or symptoms

• Confirmed by positive AFB smear, MTB direct test or culture

• Requires airborne isolation

**When to suspect active TB disease**

**High-risk individuals**

• Recent exposure to a person with known TB; history of a positive TST; HIV infection; injection or non-injection drug use; foreign birth or residence in a region in which TB incidence is high; residents and employees of high-risk congregate settings (e.g. prisons); membership in a medically underserved, low-income population; anti-TNF alpha therapy

**Clinical syndromes**

• Cough of ≥ 2 wk duration, with at least one additional symptom, including fever, night sweats, weight loss, or hemoptysis

• Any unexplained respiratory illness of ≥ 2 wk duration in a patient at high risk for TB

• Any patient with HIV infection and unexplained cough and fever

• Any patient on anti-TNF alpha therapy with unexplained fever

• Community-acquired pneumonia which has not improved after 7 days of appropriate treatment

• Incidental findings on chest radiograph suggestive of TB (even if symptoms are minimal or absent) in a patient at high risk for TB

**Radiographic findings**

• Primary TB (often unrecognized): Can resemble CAP and involve any lobes; hilar adenopathy, pleural effusions are common; cavitation is uncommon. Findings often resolve after 1–2 months. These are common findings in patients with advanced HIV infection and TB.

• Reactivation TB: Infiltrates with or without cavitation in the upper lobes or the superior segments of the lower lobes; hilar adenopathy is variable; CT scan may have “tree-in-bud” appearance.

**Diagnosis**

• Patients with characteristic syndromes and radiographic findings should have expectorated sputum obtained for AFB smear and culture.

• Sensitivity of AFB smear on expectorated sputum is 50–70%; it is lower in HIV+ patients. Morning expectorated sputum, induced sputum, bronchoscopy have higher sensitivity. AFB culture of lower respiratory tract specimens is considered the gold standard.

• AFB smear and culture should be obtained regardless of CXR findings in patients with high clinical suspicion, HIV infection or other immunocompromised states. CXR is normal in approximately 10% of HIV-infected patients with pulmonary TB.
• Obtain at least 3 sputum specimens (induced or expectorated) when trying to diagnose TB in patients who are smear negative so as to increase the chance of isolating the organism for diagnosis and susceptibility testing.

**Infection control**
Airborne precautions are required in the following cases:
• Suspicion of disease sufficiently high to warrant obtaining sputum AFB smear/culture as described above
• Positive AFB smear or culture until diagnosis of TB vs. NTM is confirmed

**Algorithm for isolation when active TB is suspected**

1. **AIRBORNE PRECAUTIONS IN NEGATIVE PRESSURE ROOM**
   - Collect specimen(s) for AFB smear and culture

2. **Expectorated sputum (3 required)**
   - **Smear positive**
   - Mycobacterium Tuberculosis Direct Test (MTD) automatically performed
   - **MTC positive**
     - Continue isolation until at least 14 days of therapy AND clinical improvement AND 3 consecutive negative smears (Call HEIC for approval to D/C isolation on smear positive patient.)
   - **MTC negative**
     - Obtain 2nd and 3rd specimen*

3. **Induced sputum or bronchoscopy**
   - **Smear positive**
   - **MTD test performed**
     - **MTD positive**
       - If pt highly suspected for TB, await culture result and continue isolation. Otherwise, CALL HEIC 5-8384 to DISCONTINUE ISOLATION
     - **MTD negative**
       - **Smear negative**
         - CALL HEIC 5-8384 TO DISCONTINUE ISOLATION

4. **Smear negative**
   - **Obtain 2nd and 3rd specimen**
   - **MTD test performed**
     - **MTD positive**
       - Continue isolation until at least 14 days of therapy AND clinical improvement AND 3 consecutive negative smears (Call HEIC for approval to D/C isolation on smear positive patient.)
     - **MTD negative**
       - **Smear negative**
         - CALL HEIC 5-8384 TO DISCONTINUE ISOLATION

*One expectorated sputum must be a first morning specimen; samples should be collected at least 8 hours apart.
TUBERCULOSIS (TB) infection

TREATMENT

Active TB
- ID consult is strongly recommended
- Therapy should be initiated for patients with positive AFB smear and clinical findings consistent with active TB.
- Therapy should be considered for patients with negative AFB smears when suspicion of TB is high and no alternate diagnosis exists. Multiple specimens should be obtained for culture prior to treatment.
- Four drugs are necessary for initial phase (2 months).
  - Isoniazid (INH) 300 mg (5 mg/kg) PO daily
  - Rifampin (RIF) 600 mg (10 mg/kg) PO daily
  - Pyrazinamide (PZA) 1000 mg PO daily (40–55 kg) OR 1500 mg PO daily (56–75 kg) OR 2000 mg PO daily (76–90 kg)
  - Ethambutol (EMB) 800 mg PO daily (40–55 kg) OR 1200 mg PO daily (56–75 kg) OR 1600 mg PO daily (76–90 kg)
- *Max dose regardless of weight.
- Pyridoxine 25 mg PO daily is recommended to prevent INH associated peripheral neuropathy in patients with HIV, malnutrition, alcohol abuse, diabetes mellitus, renal failure or in pregnant or breastfeeding women.

Drug toxicity and monitoring
- Isoniazid: asymptomatic elevation in hepatic enzymes, serious and fatal hepatitis, peripheral neurotoxicity
- Rifampin: orange discoloration of body fluids, hepatotoxicity, pruritis with or without rash
- Pyrazinamide: hepatotoxicity, nongouty polyarthralgia, asymptomatic hyperuricemia, acute gouty arthritis
- Ethambutol: retrobulbar and peripheral neuritis
- Monitoring: baseline hepatic transaminases, bilirubin, alkaline phosphatase, creatinine and CBC are recommended for all adults initiating TB treatment. Monthly hepatic panel is recommended for patients with baseline abnormalities, history of liver disease or viral hepatitis, chronic alcohol consumption, HIV, IVDU, pregnancy or immediate post-partum state or those taking other potentially hepatotoxic medications. Therapy should be discontinued immediately if AST and ALT are >3 times the upper limit of normal (ULN) in the presence of jaundice or hepatitis symptoms or >5 times the ULN in the absence of symptoms.

References:
Sepsis with no clear source

NOTE: Refer to specific sections of these guidelines for empiric treatment recommendations for specific sources of infection

EMPIRIC TREATMENT

Cultures MUST be sent to help guide therapy.

• [Piperacillin/tazobactam* 4.5 g IV Q6H OR Cefepime* 2 g IV Q8H] ± Vancomycin (see dosing section, p. 150) (if at risk for MRSA) ± Gentamicin (see dosing section, p. 146)
  OR
• Severe PCN allergy: [Aztreonam 2 g IV Q8H OR Ciprofloxacin 400 mg IV Q8H] PLUS Gentamicin (see dosing section, p. 146) PLUS Vancomycin (see dosing section, p. 150)

*NOTE: If patient has history of ESBL-producing organism or has suspected intra abdominal sepsis and recent prolonged exposure (≥ 7 days) to Piperacillin/tazobactam or Cefepime, substitute with Meropenem 1 g IV Q8H.

Risk factors for MRSA
• Central venous catheter in place
• Other indwelling hardware
• Known colonization with MRSA
• Recent (within 3 months) or current prolonged hospitalization > 2 weeks
• Transfer from a nursing home or subacute facility
• Injection drug use

TREATMENT NOTES

• For patients with renal insufficiency or aminoglycoside intolerance, a beta-lactam may be combined with a fluoroquinolone IF 2 agents are needed.
• Potential sources (e.g., pneumonia, peritonitis, etc.) should be considered when selecting therapy.
• Empiric therapy is ONLY appropriate while cultures are pending (72 hours max).
• Vancomycin should almost always be stopped if no resistant Gram-positive organisms are recovered in cultures.
Skin, soft-tissue, and bone infections

Cellulitis
• Always elevate affected extremity. Treatment failure is more commonly due to failure to elevate than failure of antibiotics.
• Improvement of erythema can take days, especially in patients with lymphedema, because dead bacteria in the skin continue to induce inflammation.

Non-suppurative cellulitis
Defined as cellulitis with intact skin and no evidence of purulent drainage. Usually caused by beta-hemolytic streptococci (e.g. group A, B, C, G streptococci) and MSSA.

TREATMENT
Oral (mild disease)
• Amoxicillin/clavulanate 875 PO Q12H
  OR
• Cephalexin 500 mg PO Q6H
  OR
• PCN allergy: Clindamycin 300 mg PO Q8H

Parenteral (moderate to severe disease)
• Ampicillin/subbactam 1.5 g IV Q6H
  OR
• Cefazolin 1 g IV Q8H
  OR
• PCN allergy: Clindamycin 600 mg IV Q8H

Duration: 5-7 days

TREATMENT NOTES
• All beta-hemolytic streptococci are susceptible to penicillin
• Clindamycin resistance is seen in 16-33% of group B, C, and G strep but remains low in group A strep (4–7%)
• Duration: 5-7 days

Suppurative cellulitis
Defined as cellulitis with purulent drainage or exudates in the absence of a drainable abscess. Usually caused by S. aureus (MSSA and MRSA).

TREATMENT
Oral (mild disease)
• TMP/SMX 1-2 DS tab PO BID
  OR
• Doxycycline 100 mg PO BID OR Minocycline 100 mg PO BID
  OR
• Clindamycin 300 mg PO Q8H
6.16 Skin, soft-tissue, and bone infections

OR
- Clindamycin 600 mg IV Q8H (if parenteral therapy is needed)

Parenteral (moderate to severe disease)
- Vancomycin (see dosing section, p. 150)

Duration: 5-7 days

TREATMENT NOTES
- Resistance to fluoroquinolones in S. aureus is common and develops quickly; ≥ 95% of MRSA isolates are resistant to fluoroquinolones. Monotherapy with fluoroquinolones for S. aureus infections is not recommended.
- Rifampin should NEVER be used as monotherapy because resistance develops rapidly.
- There is no evidence that Linezolid is superior to TMP/SMX, Doxycycline, or Clindamycin in the management of skin infection or osteomyelitis. Linezolid should only be considered when the S. aureus isolate is resistant to or the patient is intolerant to these agents.

Less common causes of cellulitis
- With bullae, vesicles, and ulcers after exposure to seawater or raw oysters, consider Vibrio vulnificus, especially in patients with liver disease. Rare, but rapidly fatal if untreated. Treat with Ceftriaxone 1 g IV Q24H PLUS Doxycycline 100 mg PO BID.
- Neutropenic, solid organ transplant, and cirrhotic patients may have cellulitis due to Gram-negative organisms. Consider expanding coverage in these cases.
- If eschar, consider angioinvasive organisms (GNR, aspergillosis, mold). ID consult is recommended.
- Animal and human bites: Pasteurella multocida should be covered in cat and dog bites. Treat with Amoxicillin/clavulanate 875 mg PO BID OR Ampicillin/sulbactam 1.5–3 g IV Q6H. If PCN allergy: Moxifloxacin 400 mg PO/IV Q24H.

Cutaneous abscess
- Incision and drainage (I&D) is the primary treatment for a cutaneous abscess.
- Lesions that appear superficial can often have associated abscess formation that is not clearly appreciated without debridement of the wound or, on occasion, additional imaging.
- At the time of I&D, a sample should be obtained for culture and sensitivity testing.
- Most studies that have been published to date suggest that antibiotics are adjunct to I&D in the management of uncomplicated skin abscesses caused by CA-MRSA.
• Indications for antimicrobial therapy in patients with cutaneous abscesses:
  • Severe or rapidly progressive infections
  • The presence of extensive associated cellulitis
  • Signs and symptoms of systemic illness
  • Associated septic phlebitis
  • Diabetes or other immune suppression
  • Advanced age
  • Location of the abscess in an area where complete drainage is difficult (e.g. face, genitalia)
  • Lack of response to incision and drainage alone
• Therapy should be given before incision and drainage in patients with prosthetic heart valves or other conditions placing them at high risk for endocarditis.

EMPIRIC TREATMENT
If antibiotic treatment is thought to be necessary, regimens are the same as for suppurative cellulitis above.

Management of recurrent MRSA skin infections

1. Education regarding approaches to personal and hand hygiene
  • Practice frequent hand hygiene with soap and water and/or alcohol based hand gels, especially after touching infected skin or wound bandages.
  • Cover draining wounds with clean, dry bandages
  • Do not share personal items (e.g. razors; used towels and clothing before washing)
  • Regular bathing
  • Avoid all shaving
  • Launder clothing, sheets, towels in hottest suitable temperature
  • Clean all personal sporting clothing/equipment

2. Decontamination of the environment
  • Clean high touch areas in the bathroom with a disinfectant active against S. aureus daily (e.g., 10% dilute bleach).

3. Topical decolonization (consider if a patient has ≥ 2 episodes in 1 year or other household members develop infection)
  • Mupirocin twice daily for 5 days may be considered in patients with documented evidence of MRSA nasal colonization; Mupirocin therapy should be initiated after resolution of acute infection. Mupirocin should not be used in patients or patients’ family members who are not documented to have MRSA nasal colonization.
6.16 Skin, soft-tissue, and bone infections

- Bathing or showering with chlorhexidine or hexachlorophine (or dilute bleach baths) every other day for 1 week then twice weekly; do not get these substances into ears or eyes
- Systemic antibiotics are NOT recommended solely for decolonization

4. Evaluation of other family members
- Intra-family transmission should be assessed and if present, all members should participate in hygiene and decolonization strategies above, starting at that same time and after the acute infection is controlled.

NOTE: Data on efficacy and durability of the decontamination and decolonization strategies described above are limited.

References:

Diabetic foot infections

EMPIRIC TREATMENT

Treatment depends on clinical severity

<table>
<thead>
<tr>
<th>Infection Severity</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninfected</td>
<td>No purulence or inflammation*</td>
</tr>
<tr>
<td>Mild</td>
<td>Presence of purulence and ≥ 1 sign of inflammation* and cellulitis (if present) ≤ 2 cm around ulcer limited to skin or superficial subcutaneous tissue</td>
</tr>
<tr>
<td>Moderate</td>
<td>Same as mild PLUS at least one of the following: &gt; 2 cm of cellulitis, lymphangitic streaking, spread beneath the superficial fascia, deep tissue abscess, gangrene, involvement of muscle, tendon, joint, or bone</td>
</tr>
<tr>
<td>Severe</td>
<td>Any of above PLUS systemic toxicity or metabolic instability</td>
</tr>
</tbody>
</table>

*Mild infections

Oral regimens
- Amoxicillin/clavulanate 875 mg PO BID
  OR
- Cephalexin 500 mg PO QID
  OR
- Clindamycin 300 mg PO TID (covers MRSA)

Parenteral regimens
- Clindamycin 600 mg IV Q8H (covers MRSA)
  OR
6.16 Skin, soft-tissue, and bone infections

- Oxacillin 1-2 g IV Q4H
  **OR**
- Cefazolin 1 g IV Q8H

### MODERATE INFECTIONS
- Ertapenem 1 g Q24H
  **OR**
- [Ciprofloxacin* 500 mg PO BID OR Ciprofloxacin* 400 mg IV Q12H] PLUS ONE of the following [Clindamycin 600 mg IV Q8H/300 mg PO TID OR Metronidazole 500 mg IV/PO TID]
  * **BUT** avoid fluoroquinolones in patients who were on them as outpatients.

**If patient at risk for MRSA, add Vancomycin to regimens that do not include Clindamycin.**

#### Risk factors for MRSA
- History of colonization or infection with MRSA
- Recent (within 3 months) or current prolonged hospitalization > 2 weeks
- Transfer from a nursing home or subacute facility
- Injection drug use

### SEVERE INFECTIONS
- Piperocillin/tazobactam 4.5 g IV Q6H
  **OR**
- [Ciprofloxacin* 400 mg IV Q8H OR Aztreonam 2 g IV Q8H] PLUS Clindamycin 600 mg IV Q8H
  * **Avoid fluoroquinolones in patients who were on them as outpatients.**

**If patient at risk for MRSA (see above)**
- Piperacillin/tazobactam 4.5 g IV Q6H **PLUS** Vancomycin (see dosing section, p. 150)
  **OR**
- [Ciprofloxacin* 400 mg IV Q8H OR Aztreonam 2 g IV Q8H] **PLUS** Metronidazole 500 mg IV Q8H **PLUS** Vancomycin (see dosing section, p. 150)
  * **Avoid fluoroquinolones in patients who were on them as outpatients**

### TREATMENT NOTES

#### Management
- A multidisciplinary approach to management should include wound care consultation, assessment of vascular supply, vascular and/or general surgery consultation and infectious diseases consultation.
- Consider necrotizing fasciitis in patients who are severely ill.
- Antibiotic therapy should be narrowed based on culture results.
6.16 Skin, soft-tissue, and bone infections

Microbiology
- Cellulitis without open wound or infected ulcer, antibiotic naïve: beta-hemolytic streptococci, *S. aureus*
- Infected ulcer, chronic or previously treated with antibiotics: *S. aureus*, beta-hemolytic streptococci, Enterobacteriaceae
- Exposure to soaking, whirlpool, hot tub: usually polymicrobial, may involve *Pseudomonas*
- Chronic wounds with prolonged exposure to antibiotics: aerobic Gram-positive cocci (GPC), Diphtheroids, Enterobacteriaceae, other Gram-negative rods (GNR) including *Pseudomonas*
- Necrosis or gangrene: mixed aerobic GPC and GNR, anaerobes

Diagnosis
- Cultures of the ulcer base after debridement can help guide therapy. Biopsy of unexposed bone is NOT recommended. Avoid swabbing non-debrided ulcers or wound drainage.
- Ulcer floor should be probed carefully. If bone can be touched with a metal probe then the patient should be treated for osteomyelitis with antibiotics in addition to surgical debridement.
- Plantar fasciitis and a deep foot-space infection can be present. Consider imaging to look for deep infections.
- Putrid discharge is diagnostic of the presence of anaerobes.
- MRI is more sensitive and specific than other modalities for detection of soft-tissue lesions and osteomyelitis.

Duration
- Duration of treatment will depend on rapidity of response and presence of adequate blood supply.
- Likely need shorter treatment with adequate surgical intervention (7–10 days post-op) and longer for osteomyelitis.
- Change to oral regimen when patient is stable.

Reference:

Surgical-site infections (SSI)

EMPIRIC TREATMENT
Infections following clean procedures (e.g. orthopedic joint replacements, open reduction of closed fractures, vascular procedures, median sternotomy, craniotomy, breast and hernia procedures)
- Oxacillin 1–2 g IV Q4H
  OR
- Cefazolin 1 g IV Q8H
  OR
• PCN allergy: Clindamycin 600 mg IV Q8H
  OR
• Involvement of hardware or MRSA suspected: Vancomycin
  (see dosing section, p. 150)

**Exception:** Saphenous vein graft harvest site infections should be treated with Ertapenem 1 g IV Q24H

**Infections following contaminated procedures** (GI/GU procedures, oropharyngeal procedures, obstetrical and gynecology procedures)

Patients not on broad-spectrum antibiotics at time of surgery and not severely ill
• Ertapenem 1 g IV Q24H
  OR
• PCN allergy: [Ciprofloxacin 500 mg PO BID OR Ciprofloxacin 400 mg IV Q12H] **PLUS** Clindamycin 600 mg IV Q8H

Patients on broad-spectrum antibiotics at time of surgery or severely ill
• Piperacillin/tazobactam 3.375 g IV Q6H ± Vancomycin
  (see dosing section, p. 150) (if hardware present or MRSA suspected)
  OR
• Non-severe PCN allergy: Cefepime 1 g IV Q8H **PLUS** Metronidazole 500 mg IV Q8H ± Vancomycin (see dosing, p. 150) (if hardware present or MRSA suspected)
  OR
• Severe PCN allergy: Vancomycin (see dosing section, p. 150) **PLUS** [Ciprofloxacin 400 mg IV Q8H OR Aztreonam 2 g IV Q8H] **PLUS** Metronidazole 500 mg IV/PO Q8H

**Deep fascia involvement**
• Treat as necrotizing fasciitis (see subsequent section)

**TREATMENT NOTES**

**Microbiology**
• Following clean procedures (no entry of GI/GU tracts)
  • *Staphylococcus aureus*
  • Streptococci, group A (especially with early onset, < 72 hours)
  • Coagulase-negative staphylococci
• Following clean-contaminated and contaminated procedures (entry of GI/GU tracts with or without gross contamination)
  • Organisms above
  • Gram-negative rods
  • Anaerobes (consider *Clostridia* spp. in early-onset infection, 1–2 days)
• Generally, empiric use of Vancomycin is not indicated because the percentage of SSIs caused by MRSA is low at Johns Hopkins Hospital (10–20%)

**Risk factors for MRSA**
• History of colonization or infection with MRSA
• Recent (within 3 months) or current prolonged hospitalization >2 weeks
• Transfer from a nursing home or subacute facility
• Injection drug use

**Other management issues**
• Many advocate that ALL infected wounds be explored both to debride and to assess depth of involvement.
• Superficial infections may be adequately treated with debridement alone.
• Deeper infections (cellulitis, panniculitis) need adjunctive antibiotics.
• Infections that extend to the fascia should be managed as necrotizing fasciitis.
• Patients with hypotension should have their wounds explored even if they are unremarkable on physical exam.

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**Serious, deep-tissue infections (necrotizing fasciitis)**

**THESE ARE SURGICAL EMERGENCIES!**
**ANTIBIOTICS ARE ONLY AN ADJUNCT TO PROMPT DEBRIDEMENT!**
ID should also be consulted

**EMPIRIC TREATMENT (adjunct to surgery)**
• Vancomycin (see dosing section, p. 150) **PLUS** [Piperacillin/tazobactam 3.375 g IV Q6H OR Cefepime 1 g IV Q8H] **PLUS** Clindamycin 600-900 mg IV Q8H

**OR**
• Severe PCN allergy: Vancomycin (see dosing section, p. 150) **PLUS** [Ciprofloxacin 400 mg IV Q8H ± Gentamicin (see dosing section, p. 146)] **PLUS** Clindamycin 600-900 mg IV Q8H

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**TREATMENT NOTES**

**Conventional nomenclature and microbiology**

**Pyomyositis**
• *S. aureus* most commonly
• Clostridial myonecrosis – *Clostridia* spp. (esp. *C. perfringens*)
• Group A streptococcal myonecrosis
Fasciitis
- Type 1 – Polymicrobial infections with anaerobes, streptococci and Gram-negative rods (Fournier’s gangrene is a type 1 necrotizing fasciitis of the perineum)
- Type 2 – Group A streptococci predominate
- Cases of fasciitis caused by community-associated MRSA strains have been reported

Diagnosis
- Can be difficult – gas production is not universal and is generally absent in streptococcal diseases.
- Maintain high index of suspicion when:
  - Patients are very ill from cellulitis (hypotension, toxic appearance)
  - Pain out of proportion to physical findings
  - Anesthesia over affected area
  - Risk factors such as diabetes, recent surgery or obesity
  - Findings such as skin necrosis or bullae
  - Putrid discharge with thin, “dishwater” pus
- CT scan can help with diagnosis but if suspicion is moderate to high, surgical exploration is the preferred diagnostic test. DO NOT delay surgical intervention to obtain CT.

Reference:

Vertebal osteomyelitis, diskitis, epidural abscess

NOTE: In absence of bacteremia, clinical instability, or signs and symptoms of spinal cord compromise strong consideration should be given to withholding antibiotics until samples of abscess or bone can be obtained for Gram-stain and culture.

EMPIRIC TREATMENT
- Vancomycin (see dosing section, p. 150) ± [Ceftriaxone 2 g Q12H OR Cefepime 2 g IV Q8H]
  OR
- Severe PCN allergy: Vancomycin (see dosing section, p. 150) ± Ciprofloxacin 400 mg IV Q8H
  OR
- Narrow therapy based on culture results.

TREATMENT NOTES
Microbiology
- Gram-positive cocci in 75% of cases with majority S. aureus
- Gram-negative rods in ~10%
Management

- Obtain two sets of blood cultures, ESR, and CRP prior to starting antibiotic therapy.
- Most intravenous drug users and patients without significant co-morbidities do not require empiric coverage for Gram-negative rods.
- Empiric Gram-negative coverage should be used in patients with diabetes, hardware in place or recent surgery, and recurrent urinary tract infections.
- MRI with contrast is the imaging method of choice.
- If blood cultures are negative CT guided needle biopsy/aspiration should be obtained for Gram stain and cultures.
- Emergent surgical consultation is recommended for patients with signs and symptoms of spinal cord compromise.
- Surgical therapy is preferred in many cases of epidural abscess/osteomyelitis (e.g. extensive infection, pre-vertebral abscess, spine instability, hardware involvement). CT-guided aspiration and/or antibiotic therapy alone may be considered in some circumstances. Discussion with infectious diseases and surgery is recommended to optimize management.
- Patients should have frequent assessment of neurologic function, particularly at the time of initial presentation.
- All patients require monitoring for adequate response throughout the treatment course; ID follow up highly recommended.

Duration

- Epidural abscess without osteomyelitis: 4–6 weeks
- Vertebral osteomyelitis ± epidural abscess: 6–12 weeks
- In patients with hardware present prolonged oral suppressive therapy is generally required after completion of IV antibiotics; these decisions should be made in consultation with infectious diseases.

References:
### Bacterial urinary tract infections (UTI)

#### Management of patients WITHOUT a urinary catheter

**NOTE:** Ciprofloxacin is not recommended for empiric treatment for in-patients with non-catheter associated UTI at JHH due to the low rate of *E. coli* susceptibility (71%).

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
<th>Empiric treatment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic bacteriuria</td>
<td>Positive urine culture $\geq 100,000$ CFU/mL with no signs or symptoms</td>
<td>No treatment unless the patient is:</td>
<td>• Obtaining routine cultures in asymptomatic patients is not recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pregnant</td>
<td>• Antibiotics do not decrease asymptomatic bacteriuria or prevent subsequent development of UTIs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• About to undergo a urologic procedure</td>
<td>• The prevalence of asymptomatic bacteriuria is high: 1%-5% in premenopausal women, 3%-9% in postmenopausal women, 40%-50% in long-term care residents and 9%-27% in women with diabetes.</td>
</tr>
<tr>
<td>Acute cystitis</td>
<td>Signs and symptoms (e.g. dysuria, urgency frequency, suprapubic pain) AND pyuria ($&gt;10$ WBC/hpf) AND positive urine culture $\geq 100,000$ CFU/mL</td>
<td>Uncomplicated:</td>
<td>UTIs in men are traditionally considered complicated. UTIs in men in the absence of obstructive pathology (e.g. BPH, stones, strictures) are uncommon. Please critically evaluate your diagnosis of UTI in male patients.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nitrofurantoin (Macrobid®) 100 mg PO Q12H for 5 days (NOT in patients with CrCl &lt;50 ml/min) OR</td>
<td>• Oral therapy is preferred and should be given unless patient is unable to tolerate oral therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cephalexin 500 mg PO Q6H for 5 days OR</td>
<td>• If IV beta-lactams are used empirically for 3 days, no additional therapy is needed for uncomplicated cystitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cefpodoxime 100 mg PO Q12H for 5 days OR</td>
<td>• If IV beta-lactams are used empirically for &lt;3 days or treating complicated cystitis, the patient can be switched to an appropriate oral beta-lactam and duration of IV therapy should be counted towards total duration of therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cefdinir 300 mg PO Q12H for 5 days OR</td>
<td>• Oral Fosfomycin can be used if susceptible for Gram-negative MDR organisms (susceptibilities must be requested)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• TMP/SMX 1 DS tab PO Q12H for 3 days OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• IV option: Cefazolin 1 g IV Q8H for 3 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complicated:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Same regimens as above except duration is 7–14 days</td>
<td></td>
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</tr>
<tr>
<td>Category</td>
<td>Definition</td>
<td>Empiric treatment</td>
<td>Notes</td>
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<tr>
<td>------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Acute pyelonephritis</td>
<td>Signs and symptoms (e.g. fever, flank pain) AND pyuria AND positive urine culture ≥ 100,000 CFU/mL. Many patients will have other evidence of upper tract disease (i.e. leukocytosis, WBC casts, or abnormalities upon imaging)</td>
<td>- Ceftriaxone 1 g IV Q24h OR Ertapeenem 1 g IV Q24h (if history of ESBL) OR PCN allergy: Aztreonam 1 g IV Q8H OR Gentamicin (see dosing section, p. 147) Duration: 7–14 days Hospitalized &gt; 48 h - Cefepine 1 g IV Q8H OR PCN allergy: Aztreonam 1 g IV Q8H OR Gentamicin (see dosing section, p. 147) Duration: 7–14 days</td>
<td>- Oral step-down therapy should be used if organism is susceptible Duration of empiric IV therapy should be counted towards total duration of therapy Oral step-down therapy if organism is susceptible: Ciprofloxacin 500 mg PO Q12H for 7 days TMP/SMX 1 DS PO Q12H for 7-10 days Cefpodoxime 400 mg PO Q12H for 14 days Oral Fosfomycin can be considered if susceptible for Gram-negative MDR organisms (susceptibilities must be requested). Consult ID Pharmacist for dosing.</td>
</tr>
<tr>
<td>Urosepsis</td>
<td>SIRS with urinary source of infection</td>
<td>- Cefepime 1 g IV Q8H OR PCN allergy: Aztreonam 1 g IV Q8H ± Gentamicin (see dosing section, p. 147) Duration: 7–10 days</td>
<td>Oral Ciprofloxacin or TMP/SMX have excellent bioavailability and should be used as step-down therapy if organism is susceptible Oral beta-lactams should not be used for bacteremia due to inadequate blood concentrations Duration of empiric IV therapy should be counted towards total duration of therapy</td>
</tr>
</tbody>
</table>
DIAGNOSIS
Specimen collection: The urethral area should be cleaned with an antiseptic cloth and the urine sample should be collected midstream or obtained by fresh catheterization. Specimens collected using a drainage bag or taken from a collection hat are not reliable and should not be sent.

Interpretation of the urinalysis (U/A) and urine culture
• Urinalysis and urine cultures must be interpreted together in context of symptoms
• Urinalysis/microscopy:
  • Dipstick
    • Nitrites indicate bacteria in the urine
    • Leukocyte esterase indicates white blood cells in the urine
    • Bacteria: presence of bacteria on urinalysis should be interpreted with caution and is not generally useful
  • Pyuria (more sensitive than leukocyte esterase): >10 WBC/hpf or >27 WBC/microliter
• Urine cultures:
  • If U/A is negative for pyuria, positive cultures are likely contamination
  • Most patients with UTI will have ≥100,000 colonies of a uropathogen. Situations in which lower colony counts may be significant include: patients who are already on antibiotics at the time of culture, symptomatic young women, suprapubic aspiration, and men with pyuria.

TREATMENT NOTES
• Pyuria either in the setting of negative urine cultures or in patients with asymptomatic bacteriuria usually requires no treatment. If pyuria persists consider other causes (e.g. interstitial nephritis or cystitis, fastidious organisms).
• Follow-up urine cultures or U/A are only warranted for ongoing symptoms. They should NOT be acquired routinely to monitor response to therapy.
• See p. 114 for discussion of treatment options for VRE and renal concentrations of antibiotics.
Management of patients WITH a urinary catheter

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
<th>Empiric treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic bacteriuria</td>
<td>Positive urine culture ≥ 100,000 CFU/mL with no signs or symptoms of infection</td>
<td>Remove the catheter No treatment unless the patient is:  • Pregnant  • About to undergo a urologic procedure  • Post renal transplant  • Neutropenic Antibiotics do not decrease asymptomatic bacteriuria or prevent subsequent development of UTI</td>
</tr>
<tr>
<td></td>
<td>NOTE: obtaining routine cultures in asymptomatic patients is not recommended</td>
<td></td>
</tr>
<tr>
<td>Catheter-associated UTI (CA-UTI)</td>
<td>Signs and symptoms (fever with no other source is the most common; patients may also have suprapubic or flank pain) AND pyuria (&gt;10 WBC/hpf) AND positive urine culture ≥ 1,000 CFU/mL (see information below regarding significant colony counts)</td>
<td>• Remove catheter when possible Patient stable with no evidence of upper tract disease:  • If catheter removed, consider observation alone OR  • Ertapenem 1 g IV Q24H OR  • Ceftriaxone 1 g IV Q24H OR  • Ciprofloxacin 500 mg PO BID or 400 mg IV Q12H (avoid in pregnancy and in patients with prior exposure to quinolones) Duration: see below</td>
</tr>
<tr>
<td>Uropesis in a patient with nephrostomy tubes</td>
<td>SIRS with urinary source and nephrostomy tubes</td>
<td>• Piperacillin/tazobactam 3.375 mg IV Q6H If prior urine culture data are available, tailor therapy based on those results</td>
</tr>
</tbody>
</table>

**DIAGNOSIS**

**Specimen collection:** The urine sample should be drawn from the catheter port using aseptic technique, NOT from the urine collection bag. In patients with long term catheters (≥ 2 weeks), replace the catheter before collecting a specimen. Urine should be collected before antibiotics are started.

**Symptoms:** Catheterized patients usually lack typical UTI symptoms. Symptoms compatible with CA-UTI include:
• New fever or rigors with no other source
• New onset delirium, malaise, lethargy with no other source
• CVA tenderness, flank pain, pelvic discomfort
• Acute hematuria

**Interpretation of the urinalysis (U/A) and urine culture**
• Pyuria: In the presence of a catheter, pyuria does not correlate with the presence of symptomatic CAUTI and must be interpreted based on the clinical scenario. The absence of pyuria suggests an alternative diagnosis.
• Positive urine culture: ≥ 1,000 colonies
**DURATION**
The duration of treatment has not been well studied for CA-UTI and optimal duration is not known.
- 7 days if prompt resolution of symptoms
- 10–14 days if delayed response
- 3 days if catheter removed in female patient ≤ 65 years with lower tract infection.

**TREATMENT NOTES**
- Remove the catheter whenever possible
- Replace catheters that have been in ≥ 2 weeks if still indicated
- Prophylactic antibiotics at the time of catheter removal or replacement are NOT recommended due to low incidence of complications and concern for development of resistance.
- Catheter irrigation should not be used routinely

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**Treatment of Enterococci**

- Almost all *E. faecalis* isolates are susceptible to Amoxicillin 500 mg PO TID OR Ampicillin 1 g IV Q6H and should be treated with these agents. For patients with PCN allergy: Nitrofurantoin (Macrobid®) 100 mg PO Q12H (do NOT use in patients with CrCl < 50 mL/min).
- *E. faecium* (often Vancomycin resistant)
  - Nitrofurantoin (Macrobid®) 100 mg PO Q12H if susceptible (do NOT use in patients with CrCl < 50 mL/min).
  - Tetracycline 500 mg PO Q6H if susceptible
  - Fosfomycin 3 g PO once (if female without catheter or catheter is removed; ask the micro lab for susceptibility)
  - Linezolid 600 mg PO BID OR Fosfomycin 3 g PO every 2–3 days (max 21 days) if complicated UTI or catheter can not be removed

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**Renal excretion/concentration of selected antibiotics**

- **Good (≥60%)**: aminoglycosides, Amoxicillin, Amoxicillin/clavulanate, Fosfomycin, Cefazolin, Cefepime, Cephelexin, Ciprofloxacin, Colistin, Ertaipenem, Trimethoprim/sulfamethoxazole, Vancomycin, Amphotericin B, Fluconazole, Fluconosine
- **Variable (30-60%)**: Cefpodoxime, Linezolid (30%), Doxycycline (29–55%), Ceftriaxone, Tetracycline (∼60%)
- **Poor (<30%)**: Azithromycin, Clindamycin, Moxifloxacin, Oxacillin, Tigecycline, Micafungin, Posaconazole, Voriconazole

References:
Candidiasis in the non-neutropenic patient

Oropharyngeal disease (thrush)

Initial treatment
- Clotrimazole 10 mg troche 5 times a day
  OR
- Nystatin suspension 500,000 units/5mL 4 times a day

Recurrent or intractable disease
- Fluconazole 100–200 mg PO once daily

Duration: 5–10 days

NOTE: If refractory to Fluconazole consider fungal culture and susceptibilities

Esophageal candidiasis

Initial treatment
- Fluconazole 200–400 mg IV/PO once daily

Duration: 14–21 days

Relapse
- Fluconazole 400–800 mg IV/PO once daily

Refractory to Fluconazole 800 mg daily (fungal culture and susceptibilities are recommended)
- Micafungin 150 mg IV once daily
  OR
- Amphotericin B 0.3–0.7 mg/kg IV once daily
  OR
- Oral therapy: Itraconazole oral solution 200 mg daily

Duration: 14–21 days

Candiduria
- Urinary catheter removal will resolve the candiduria in 40% of cases.

TREATMENT

Asymptomatic cystitis
- Therapy not usually indicated
- Consider in the following conditions (see regimens under “symptomatic cystitis”):
  - Neutropenic patients
  - Renal transplant
  - Urinary obstruction or abnormal GU tract
  - When recovered in urine prior to urologic procedures
Symptomatic cystitis

Preferred therapy
- Fluconazole 200 mg IV/PO once daily

**Duration:** 7–14 days

Fluconazole-resistant organism suspected or confirmed
- Amphotericin B 0.3-0.6 mg/kg IV once daily

**Duration:** 1–7 days

Pyelonephritis

**NOTE:** Candida pyelonephritis is usually secondary to hematogenous spread except for patients with renal transplant or abnormalities of the urogenital tract.

Preferred therapy
- Fluconazole 200–400 mg IV/PO once daily

**Duration:** 14 days

Fluconazole-resistant organism suspected or confirmed
- Amphotericin B 0.5–0.7 mg/kg IV once daily

**OR**
- Micafungin 100 mg IV once daily

**Duration:** 14 days

**TREATMENT NOTES**

- Remove urinary catheter if possible.
- Therapy of candiduria in the non-neutropenic, non-ICU catheterized patient has not been shown to be beneficial and promotes resistance.
- AmBisome®, Voriconazole, Itraconazole, and Posaconazole are not recommended due to poor penetration into the urinary tract.
- Micafungin penetrates poorly in the urine, but does penetrate into renal tissue.
- Amphotericin B bladder washes are not recommended.

Candida vaginitis

**Initial Therapy**
- Fluconazole 150 mg PO X 1 dose

**OR**
- Miconazole 2% cream 5 g intravaginally once daily X 7 days

**Recurrent** (> 4 episodes/year of symptomatic infection)
- Fluconazole 150 mg PO Q72H X 3 doses, then 150 mg a week X 6 months
Candidemia

- YEAST IN A BLOOD CULTURE SHOULD NOT BE CONSIDERED A CONTAMINANT.

NOTE: Micafungin does not have activity against Cryptococcus

TREATMENT
Unspeciated candidemia

Patients who are clinically stable and have not received prior long-term azole therapy
- Fluconazole 800 mg IV/PO X 1 dose, then 400 mg IV/PO once daily

Patients who are NOT clinically stable due to Candidemia or have received prior long-term azole therapy
- Micafungin 100 mg IV once daily

If the yeast is *C. albicans* or *C. glabrata* based on PNA FISH results, follow the recommendations for *C. albicans* or *C. glabrata* noted below. Otherwise, await speciation before modifying therapy as recommended below, unless the patient becomes clinically unstable on Fluconazole.

*Candida albicans*

- Fluconazole 800 mg IV/PO X 1 dose, then 400 mg IV/PO once daily

Patients who are NOT clinically stable due to Candidemia or have received prior long-term azole therapy
- Micafungin 100 mg IV once daily

Patients should be transitioned to Fluconazole once stable.

*Candida glabrata*

- Micafungin 100 mg IV once daily
  OR
  - Fluconazole 800 mg IV/PO X 1 dose, then 400 mg IV/PO once daily IF the isolate is susceptible with MIC ≤ 8 mcg/mL and the patient is stable.

If isolate is intermediate to Fluconazole and oral therapy is desired, consult ID. Other azoles such as Voriconazole should not be used in Fluconazole-resistant strains due to the same mechanism of resistance.

*Candida krusei*

- Micafungin 100 mg IV once daily

Fluconazole should NEVER be used to treat infections due to *C. krusei* because the organism has intrinsic resistance to Fluconazole. This mechanism of resistance is not shared with Voriconazole; therefore, oral Voriconazole can be used if isolate is susceptible (for dosing see Voriconazole specific guidelines, p. 19).
Candida lusitaniae
- Fluconazole 800 mg IV/PO X 1 dose, then 400 mg IV/PO once daily. C. lusitaniae is resistant to Amphotericin B in approximately 20% of cases.

Candida parapsilosis
- Fluconazole 800 mg IV/PO X 1 dose, then 400 mg IV/PO once daily
- Fluconazole-intermediate isolate
- Fluconazole 800 mg IV/PO once daily
- Fluconazole-resistant isolate
- Micafungin 100 mg IV once daily

If the patient is not responding to Micafungin then consider changing to Amphotericin B. The minimum inhibitory concentrations (MICs) of echinocandins are higher for C. parapsilosis than any other Candida spp.; this has led to concern that some infections with C. parapsilosis may not respond well to echinocandins.

Candida tropicalis
- Fluconazole 800 mg IV/PO X 1 dose, then 400 mg IV/PO once daily
- Fluconazole-intermediate isolate
- Fluconazole 800 mg IV/PO once daily
- Fluconazole-resistant isolate
- Micafungin 100 mg IV once daily

TREATMENT NOTES

Amphotericin B use in Candidemia
- Amphotericin B is highly effective against all Candida spp. except for C. lusitaniae; however, azoles and echinocandins are favored in susceptible strains over Amphotericin B products due to toxicity.

Doses for Candidemia
- Amphotericin B 0.7 mg/kg IV once daily
  OR
- AmBisome® 3 mg/kg IV once daily (if patient cannot tolerate conventional Amphotericin B)

Duration
- 14 days following documented clearance of blood cultures and clinical symptoms
- Patients with persistent candidemia and/or metastatic complications (e.g. endophthalmitis, endocarditis) need a longer duration of therapy and evaluation by Ophthalmology and ID.
Non-pharmacologic management
- Removal of all existing central venous catheters is highly recommended.
- Patients should have blood cultures daily or every other day until candidemia is cleared.
- Patients should have an ophthalmologic examination to exclude candidal endophthalmitis prior to discharge, preferably once the candidemia is controlled.
- Echocardiography can be considered if the patient has persistent candidemia on appropriate therapy.

Endophthalmitis
- Management in conjunction with Ophthalmology
- Due to poor CNS and vitreal penetration, treatment with echinocandins is NOT recommended.

Preferred therapy
- Amphotericin B 1 mg/kg IV once daily ± Flucytosine 25 mg/kg PO Q6H
  OR
- AmBisome® 5 mg/kg IV once daily ± Flucytosine 25 mg/kg PO Q6H

Alternate therapy
- Fluconazole 400-800 mg IV/PO once daily ± Flucytosine 25 mg/kg PO Q6H

Duration: 4–6 weeks

Endocarditis
Consultation with ID and Cardiac Surgery is recommended. Surgical valve replacement is considered a critical component for cure. If the patient is not a candidate for surgery then life-long Fluconazole suppression is likely required.
6.18 Candidiasis in the non-neutropenic patient

Preferred therapy
- AmBisome® 5 mg/kg IV once daily

Alternative therapy
- Micafungin 150 mg IV once daily ± Fluconazole 400–800 mg IV/PO once daily

Duration: 6 weeks or longer

Notes on antifungal susceptibility testing
- Susceptibility testing for Fluconazole, Itraconazole, Voriconazole, Fluocytosine, and Micafungin is performed routinely on the first yeast isolate recovered from blood.
- Fluconazole and Micafungin susceptibility are reported on all isolates.
- Organisms that have Micafungin MICs in the range of 1–2 mcg/mL (reported as susceptible) may not respond to treatment. ID consult is recommended in these cases.
- Susceptibility testing for conventional Amphotericin B is done routinely for C. lusitaniae and C. guillermondii, and for other organisms by request.
- If the organism is intermediate (I) to Fluconazole, then 800 mg IV/PO once daily can be used. This choice is NOT recommended in an immunocompromised patient, in a patient who is clinically unstable due to candidemia, or in patients with endocarditis, meningitis or endophthalmitis.
- Susceptibility testing should be considered when:
  - Mucocutaneous candidiasis is refractory to Fluconazole
  - Treating osteomyelitis, meningitis, or endophthalmitis with Fluconazole
  - Blood cultures are persistently positive on Fluconazole
- Non-routine susceptibility testing can be arranged by calling the mycology lab at 5-6148

Notes on Fluconazole prophylaxis
- Fluconazole prophylaxis should be limited to the following settings
  - Patients expected to remain in the SICU or WICU for ≥ 72 hours (Criteria from Hopkins SICU prophylaxis study; prophylaxis in other ICUs has NOT been studied and is NOT recommended).
  - Neutropenic patients undergoing bone marrow transplantation or treatment for leukemia/lymphoma
  - Patients who are post-op from liver or pancreas transplants.
- Fluconazole prophylaxis should be stopped when SICU or WICU patients are transferred to the floor

References:
6.19 Guidelines for use of prophylactic antimicrobials

Pre-operative and pre-procedure antibiotic prophylaxis

For specific procedures and agents see “Peri-operative antibiotic prophylaxis document” at www.insidehopkinsmedicine.org/amp

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dose</th>
<th>Redosing during procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>&lt; 120 kg: 2 g, ≥ 120 kg: 3 g</td>
<td>Q4H (Q2H for cardiac surgery)</td>
</tr>
<tr>
<td>Cefotetan</td>
<td>&lt; 120 kg: 2 g, ≥ 120 kg: 3 g</td>
<td>Q6H</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>600 mg</td>
<td>Q6H</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>400 mg</td>
<td>None</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>5 mg/kg</td>
<td>None</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>500 mg</td>
<td>None</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>&lt; 70 kg: 1 g, 71-99 kg: 1.25 g, &gt; 100 kg: 1.5 g</td>
<td>Q12H</td>
</tr>
</tbody>
</table>

Important notes

- **Timing is crucial. Antibiotics must be in the skin when the incision is made to be effective.**
- Cephalosporins can be administered over 3–5 min IV push just before the procedure and will achieve appropriate skin levels in minutes. Vancomycin and Ciprofloxacin must be given over 60 min. Clindamycin should be infused over 10–20 min.
- For antibiotics with longer infusion times (e.g. Vancomycin, Ciprofloxacin) the infusion should start 30 minutes prior to incision.
- **Post-procedure doses are NOT needed (exceptions are noted in table). Single doses pre-procedure have been as effective as post-procedure doses in all studies.**
- Patients receiving pre-operative antibiotics generally do NOT need additional antibiotics for endocarditis prophylaxis.
- Prophylaxis for patients already on antibiotics:
  - For antibiotics other than Vancomycin: Hold standing dose until 1 hour before incision
  - For Vancomycin: Redose a full dose if 8 hours have passed since the last dose or a half dose if fewer than 8 hours have passed in patient with normal renal function
- Gentamicin should be given as a single dose of 5 mg/kg to maximize tissue penetration and minimize toxicity.
  - If on dialysis or CrCl < 20 mL/min, use 2 mg/kg
  - Do not redose
  - Use actual body weight unless patient is ≥ 20% over ideal body weight (see p. 145)
### 6.19 Guidelines for use of prophylactic antimicrobials

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Prophylaxis recommendations</th>
<th>PCN allergy alternate prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urologic surgery/procedures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transrectal prostate biopsy¹</td>
<td>Cefazolin</td>
<td>Ciprofloxacin OR Gentamicin²</td>
</tr>
<tr>
<td>Transurethral surgery (e.g. TURP, TURBT, ureteroscopy, cystoureteroscopy)</td>
<td>Cefazolin</td>
<td>Gentamicin²</td>
</tr>
<tr>
<td>Lithotripsy</td>
<td>Cefazolin</td>
<td>Gentamicin²</td>
</tr>
<tr>
<td>Nephrectomy or radical prostatectomy</td>
<td>Cefazolin</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Radical cystectomy, ileal conduit, cystoprostatectomy or anterior exenteration</td>
<td>Cefotetan</td>
<td>Clindamycin PLUS Gentamicin²</td>
</tr>
<tr>
<td>Penile or other prostheses</td>
<td>(Cefazolin OR Vancomycin) PLUS Gentamicin²</td>
<td>(Clindamycin OR Vancomycin) PLUS Gentamicin²</td>
</tr>
<tr>
<td><strong>Cardiac surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median sternotomy, heart transplant³</td>
<td>Cefazolin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Median sternotomy, heart transplant with previous VAD or MRSA colonization/infection³</td>
<td>Cefazolin PLUS Vancomycin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Pacemaker or ICD insertion</td>
<td>Cefazolin</td>
<td>Clindamycin OR Vancomycin</td>
</tr>
<tr>
<td>Pacemaker or ICD insertion with MRSA colonization/infection or generator exchange</td>
<td>Cefazolin PLUS Vancomycin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>VAD insertion</td>
<td>Cefazolin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>VAD insertion with MRSA colonization/infection</td>
<td>Cefazolin PLUS Vancomycin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>VAD insertion with open chest³</td>
<td>Cefazolin PLUS Vancomycin</td>
<td>Vancomycin PLUS Ciprofloxacin</td>
</tr>
<tr>
<td>Lung transplant⁴</td>
<td>Cefepime</td>
<td>Consult transplant ID</td>
</tr>
<tr>
<td><strong>Vascular surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid and brachiocephalic procedures without prosthetic grafts</td>
<td>Prophylaxis not recommended</td>
<td>Prophylaxis not recommended</td>
</tr>
<tr>
<td>Upper extremity procedures with prosthetic grafts and lower extremity procedures</td>
<td>Cefazolin</td>
<td>Clindamycin OR Vancomycin</td>
</tr>
<tr>
<td>Abdominal aorta procedure or groin incision</td>
<td>Cefotetan</td>
<td>Vancomycin + Gentamicin²</td>
</tr>
<tr>
<td><strong>Thoracic surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobectomy, pneumonectomy, lung resection, thoracotomy, VATS</td>
<td>Cefazolin</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Esophageal cases</td>
<td>Cefotetan</td>
<td>Clindamycin</td>
</tr>
<tr>
<td><strong>Neurosurgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranietomy, cerebrospinal fluid-shunting procedures, implantation of intrathecal pumps</td>
<td>Cefazolin</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Laminctomy</td>
<td>Cefazolin</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Spinal fusion</td>
<td>Cefazolin</td>
<td>Clindamycin OR Vancomycin</td>
</tr>
<tr>
<td>Spinal fusion with MRSA colonization/infection</td>
<td>Cefazolin PLUS Vancomycin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Transsphenoidal procedures</td>
<td>Ceftriaxone</td>
<td>Moxifloxacin 400 mg</td>
</tr>
<tr>
<td><strong>Orthopedic surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clean operations involving hand, knee, or foot, arthroscopy</td>
<td>Prophylaxis not recommended</td>
<td>Prophylaxis not recommended</td>
</tr>
<tr>
<td>Total joint replacement</td>
<td>Cefazolin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Total joint replacement with MRSA colonization/infection</td>
<td>Cefazolin PLUS Vancomycin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Open reduction of fracture/internal fixation</td>
<td>Cefazolin</td>
<td>Clindamycin OR Vancomycin</td>
</tr>
<tr>
<td>Lower limb amputation</td>
<td>Cefotetan</td>
<td>Clindamycin PLUS Gentamicin²</td>
</tr>
<tr>
<td>Spinal fusion</td>
<td>Cefazolin</td>
<td>Clindamycin OR Vancomycin</td>
</tr>
<tr>
<td>Spinal fusion with MRSA colonization/infection</td>
<td>Cefazolin PLUS Vancomycin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Laminctomy</td>
<td>Cefazolin</td>
<td>Clindamycin</td>
</tr>
</tbody>
</table>
### 6.19 Guidelines for use of prophylactic antimicrobials

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Prophylaxis recommendations</th>
<th>PCN allergy alternate prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedures involving entry into lumen of upper GI tract, gastric bypass procedures, pancreaticoduodenectomy, highly selective vagotomy, Nissen fundoplication</td>
<td>Cefotetan</td>
<td>Clindamycin ± Gentamicin²</td>
</tr>
<tr>
<td>Biliary tract procedures (e.g. cholecystectomy, choledochoenterostomy)</td>
<td>Cefotetan</td>
<td>Clindamycin ± Gentamicin²</td>
</tr>
<tr>
<td>Hepatectomy</td>
<td>Cefotetan</td>
<td>Clindamycin ± Gentamicin²</td>
</tr>
<tr>
<td>Whipple procedure or pancreactectomy</td>
<td>Cefotetan</td>
<td>Clindamycin PLUS Ciprofloxacin</td>
</tr>
<tr>
<td>Small bowel procedures</td>
<td>Cefotetan</td>
<td>Clindamycin PLUS Gentamicin²</td>
</tr>
<tr>
<td>PEG</td>
<td>Cefazolin OR Cefotetan</td>
<td>Clindamycin ± Gentamicin²</td>
</tr>
<tr>
<td>Appendectomy (if complicated or perforated, treat as secondary peritonitis)</td>
<td>Cefotetan</td>
<td>Clindamycin PLUS Gentamicin²</td>
</tr>
<tr>
<td>Colorectal procedures, penetrating abdominal trauma</td>
<td>Cefotetan</td>
<td>Clindamycin PLUS Gentamicin²</td>
</tr>
<tr>
<td>Inguinal hernia repair</td>
<td>Cefazolin</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Complicated, emergent or repeat inguinal hernia repair</td>
<td>Cefotetan</td>
<td>Clindamycin ± Gentamicin²</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>Prophylaxis not recommended</td>
<td>Prophylaxis not recommended</td>
</tr>
<tr>
<td>Mastectomy with lymph node dissection</td>
<td>Cefazolin</td>
<td>Clindamycin PLUS Gentamicin²</td>
</tr>
<tr>
<td><strong>Gynecologic surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesarean delivery procedures</td>
<td>Cefazolin</td>
<td>Clindamycin PLUS Gentamicin²</td>
</tr>
<tr>
<td>Hysterectomy (vaginal or abdominal)</td>
<td>Cefazolin OR Cefotetan</td>
<td>Clindamycin PLUS Gentamicin²</td>
</tr>
<tr>
<td>Oncology procedures</td>
<td>Cefotetan</td>
<td>Clindamycin PLUS Gentamicin²</td>
</tr>
<tr>
<td>Repair of cystocele or rectocele</td>
<td>Cefazolin</td>
<td>Clindamycin</td>
</tr>
<tr>
<td><strong>Head and neck surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parotidectomy, thyroidectomy, tonsillectomy</td>
<td>Prophylaxis not recommended</td>
<td>Prophylaxis not recommended</td>
</tr>
<tr>
<td>Reconstructive procedure w/prosthesis placement</td>
<td>Cefazolin</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Adenoidectomy, rhinoplasty, tumor-debulking, or mandibular fracture repair</td>
<td>Cefotetan OR Clindamycin</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Major neck dissection</td>
<td>Cefazolin</td>
<td>Clindamycin</td>
</tr>
<tr>
<td><strong>Plastic surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clean with risk factors or clean-contaminated</td>
<td>Cefazolin</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Tissue expander insertion/implants/all flaps</td>
<td>Cefazolin</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Rhinoplasty</td>
<td>No prophylaxis OR Cefazolin</td>
<td>No prophylaxis OR Clindamycin</td>
</tr>
<tr>
<td><strong>Abdominal transplant surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas or pancreas/kidney transplant</td>
<td>Cefotetan</td>
<td>Clindamycin PLUS Ciprofloxacin</td>
</tr>
<tr>
<td>Renal transplant/adult live donor</td>
<td>Cefazolin</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Liver transplant⁴</td>
<td>Cefotetan</td>
<td>Clindamycin PLUS Ciprofloxacin</td>
</tr>
</tbody>
</table>

¹If pre-op rectal screen performed: see p. 124
²Do not give additional doses of Gentamicin post-op for prophylaxis
³For open chest, continue antibiotic prophylaxis until closure
⁴Listed recommendations are for patients with no relevant microbiology data that would suggest resistant organisms; prophylactic regimen should be tailored based on known microbiology data with assistance of transplant ID (page in PING)
## Prophylaxis for Prostate Biopsy Based on Rectal Screen Results

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Pre-op prophylaxis regimen¹</th>
<th>Post-op oral options²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin susceptible</td>
<td>Ciprofloxacin 750 mg PO 2 hours before procedure for any renal function</td>
<td>Ciprofloxacin 500 mg PO once 12 hours after the procedure. If GFR &lt;30 ml/min no need for post-op dose.</td>
</tr>
<tr>
<td>Ciprofloxacin resistant, TMP/SMX susceptible</td>
<td>TMP/SMX 1 DS 1 hour before procedure, and 1 DS 3 hours before</td>
<td>TMP/SMX 1 DS PO once 12 hours after the procedure. If GFR &lt;30 ml/min no need for post-op dose.</td>
</tr>
<tr>
<td>Ciprofloxacin and TMP/SMX resistant, Cefazolin susceptible</td>
<td>Cefazolin 2 g IV push (3-5 min) within 1 hour of procedure</td>
<td>Cefpodoxime 100 mg PO once OR Cefdinir 300 mg PO once</td>
</tr>
<tr>
<td>Gentamicin 5 mg/kg IV once over 30-60 min OR Ceftriaxone 1 g IV over 30 min if susceptible</td>
<td>No need for additional doses as Gentamicin and Ceftriaxone retain therapeutic levels for 24 hours</td>
<td></td>
</tr>
</tbody>
</table>

### Other resistance patterns
Call ID Pharmacist

¹ All doses are for any renal function ² Post-op antibiotics are not required by SCIP

---

### 1.1.9 Guidelines for use of prophylactic antimicrobials

#### Prophylaxis for Prostate Biopsy Based on Rectal Screen Results

- **Pre-op prophylaxis regimen**
  - Ciprofloxacin 750 mg PO 2 hours before procedure for any renal function
  - TMP/SMX 1 DS 1 hour before procedure, and 1 DS 3 hours before
  - Cefazolin 2 g IV push (3-5 min) within 1 hour of procedure
  - Gentamicin 5 mg/kg IV once over 30-60 min OR Ceftriaxone 1 g IV over 30 min if susceptible

- **Post-op oral options**
  - Ciprofloxacin 500 mg PO once 12 hours after the procedure. If GFR <30 ml/min no need for post-op dose.
  - TMP/SMX 1 DS PO once 12 hours after the procedure. If GFR <30 ml/min no need for post-op dose.
  - Cefpodoxime 100 mg PO once OR Cefdinir 300 mg PO once

- **Other resistance patterns**
  - Call ID Pharmacist

---

### Intervventional radiology procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Prophylaxis recommendations</th>
<th>PCN allergy alternate prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary/GI; chemo embolization/ percutaneous liver ablation (hx. of biliary surgery/instrumentation); cecostomy</td>
<td>Cefotetan</td>
<td>Clindamycin PLUS Gentamicin</td>
</tr>
<tr>
<td>Chemo embolization; fibroid/urine artery embolization; percutaneous liver/renal/lung* ablation; vascular vascular malformation embolization†</td>
<td>Prophylaxis not recommended</td>
<td></td>
</tr>
<tr>
<td>Urologic procedure (not ablation)</td>
<td>Cefazolin</td>
<td>Gentamicin</td>
</tr>
<tr>
<td>Lymphangiography/embolization</td>
<td>Cefazolin</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Placement of tunneled catheters (e.g. central line); venous/arterial procedures. Placement of implantable access port (e.g. Mediport®)</td>
<td>Prophylaxis not recommended</td>
<td>Cefazolin Clindamycin</td>
</tr>
</tbody>
</table>

---

*Pre-treatment w/ antibiotics can be considered for patients w/ COPD or h/o recurrent post-obstructive pneumonia
† Lymphatic or patients w/ necrotic skin undergoing vascular graft should receive prophylaxis w/Cefazolin
Prophylaxis against bacterial endocarditis

NOTES:
• Patients who have received antibiotics for surgical prophylaxis do not need additional prophylaxis for endocarditis.

Antibiotic prophylaxis solely to prevent endocarditis is not recommended for GU or GI tract procedures.

Cardiac conditions associated with a high risk of endocarditis for which prophylaxis is recommended prior to some dental and respiratory tract procedures and procedures involving infected skin or musculoskeletal tissue
• Prosthetic cardiac valve
• Previous episode of infective endocarditis
• Congenital heart disease (CHD)
  • Unrepaired cyanotic CHD, including palliative shunts and conduits
  • Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure
  • Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device
• Cardiac transplantation recipients who develop cardiac valvulopathy

Antibiotic prophylaxis is recommended for the following dental procedures ONLY:
• Manipulation of gingival tissues or periapical region of teeth
• Perforation of oral mucosa

Antibiotic prophylaxis is recommended for the following respiratory tract procedures ONLY:
• Incision or biopsy of the respiratory mucosa

Antibiotic regimens
• Amoxicillin 2 g PO 1 hour before procedure
  OR
• PCN allergy: Clindamycin 600 mg PO 1 hour before procedure
  OR
• PCN allergy: Azithromycin 500 mg PO 1 hour before procedure
  OR
• Patient unable to take oral medication: Ampicillin 2 g IM/IV 1 hour before procedure OR Cefazolin 1 g IM/IV 5 minute push prior to procedure

Reference:
# Prophylactic antimicrobials for patients with solid organ transplants

**NOTE:** All doses assume normal renal function; dose modifications may be indicated for reduced CrCl.

## Kidney, kidney-pancreas, pancreas transplants

<table>
<thead>
<tr>
<th>Indication</th>
<th>Agent and dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-viral prophylaxis (CMV, HSV, VZV)</strong></td>
<td>CMV D-/R- Acyclovir 400 mg PO BID OR</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>Valacyclovir 500 mg PO BID</td>
<td></td>
</tr>
<tr>
<td>CMV D+ or D+/R+</td>
<td>Valganciclovir† 450 mg PO daily</td>
<td>3 months</td>
</tr>
<tr>
<td>CMV D+/R-</td>
<td>Valganciclovir† 900 mg PO daily</td>
<td>6 months</td>
</tr>
<tr>
<td><strong>Anti-fungal prophylaxis</strong></td>
<td>Kidney Clotrimazole troches 10 mg PO QID OR</td>
<td>1 month‡</td>
</tr>
<tr>
<td></td>
<td>Nystatin suspension 500,000 units QID</td>
<td></td>
</tr>
<tr>
<td>Pancreas and kidney</td>
<td>Fluconazole 400 mg PO daily</td>
<td>1 month</td>
</tr>
<tr>
<td><strong>PCP prophylaxis</strong></td>
<td>First line: TMP/SMX one SS tablet PO daily</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>Second line: Atovaquone 1500 mg PO daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Third line: Dapsone * 100 mg PO daily OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>aerosolized Pentamidine</td>
<td></td>
</tr>
</tbody>
</table>

## Liver transplants

<table>
<thead>
<tr>
<th>Indication</th>
<th>Agent and dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-viral prophylaxis (CMV, HSV, VZV)</strong></td>
<td>CMV D-/R- Acyclovir 400 mg PO BID OR</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>Valacyclovir 500 mg PO BID</td>
<td></td>
</tr>
<tr>
<td>CMV D+ or D+/R+</td>
<td>Valganciclovir† 450 mg PO daily</td>
<td>3 months</td>
</tr>
<tr>
<td>CMV D+/R-</td>
<td>Valganciclovir† 900 mg PO daily, followed by PCR monitoring</td>
<td>6 months</td>
</tr>
<tr>
<td><strong>Anti-fungal prophylaxis</strong></td>
<td>Fluconazole 400 mg PO daily</td>
<td>6 weeks</td>
</tr>
<tr>
<td><strong>PCP prophylaxis</strong></td>
<td>First line: TMP/SMX one SS tablet PO daily</td>
<td>12 months</td>
</tr>
<tr>
<td></td>
<td>Alternatives: Atovaquone 1500 mg PO daily or Dapsone 100 mg PO daily</td>
<td></td>
</tr>
</tbody>
</table>
### Heart transplants

<table>
<thead>
<tr>
<th>Indication</th>
<th>Agent and dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-viral prophylaxis (CMV, HSV, VZV)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV D+/R-</td>
<td>No prophylaxis unless HSV IgG or VZV IgG positive. If positive serology, Valacyclovir 500 mg PO BID</td>
<td>3 months</td>
</tr>
<tr>
<td>CMV D+ or D+/R+</td>
<td>Valganciclovir† 900 mg PO daily</td>
<td>3 months</td>
</tr>
<tr>
<td>CMV D+/R-</td>
<td>Valganciclovir† 900 mg PO daily</td>
<td>6 months</td>
</tr>
<tr>
<td><strong>Anti-fungal prophylaxis</strong></td>
<td>Nystatin suspension 500,000 units QID</td>
<td>Until prednisone dose ≤ 10 mg/d x 3 months</td>
</tr>
<tr>
<td><strong>PCP prophylaxis</strong></td>
<td>First line: TMP/SMX SS one tablet PO daily OR TMP/SMX one DS tablet PO three times/week Second line: Dapsone* 100 mg PO daily Third line: Atovaquone 1500 mg PO daily</td>
<td>12 months</td>
</tr>
<tr>
<td><strong>Toxoplasmosis prophylaxis</strong></td>
<td>First line: TMP/SMX one SS tablet PO daily Second line: Dapsone* 100 mg PO daily PLUS Pyrimethamine and Leucovorin</td>
<td>12 months</td>
</tr>
</tbody>
</table>

### Lung transplants

<table>
<thead>
<tr>
<th>Indication</th>
<th>Agent and dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-viral prophylaxis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV D+/R- Received</td>
<td>Ganciclovir 5 mg/kg IV Q12H x 14 days, then Ganciclovir 5 mg/kg IV Q24H x 16 days, then Valacyclovir 500 mg PO BID or Acyclovir 800 mg PO TID x 1 year followed by Acyclovir 200 mg PO TID</td>
<td>Lifelong</td>
</tr>
<tr>
<td>CMV D+/R- Received leukoreduced or CMV unscreened PRBCs</td>
<td>Valganciclovir 500 mg PO BID or Acyclovir 800 mg PO TID x 1 year followed by Acyclovir 200 mg PO TID</td>
<td>Lifelong</td>
</tr>
<tr>
<td>CMV D+ or D+/R+</td>
<td>Ganciclovir 5 mg/kg IV Q12H x 14 days, then Valganciclovir 900 mg PO daily x 3 months (until CMV shell vial negative from 3 month surveillance bronchoscopy), then Valacyclovir 500 mg po BID or Acyclovir 800 mg PO TID x 1 year, then Acyclovir 200 mg PO TID lifelong.</td>
<td>Lifelong</td>
</tr>
</tbody>
</table>
| CMV D+/R- | Ganciclovir 5 mg/kg IV Q12H x 14 days, then Ganciclovir 5 mg/kg IV daily x 3 months, then Valganciclovir 900 mg PO daily (until CMV shell
6.19 Guidelines for use of prophylactic antimicrobials

vial negative from 6 month surveillance BAL), then Valacyclovir 500 mg PO BID or Acyclovir 800 mg PO TID x 1 year, then Acyclovir 200 mg PO TID lifelong.

<table>
<thead>
<tr>
<th>Anti-fungal prophylaxis</th>
<th>Inhaled Amphotericin B per protocol</th>
<th>During initial hospitalization stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Aspergillus colonization</td>
<td>Nystatin 500,000 units NG Q6H until extubated, then Clotrimazole troches 10 mg PO Q6H until prednisone dose &lt; 10 mg daily</td>
<td>3–6 months</td>
</tr>
<tr>
<td>Aspergillus colonization</td>
<td>Voriconazole (dosed by weight)</td>
<td></td>
</tr>
<tr>
<td>&lt; 69 kg: Voriconazole 200 mg PO BID</td>
<td>3–6 months</td>
<td></td>
</tr>
<tr>
<td>= 69 kg to &lt; 94 kg: Voriconazole 300 mg PO BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 94 kg: Voriconazole 400 mg PO BID</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| PCP prophylaxis | First line: TMP/SMX one DS tablet PO three times/week OR TMP/SMX one SS tablet PO daily | Lifelong |
| Second line: Dapsone * 100 mg PO daily | |
| Third line: Atovaquone 1500 mg PO daily | |

D = donor, R = recipient, (−) = seronegative, (+) = seropositive

NOTES:

TMP/SMX therapy reduces risk of infection with *Listeria* spp., *Nocardia* spp., and *Toxoplasmosis*, but does not eliminate risk.

For splenectomized patients, antibacterial prophylaxis with Amoxicillin 500 mg PO BID (or Doxycycline if PCN allergy) is recommended for 1 year.

*Recommended screening for G6PD deficiency prior to initiation of Dapsone.

†If Valgancylovir is stopped prior to recommended duration of therapy due to intolerance, recommend initiation of Acyclovir or Valacyclovir for antiviral prophylaxis.

‡INKTP–3 months
Neutropenic fever

NOTE: These guidelines were developed for use in BMT and leukemia patients and may not be fully applicable in other instances.

Definitions
• Neutropenia: ANC < 500/mm³
• Fever: Temp > 38.0° C times two at least 2 hours apart OR Temp > 38.3° C times one

TREATMENT
Always tailor antibiotics based on susceptibility profiles

If the patient is hypotensive or otherwise unstable, see “Treatment of clinically unstable patients” (opposite).

Initial fever
• Cefepime 2 g IV Q8H ± Vancomycin* (see dosing section p. 150)
   OR
• Piperacillin/tazobactam 3.375 g IV Q4H ± Vancomycin* (see dosing section p. 150)

*Indications for Vancomycin: suspected CR-BSI, skin and soft-tissue infections, pneumonia, severe oral or pharyngeal mucositis, history of MRSA infection or colonization.

   OR
• Severe PCN allergy (anaphylaxis or Stevens-Johnson Syndrome): Strongly consider allergy consult to verify allergy in patients with unclear histories (see section on Penicillin allergy, p. 137)
• Aztreonam 2 g IV Q8H PLUS Gentamicin† (see dosing section, p. 146)
   PLUS Vancomycin (see dosing section, p. 150)

†If strong concern for nephrotoxicity and no prior fluoroquinolone use, can substitute Ciprofloxacin 400 mg IV Q8H for Gentamicin.

Step-down therapy for discharge
• Ciprofloxacin 750 mg PO BID PLUS Amoxicillin/clavulanate 875 mg PO BID
   OR
• Moxifloxacin 400 mg PO daily
Persistent fever or new fever after 4-7 days in clinically stable patients without established bacterial infection

- Continue antibiotics above and ADD antifungal coverage

If receiving Fluconazole prophylaxis or no fungal prophylaxis:
- Micafungin 100 mg IV Q24H if sinus and/or chest CT not suggestive of fungal infection
  - OR
- Voriconazole 6 mg/kg IV/PO Q12H times two doses then 4 mg/kg IV/PO Q12H if chest CT suggestive of fungal infection

If receiving Voriconazole or Posaconazole prophylaxis or sinus CT suggestive of fungal infection:
- AmBisome® 5 mg/kg IV Q24H

Clinically unstable patient and/or persistent fever despite appropriate antibacterial and antifungal coverage

- Consult Oncology/Transplant ID
- Vancomycin (see dosing section, p. 150) PLUS Meropenem 1 g IV Q8H ± Amikacin if patient unstable (see dosing section p. 146)
  - OR
- Severe PCN allergy: Consult Oncology/Transplant ID
# Prophylactic antimicrobials for patients with expected prolonged neutropenia

**NOTE:** All doses assume normal renal function; dose modifications may be indicated for reduced CrCl.

## 1. Leukemia patients

<table>
<thead>
<tr>
<th>Indication</th>
<th>Agent and dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibacterial prophylaxis</strong></td>
<td>Moxifloxacin 400 mg PO daily PLUS Amoxicillin 500 mg PO TID (start on day 5)</td>
<td>Day 1 until ANC &gt; 100/mm³ OR initiation of “First Fever” antibiotics</td>
</tr>
<tr>
<td><strong>Antifungal prophylaxis</strong></td>
<td>First line: Voriconazole (see dosing in BMT section) Second line: Posaconazole suspension 200 mg PO TID OR 300 mg tablet daily Alternatives: Micafungin 100 mg IV Q24H OR Fluconazole 400 mg PO daily</td>
<td>Day 1 until ANC &gt; 100/mm³</td>
</tr>
<tr>
<td><strong>Antiviral prophylaxis</strong></td>
<td>Valacyclovir 500 mg PO BID OR Acyclovir 800 mg PO BID If vomiting or diarrhea: Acyclovir 250 mg/m² IV Q12H†</td>
<td>Day 1 until ANC &gt; 100/mm³</td>
</tr>
<tr>
<td><strong>PCP prophylaxis in high risk patients‡</strong></td>
<td>First line: TMP/SMX one SS tab PO daily Second line: Dapsone 100 mg PO daily Third line: Atovaquone 750 mg PO BID</td>
<td>Day 1 until immunosuppression resolves</td>
</tr>
</tbody>
</table>

## 2. Lymphoma, myeloma patients

<table>
<thead>
<tr>
<th>Indication</th>
<th>Agent and dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibacterial prophylaxis</strong> (lymphoma only)</td>
<td>Moxifloxacin 400 mg PO daily</td>
<td>Day 7 of chemo until ANC &gt; 500/mm³</td>
</tr>
<tr>
<td><strong>Antifungal prophylaxis</strong></td>
<td>Fluconazole 200 mg PO daily</td>
<td>Day 1 through all cycles of chemo-therapy in high risk patients.</td>
</tr>
<tr>
<td><strong>Antiviral prophylaxis</strong></td>
<td>Valacyclovir 500 mg PO BID OR Acyclovir 800 mg PO BID If vomiting or diarrhea: Acyclovir 250 mg/m² IV Q12H†</td>
<td>Day 7 through all cycles of chemo-therapy</td>
</tr>
<tr>
<td><strong>PCP prophylaxis in high risk patients‡</strong></td>
<td>First line: TMP/SMX one SS tab PO daily Second line: Dapsone 100 mg PO daily Third line: Atovaquone 750 mg PO BID</td>
<td>Day 7 through all cycles of chemo-therapy</td>
</tr>
</tbody>
</table>
### 3. Bone marrow transplant patients/peripheral blood stem cell transplant patients

<table>
<thead>
<tr>
<th>Indication</th>
<th>Agent and dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibacterial prophylaxis</strong>*</td>
<td>Moxifloxacin 400 mg PO daily</td>
<td>Day zero until engraftment</td>
</tr>
<tr>
<td><strong>Antifungal prophylaxis</strong></td>
<td>Fluconazole 400 mg PO daily</td>
<td>Day zero until ANC &gt; 500/mm³</td>
</tr>
</tbody>
</table>
| **Antifungal prophylaxis in patients with GVHD†** | First line: Posaconazole suspension 200 mg PO TID OR 300 mg tablets daily  
Second line: Voriconazole (dosed by weight)  
<69 kg Voriconazole 200 mg PO BID  
≥69 kg to <94 kg Voriconazole 300 mg PO BID  
≥94 kg Voriconazole 400 mg PO BID |                                      |
| **Antiviral prophylaxis**    | Valacyclovir 500 mg PO BID OR 
Acyclovir 800 mg PO BID 
If vomiting or diarrhea: Acyclovir 250 mg/m² IV Q12H † | Day zero until 1 yr (allogeneic transplants) or 6 months (autologous transplants) |
| **PCP prophylaxis†**         | First line: TMP/SMX one SS tab PO daily 
Second line: TMP/SMX DS tab 2 times weekly 
OR Dapsone 100 mg PO daily 
Third line: Atovaquone 750 mg PO BID 
Fourth line: Pentamidine 300 mg INH Q28 days | Allogeneic transplant: Day 21 or engraftment ( whichever is later) until at least 1 year (longer if steroids or ongoing risk) Autologous transplant: Engraftment until 6 months |

**NOTES:**
- TMP/SMX therapy reduces risk of infection with encapsulated bacteria, Listeria spp., Nocardia spp., and Toxoplasmosis, but does not eliminate risk. It is the preferred antibiotic regimen for PCP prophylaxis.
- *In patients with fluoroquinolone allergy or who cannot tolerate a fluoroquinolone due to QTc prolongation, consider Cefpodoxime 400 mg PO BID.
- †Acyclovir should be dosed by ideal body weight
- ‡Myeloma patients if on steroids; Lymphoma patients if HIV+, on chronic steroids, fludarabine. Leukemia patients: ALL, chronic steroids, s/p BMT until 1 year after transplant, or patient who received cladribine, fludarabine, or alemtuzumab.
- ¶Other prophylaxis in acute GVHD: Moxifloxacin, TMP/SMX.
Guidelines for the use of antifungal agents in hematologic malignancy patients

Filamentous fungi

ID consult recommended for assistance with antifungal selection

TREATMENT

Aspergillus spp.

Initial therapy
• Voriconazole 6 mg/kg IV/P0 Q12H times two doses then 4 mg/kg IV/ P0 Q12H (see Voriconazole guidelines, p. 19, for more information).
  OR
• AmBisome® 5 mg/kg IV Q24H

NOTES:
• Voriconazole is considered by many to be the first-line treatment of suspected filamentous fungal infections in the immunocompromised host as most of these infections are caused by Aspergillus species. Although the data are limited, Voriconazole appears more effective than Amphotericin for this very serious infection.
• Combination antifungal therapy consisting of Voriconazole PLUS Micafungin should be considered for the treatment of confirmed invasive aspergillosis that is documented by culture, positive galactomannan assay, or histopathology for the first two weeks of therapy. Longer duration of combination therapy has not been evaluated.

Fusarium spp.

• ID consult should be involved in these cases.
• Voriconazole 6 mg/kg IV/P0 Q12H times two doses then 4 mg/kg IV/P0 Q12H PLUS AmBisome 5 mg/kg IV Q24H (see Voriconazole guidelines, p. 19, for more information). Dose escalation may be necessary for some patients.

Scedosporium apiospermum

• Voriconazole 6 mg/kg IV/P0 Q12H times two doses then 4 mg/kg IV/P0 Q12H PLUS Micafungin 100 mg IV Q24H (see Voriconazole guidelines, p. 19, for more information).

NOTE:
• Treatment with other agents has yielded disappointing results. Voriconazole appears to be the best option but the data are limited.
Zygomycoses (Mucor, Rhizopus, Cunninghamella, etc.).
- AmBisome® 5 mg/kg IV once daily PLUS a second antifungal agent
- ID consult required.
- Surgical debridement and correction of underlying risk factors (e.g. acidosis, hyperglycemia) are critical.

Candida

TREATMENT
- YEAST IN A BLOOD CULTURE SHOULD NEVER BE CONSIDERED A CONTAMINANT.
  - See sections below on empiric therapy and on pathogen-specific therapy.

Unspeciated candidemia
- Micafungin 100 mg IV Q24H
  - OR
  - AmBisome® 5 mg/kg IV Q24H

If the yeast is C. albicans or C. glabrata, the recommendations for C. albicans noted below can be followed. If the yeast is not C. albicans, await speciation before modifying therapy as recommended below.

NOTE: Micafungin does not cover Cryptococcus

Candida albicans
- Micafungin 100 mg IV Q24H
  - OR
  - AmBisome® 3–5 mg/kg IV Q24H

NOTE: Patients who are clinically stable and no longer neutropenic can be switched to Fluconazole if the organism is susceptible.

Candida glabrata
- Micafungin 100 mg IV Q24H
  - OR
  - AmBisome® 5 mg/kg IV Q24H

Candida krusei
- Micafungin 100 mg IV Q24H
  - OR
  - AmBisome® 5 mg/kg IV Q24H
**NOTE:** *C. krusei* is intrinsically resistant to Fluconazole and these infections can be difficult to treat. In stable patients, Voriconazole can be used if susceptible and oral therapy is desired. (See p. 19 for dosing).

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**Candida parapsilosis**

- AmBisome® 3–5 mg/kg IV Q24H

**NOTES:**

- Most *C. parapsilosis* isolates remain susceptible to Fluconazole, which can be used in stable and non-neutropenic patients.
- There are limited data that suggest that Micafungin may be inferior to Amphotericin B in these infections.

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**Candida tropicalis**

- Micafungin 100 mg IV Q24H
  - OR
  - AmBisome® 3–5 mg/kg IV Q24H

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### TREATMENT NOTES

Hidden Content
- JHH Internal use only

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**Notes on antifungal susceptibility testing**

- Susceptibility testing for Fluconazole, Itraconazole, Voriconazole, Flucytosine (5-FC), and Micafungin is performed routinely on the first yeast isolate recovered from blood.
• Fluconazole and Micafungin susceptibilities are reported on all blood isolates.
• Organisms that have Micafungin MICs in the range of 1–2 mcg/mL (reported as susceptible) may not respond to treatment. ID consult is recommended in these cases.
• Susceptibility testing for conventional Amphotericin B is done routinely for *C. lusitaniae* and *C. guilliermondii* and for other organisms by request.
• Susceptibility testing should be considered when:
  • Mucocutaneous candidiasis is refractory to Fluconazole
  • Treating osteomyelitis, meningitis, or endophthalmitis with Fluconazole
  • Blood cultures are persistently positive on Fluconazole
• Non-routine susceptibility testing can be arranged by calling the mycology lab at 5-6148

Reference:
Approach to the patient with a history of penicillin allergy

**Penicillin reactions – Incidence**
- 80-90% of patients who report they are “allergic” to PCN actually have negative skin tests and are not at increased risk of an allergic reaction.
- Penicillin reactions of some type occur in 0.7 to 10% of all patients who get the drug.
  - BUT: The incidence of anaphylactic reactions is 0.004% to 0.015%.
- Rates of cross-reaction allergies to cephalosporins are unknown but thought to be low.
- Rates of PCN and carbapenem skin test cross reactivity are 47%, although clinical rates of hypersensitivity reactions in patients with reported PCN allergy who receive carbapenems are 9–11%.
- Cross reactions to monobactams (Aztreonam) do NOT appear to occur.

**Penicillin skin testing**
- When done correctly, is highly predictive of serious, anaphylactic reactions.
- Patients with a negative skin test are NOT at risk for anaphylactic reactions.
- Rarely, skin test negative patients may get mild hives and itching following penicillin administration but these RESOLVE with continued treatment.
- Skin tests cannot predict dermatologic or GI reactions or drug fevers.
- Skin testing is now available at JHH. Please consult Allergy and Immunology.

**Penicillin reactions—Types**
- **Immediate** (type 1) – Anaphylaxis, hypotension, laryngeal edema, wheezing, angioedema, urticaria
  - Almost always occur **within 1 hour** of administration. Hypotension **always** occurs soon after administration
  - Can be predicted by skin tests
- **Accelerated** – Laryngeal edema, wheezing, angioedema, urticaria (NOT hypotension)
  - Occur within 1-72 hours of administration
  - Can be predicted by skin tests
- **Late** – Rash (maculopapular or morbilliform or contact dermatitis), destruction of RBC, WBC, platelets, serum sickness
  - Almost always occur after 72 hours of administration
  - Rashes sometimes go away despite continued treatment
  - Maculopapular and morbilliform rashes DO NOT progress to Stevens-Johnson syndrome
  - Late reactions are NOT predicted by skin tests
- **Stevens-Johnson Syndrome** – exfoliative dermatitis with mucous membrane involvement
7.1 Approach to the patient with reported penicillin allergy

- Brief, focused history can be VERY helpful.
- Questions to ask:
  1. How long after beginning penicillin did the reaction occur?
  2. Was there any wheezing, throat or mouth swelling, urticaria?
  3. If a rash occurred, what was the nature of the rash? Where was it and what did it look like?
  4. Was the patient on other medications at the time of the reaction?
  5. Since then, has the patient ever received another penicillin or cephalosporin (ask about trade names like: Augmentin, Keflex, Trimox, Ceftin, Vantin)?
  6. If the patient received a beta-lactam, what happened?

Interpreting the history of the patient reporting penicillin allergy

- ANY patient who has a history consistent with an immediate reaction (laryngeal edema, wheezing, angioedema, urticaria) SHOULD NOT receive beta-lactams without undergoing skin testing first EVEN IF they have received beta-lactams with no problems after the serious reaction.
  - Patients who report non-anaphylactic reactions and have received other penicillins without problems DO NOT have penicillin allergy and are not at increased risk for an allergic reaction compared to the general population.
  - Patients who report non-anaphylactic reactions and have received cephalosporins can get cephalosporins but not necessarily PCNs.
  - Patients who report a history of a non-urticarial rash that is NOT consistent with Stevens-Johnson syndrome (target lesions with mucous membrane inflammation) and developed after ≥ 72 hours of penicillin are not at increased risk for an adverse reaction. They should, however, be watched closely for development of rashes.
  - Patients who report reactions consistent with serum sickness (rare) can receive either penicillins or cephalosporins with careful monitoring for recurrence.
  - Patients who report GI symptoms (diarrhea, nausea) probably do not have penicillin allergy and do not appear to be at increased risk for an adverse reaction. They should be closely observed for recurrent symptoms and be given supportive therapy if they occur.

References:
Hand hygiene
- If hands are not visibly soiled, then alcohol-based hand sanitizers are recommended for cleaning. If hands are visibly soiled, wash hands with soap and water for at least 15 seconds.
- Hand hygiene is required upon entering a patient room, upon exiting, between patients in a semi-private room, and other times per hospital policy.
- Use soap and water upon exiting the room of a patient with *C. difficile* infection.
- No artificial fingernails are permitted for any staff member who has patient contact or handles sterile supplies.

Bloodborne pathogen exposures (needlestick or other exposure)
The prompt treatment of injuries and exposures is vital to prevent the transmission of disease. Whatever the exposure, IMMEDIATE cleaning of the exposure site is the first priority.
- Skin wounds should be cleaned with soap and water
- Mucous membranes should be flushed thoroughly with water
- Eyes should be irrigated with a liter of normal saline

After cleaning the exposure site, call 5-STIX (5-7849) and follow instructions to contact the ID physician. Workplace injuries should be reported immediately on the “Employee Report of Incident Form” and to the *Occupational Injury Clinic* (Blalock 139, Monday–Friday, 7:30 a.m. to 4 p.m., 5-6433), and to your supervisor.

Standard Precautions

<table>
<thead>
<tr>
<th>Routine hand hygiene</th>
<th>Bag contaminated linen at point of use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistent and correct glove use</td>
<td>Regular cleaning of environmental surfaces</td>
</tr>
<tr>
<td>Appropriate use of gowns to prevent contamination of uniform/clothing</td>
<td>Routine cleaning or disposal of patient-care equipment</td>
</tr>
<tr>
<td>Appropriate use of masks, eye protection and face shields (i.e., when suctioning, or when splash likely)</td>
<td>Strict adherence to occupational safety requirements</td>
</tr>
</tbody>
</table>
Communicable diseases—exposures and reporting

HEIC should be notified:

- If patients or HCWs are exposed to a communicable disease (i.e. meningococcal disease, varicella, TB etc.)
- About HCWs with acute hepatitis A, B or C, Salmonella, Shigella, Campylobacter, or pneumonia requiring hospital admission
- About any unusual occurrence of disease or cluster, particularly diseases that have the potential to expose many susceptible individuals
- Suspicion or diagnoses of the following diseases (diseases with require immediate notification by phone or pager). If disease is in a HCW, notify HEIC and Occupational Health (98 N. Broadway, Suite 421, Monday–Friday, 7:30 a.m. to 4:00 p.m., 5-6211) immediately

<table>
<thead>
<tr>
<th>Anthrax</th>
<th>Rabies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avian influenza</td>
<td>Ricin toxin</td>
</tr>
<tr>
<td>Botulism</td>
<td>Rubella (German measles)</td>
</tr>
<tr>
<td>Brucellosis</td>
<td>Salmonellosis</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob disease (CJD)</td>
<td>SARS</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Scabies</td>
</tr>
<tr>
<td>Glanders</td>
<td>Shigellosis</td>
</tr>
<tr>
<td>Highly resistant organisms (i.e. VISA, VRSA)</td>
<td>Smallpox (orthopox viruses)</td>
</tr>
<tr>
<td>Legionellosis</td>
<td>Streptococcal Group A or B invasive disease</td>
</tr>
<tr>
<td>Measles (rubeola)</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Meningococcal disease</td>
<td>Tularemia</td>
</tr>
<tr>
<td>Monkeypox</td>
<td>Varicella (chickenpox or disseminated zoster)</td>
</tr>
<tr>
<td>Mumps</td>
<td>Viral hemorrhagic fever</td>
</tr>
<tr>
<td>Pertussis</td>
<td>Yellow Fever</td>
</tr>
<tr>
<td>Plague</td>
<td></td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td></td>
</tr>
<tr>
<td>Q Fever</td>
<td></td>
</tr>
</tbody>
</table>

### JHH Precautions Categories

These precaution categories must be used in addition to Standard Precautions. The following table includes general requirements for precaution categories. The complete table and the type of isolation required for each organism can be found on the HEIC website. If recommendations on this table cannot be followed, please contact HEIC.

<table>
<thead>
<tr>
<th>(sign color)</th>
<th>Contact Precautions (pink)</th>
<th>Droplet Precautions (orange)</th>
<th>Airborne Precautions (blue) ¶</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Private room</strong></td>
<td>Required unless cohorted</td>
<td>Required unless cohorted*</td>
<td>Required</td>
</tr>
<tr>
<td><strong>Door closed</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Mask/Eye Protection</strong></td>
<td>No</td>
<td>If within 6 feet of patient</td>
<td>PAPR or N95‡ to enter room‡</td>
</tr>
<tr>
<td><strong>Gown and Gloves</strong></td>
<td>To enter room</td>
<td>To enter room</td>
<td>No</td>
</tr>
<tr>
<td><strong>Examples</strong></td>
<td>MRSA, C. diff, zoster§</td>
<td>Influenza, bacterial meningitis</td>
<td>TB, disseminated zoster§</td>
</tr>
</tbody>
</table>

* Required for pertussis and diphtheria
† Fit-testing is required to use an N95 mask for airborne precautions
‡ HCWs who are Varicella-immune do not have to wear a PAPR or N95 if patient is in isolation for zoster or chickenpox
§ Disseminated zoster, zoster in an immunocompromised host, and chickenpox require both Contact and Airborne Precautions.
Disease-specific infection control recommendations

**Carbapenem-resistant Enterobacteriaceae (CRE)**
Routine active surveillance cultures for CRE are performed in patients who have been hospitalized in a country other than the U.S. **in the past 6 months**. Patients are placed on Contact Precautions pending culture results. The results are to be used for isolation purposes, not to guide therapy or clinical care. **The overwhelming majority of positive surveillance cultures represents colonization, not infection, and should not prompt any antimicrobial therapy.**

**Creutzfeldt-Jakob disease (CJD)**
CJD, variant CJD and other diseases caused by prions are resistant to a number of standard sterilization and disinfection procedures. Iatrogenic transmission of CJD has been associated with percutaneous exposure to medical instruments contaminated with prion/central nervous system (CNS) tissue residues, transplantation of CNS and corneal tissues and recipients of human growth hormone and gonadotropin. Transmission of CJD has not been associated with environmental contamination or from person-to-person via skin contact. The following additional precautions must be made when processing equipment that could be contaminated with prion related material:

- Notify HEIC and the unit manager/charge nurse immediately of any suspected or confirmed CJD case and refer to the CJD policy on the HEIC Web site.
- Use disposable equipment whenever possible. If non-disposable equipment is used, Central Sterile Department shall be notified prior to the start of the procedure.
- Label all laboratory and pathology requisitions as suspected CJD and notify the lab before sending specimens.
- The following are considered highly infective and should be handled with extreme caution: brain, spinal cord, optic tissues and pituitary gland
- The following are considered to be of lower infectivity: CSF, kidney, liver, lung, lymph nodes, spleen, placenta, tonsillar tissue and olfactory tissue.

**Methicillin-resistant Staphylococcus aureus (MRSA)**
Routine active surveillance cultures for MRSA are performed on select units to identify patients with MRSA. When a culture is positive for MRSA the patient is placed on **Contact Precautions**. The results are to be used for isolation purposes, not to guide therapy or clinical care. **The overwhelming majority of positive surveillance cultures**
represents colonization, not infection, and should not prompt any antimicrobial therapy.

Surveillance cultures should be obtained upon admission and weekly in the following units: MICU, WICU, CVSICU, SICU, CTU (9W), NCCU, CCU/PCCU, PICU, NICU, oncology units, Nelson 4.

To remove a patient from MRSA precautions, cultures from the original site of infection and 2 nares cultures taken ≥ 72 hours apart must be negative. Nares cultures should not be sent if the patient has received antibiotics active against MRSA in the previous 48 hours. Once this is accomplished, call HEIC to review culture data and initiate deflagging.

**Pertussis**

All patients with pertussis should be placed on Droplet Precautions for five days from the start of therapy. If the patient is not on therapy, Droplet Precautions should be continued for three weeks from the onset of cough. Private room is required. **Treatment:**

- Azithromycin 500 mg PO once on day 1, then 250 mg PO daily on days 2–5
  - OR
- Macrolide allergy: TMP/SMX 1 DS tablet PO BID for 14 days

Prophylaxis with the above regimens is required for all household contacts within three weeks of exposure. Use the same antibiotic as for treatment. All household contacts and HCWs with exposure to the patient should also have up-to-date immunizations for *Bordetella pertussis*.

**Scabies**

All patients with conventional or Norwegian scabies should be placed on Contact Precautions. Norwegian scabies is a severe form of heavy mite infestation.

- Private room required.
- Patients with conventional scabies must be treated with a scabicide once, and the precautions may be discontinued 24 hours after the treatment is completed.
- Patients with Norwegian scabies require 2 treatments with a scabicide 1 week apart. Contact precautions may be discontinued 24 hours after the second treatment is completed.
- Infested clothing and linen should be sealed in a plastic bag for 48 hours. The mite will not survive off a human host for more than 48 hours. Clothing/patient belongings should be sent home with the patient’s family/caretaker. Linens and clothing should be washed in the washing machine on the hot cycle.
• If prolonged skin-to-skin contact occurs with a scabies patient, prophylactic treatment is required. Healthcare workers should contact HEIC if an exposure is suspected.

### Vancomycin-resistant enterocci (VRE)

Routine active surveillance cultures for VRE are performed on select units to identify patients with VRE. Surveillance culture results are found in the electronic patient record with the test name “Bacteriology-Stool-VRE Stool Surv. Cult.” When a culture grows VRE, the patient is flagged for **Contact Precautions.** The results are to be used for isolation purposes, not to guide therapy or clinical care. The **overwhelming majority of positive surveillance cultures represents colonization, not infection, and should not prompt any antimicrobial therapy.**

Surveillance cultures should be obtained upon admission and weekly in the following units: MICU, WICU, CVSICU, SICU, CTU (9W), BMT and Leukemia units, NCCU, PICU.

The patient must be off antibiotics for ≥ 48 hours and cultures from original site of infection AND 3 stool or perirectal cultures taken ≥ 1 week apart must be negative. Once this is accomplished, call HEIC to review culture data and initiate deflagging.

### Varicella-Zoster

Immunocompetent patients with disseminated zoster and all immunosuppressed patients with zoster need **Contact AND Airborne Precautions.** The following definitions apply to patients with zoster:

- **Immunosuppressed:** bone marrow transplant within the past year; acute leukemia; solid organ transplant recipients; patients receiving cytotoxic or immunosuppressive treatments, including steroid treatment for ≥ 30 days with the following doses: dexamethasone 3 mg daily, cortisone 100 mg daily, hydrocortisone 80 mg daily, prednisone 20 mg daily, methylprednisone 16 mg daily; HIV+ patients with CD4 < 200
- **Disseminated:** lesions outside of 2 contiguous dermatomes
Aminoglycoside dosing and monitoring

Aminoglycosides enhance the efficacy of some antibiotics. Except for urinary tract infections, aminoglycosides should seldom be used alone to treat infections.

**Aminoglycoside dosing weight:**

**Calculate Ideal Body Weight (IBW)**

\[
\text{IBW female (kg)} = (2.3 \times \text{inches over 5'}) + 45.5
\]

\[
\text{IBW male (kg)} = (2.3 \times \text{inches over 5'}) + 50
\]

*For patients < 20\% over IBW, use Actual Body Weight (ABW)*

*For patients ≥ 20\% over IBW, use Dosing Body Weight (DBW)*

\[
\text{(DBW)} = [\text{IBW} + 0.4(\text{ABW} - \text{IBW})]
\]

**Estimation of creatinine clearance (CrCl) by Cockcroft-Gault equation:**

(If a patient’s renal function is declining, this equation may overestimate CrCl)

\[
\text{CrCl} = \frac{(140 - \text{age}) \times \text{weight in kg}^*}{72 \times \text{serum creatinine}} \times 0.85 \text{ (if female)}
\]

* Use Actual Body Weight (ABW) unless patient ≥ 20\% over IBW, use DBW as described above

**Extended-interval dosing**, also sometimes referred to as “once-daily” administration, utilizes higher dose and less frequent aminoglycoside administration, whereas patient-specific dosing, previous referred to as “traditional dosing”, typically utilizes smaller doses with more frequent administration. See table below for dosing recommendation based on indication and patient’s renal function. For mycobacterial infections, urinary tract infections, SICU/WICU protocol and gram-positive synergy (e.g. endocarditis), please see separate sections below. For cystic fibrosis patients, see the Cystic Fibrosis section (p.92)
## Aminoglycoside dosing for Gram-negative infections

<table>
<thead>
<tr>
<th>Indications</th>
<th>Patient-specific dosing</th>
<th>Extended-interval dosing</th>
</tr>
</thead>
</table>
| **Dosing**                                                                  | Dose (mg) = desired peak x [Weight (kg) x Vd (L/kg)]  
- Desired peak: choose from below  
- Weight: ABW or DBW  
- Volume of distribution (Vd) typically ranges between 0.25 – 0.5 L/kg in most patients. Higher Vd should be used in critically ill and volume overloaded patients.  
Dosing interval based on CrCl:  
CrCl >60: Q8H*  
CrCl 30-60: Q12  
CrCl <30/CWHD/HD: dose by level  
*If targeting high peaks, use maintenance dose frequency of Q12-24H. | Gentamicin/Tobramycin:  
5-7 mg/kg IV Q24H  
Amikacin:  
15-20 mg/kg IV Q24H |

<table>
<thead>
<tr>
<th>Desired Peaks and Troughs</th>
<th><strong>Peak</strong></th>
<th>Gentamicin/Tobramycin</th>
<th>Amikacin</th>
<th><strong>Trough</strong></th>
<th>Gentamicin/Tobramycin</th>
<th>Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia Septic shock</td>
<td>10 mcg/mL</td>
<td>25-35 mcg/mL</td>
<td></td>
<td>1-2 mcg/mL</td>
<td>&lt;10 mcg/mL</td>
<td></td>
</tr>
<tr>
<td>Endocarditis Osteomyelitis</td>
<td>8-10 mcg/mL</td>
<td>20-30 mcg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDR organisms</td>
<td>10-20 mcg/mL based on MIC</td>
<td>45-50 mcg/mL based on MIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Indications</td>
<td>&lt;1-2 mcg/mL</td>
<td>&lt;10 mcg/mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Therapeutic Drug Monitoring | **Trough**: draw 30 minutes prior to the 3rd dose  
**Peak**: obtain 1 hour after end of infusion, after the 3rd dose.  
**Frequency of monitoring**  
- Once a week after desired peak/trough is established in patients with normal renal function  
- More than once weekly:  
  - After changes in dosing regimen  
  - Patient is on dialysis  
  - Patient in acute renal failure, SCr increased by 0.5 mg/dL or 30% from baseline  
  - Major changes in the patient’s volume status | **If the patient meets ANY of the criteria below, a trough level is recommended prior to the 2nd dose:**  
- Concomitant nephrotoxic medications  
- Contrast exposure  
- Age ≥ 60 years  
- Patient is in the ICU  
- Other risks for nephrotoxicity (e.g. diabetes, kidney TX)  
If trough higher than desired troughs, use patient specific dosing to adjust dose. |

*Normal renal function (CrCl >60 mL/min) and all other indications not listed under patient specific dosing*
Aminoglycoside dosing in mycobacterial infections

Amikacin is the preferred agent to treat all mycobacterial infections, except *Mycobacterium chelonae*. For *M. chelonae* infections, Tobramycin is the recommended aminoglycoside. Streptomycin is another aminoglycoside sometimes used to treat mycobacterial infections such as *M. tuberculosis*. Please contact the Antimicrobial Stewardship Program pharmacist for Tobramycin/Streptomycin dosing recommendation for this indication.

**Amikacin:**

**Normal renal function:**
Once daily: 15 mg/kg IV Q24H (or 10 mg/kg IV Q24H if >50 years of age)
Thrice weekly: 25 mg/kg IV three times a week (may be more difficult to tolerate)

**Abnormal renal function:** Discuss with pharmacy clinical specialist

**Therapeutic drug monitoring:** Peak and trough not generally necessary, except in those with renal insufficiency (GFR <60 mL/min) and if SCr increases by 0.5 mg/dL or >30% from baseline while patient on aminoglycoside therapy. Check a trough concentration to monitor for toxicity. Peaks in the low 20 mcg/mL range are acceptable, and trough concentrations are preferably <4 mcg/mL or undetectable.

### Aminoglycoside dosing in urinary tract infections

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Gentamicin/Tobramycin</th>
<th>Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>3 mg/kg IV Q24H or</td>
<td>10 mg/kg IV Q24H or</td>
</tr>
<tr>
<td></td>
<td>1 mg/kg IV Q8H</td>
<td>3 mg/kg IV Q8H</td>
</tr>
<tr>
<td>40-59</td>
<td>1 mg/kg Q12H</td>
<td>3 mg/kg IV Q12H</td>
</tr>
<tr>
<td>20-39</td>
<td>1 mg/kg Q24H</td>
<td>3 mg/kg IV Q24H</td>
</tr>
<tr>
<td>&lt;20</td>
<td>1 mg/kg ONCE*</td>
<td>3 mg/kg IV ONCE*</td>
</tr>
</tbody>
</table>

*Give one dose, check level in 24 hours, redose when Gentamicin/Tobramycin level <1 mcg/mL or Amikacin <4 mcg/mL

Aminoglycosides are highly concentrated in urine; therefore, therapeutic drug monitoring is not necessary in patients with normal renal function. Suggested doses in the above table will likely provide adequate urine concentrations for highly susceptible organisms. Trough should be checked to monitor for toxicity in patients with renal insufficiency (GFR <60 mL/min) and if SCr increases by 0.5 mg/dL or >30% from baseline while patient on aminoglycoside therapy.

- **Gentamicin/Tobramycin:** desired trough <1 mcg/mL or undetectable.
- **Amikacin:** desired trough <4 mcg/mL or undetectable.
Aminoglycoside dosing in the SICU/WICU

Gentamicin/Tobramycin
Loading dose 4 mg/kg using actual body weight, followed by a patient-specific maintenance dose.

Amikacin
Loading dose 16 mg/kg using actual body weight, followed by a patient-specific maintenance dose.

Therapeutic Drug Monitoring
After loading dose: 1 hour peak and 8 hour level after the end of the infusion to facilitate calculating patient specific kinetic parameters.

Aminoglycoside dosing for Gram-positive synergy

Dosing for patients with normal renal function:

- **Gentamicin**: 3 mg/kg IV once daily is recommended for treatment of endocarditis with Viridans streptococci or *S. bovis* in patients with normal renal function (CrCl ≥ 60 ml/min).
- **Gentamicin**: 1 mg/kg IV Q8H is recommended for treatment of Enterococcal and other Gram-positive endocarditis infections in patients with normal renal function (CrCl ≥ 60 ml/min). Patients >65 years old should be started on Q12H if normal renal function.

Dosing adjustment for renal insufficiency

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–59</td>
<td>1 mg/kg Q12H</td>
</tr>
<tr>
<td>20–39</td>
<td>1 mg/kg Q24H</td>
</tr>
<tr>
<td>&lt;20</td>
<td>1 mg/kg ONCE*</td>
</tr>
</tbody>
</table>

* Give one dose, check level in 24 hours, redose when level <1 mg/L

NOTE: See infective endocarditis guidelines (p. 65) for duration.

THERAPEUTIC DRUG MONITORING

- Peak and trough are recommended around the third dose to assure appropriate dosing.
- Desired serum concentrations of **Gentamicin**
  - **Peak levels**: 3–5 mcg/mL
  - **Trough levels**: < 1 mcg/mL
**NEPHROTOXICITY**
- **Serum creatinine** should be measured at least every other day. If creatinine increases by 0.5 mg/dL or >30% from baseline, use patient specific dosing.
- Measure **serum aminoglycoside** levels as needed. See each dosing section above for frequency.
- Some data suggest that lowest level of nephrotoxicity occurs when aminoglycosides are administered during the activity period (e.g. 13:30), therefore afternoon administration is preferred.

**OTOTOXICITY**
- Consider biweekly clinical screening for ototoxicity
  - Check baseline visual acuity using a Snellen pocket card
  - To screen for ototoxicity, have patient shake head and then re-read card.
  - Concern should be raised if patient loses 2 lines of visual acuity. Consider formal audiology testing.
  - Contact Audiology (5-6153) for help with testing for ototoxicity

References:
PK/PD parameter: J Infect Dis 1987; 155:93–99
Vancomycin dosing and monitoring

DOSING
1. Estimate creatinine clearance (CrCl) using Cockcroft-Gault equation:
   \[
   \text{CrCl} = \frac{(140 - \text{age}) \times (\text{weight in kg})}{72} \times 0.85 \text{ (if female)}
   \]
   * For patients with low muscle mass (i.e. many patients > 65 yrs), some advocate using a minimum value of 1 to avoid overestimation of CrCl

2. Patients who are seriously ill with complicated infections such as meningitis, pneumonia, osteomyelitis, endocarditis, and bacteremia and normal renal function should receive initial loading dose of 20-25 mg/kg, followed by 15-20 mg/kg Q8-12H using Actual Body Weight (ABW). For other indications see nomogram dosing below.

3. Calculate maintenance dose (using ABW) based on estimated or actual CrCl. See suggested nomogram dosing below.

   Note: Younger patients with normal renal function may need higher or more frequent dosing than suggested below.

### Weight (kg) | CrCl (mL/min)
---|---
<40 | Consult Pharmacy
40–60 | 750 mg Q12H | 750 mg Q24H | 750 mg Q48H | 1000 mg, then redose by level<sup>†</sup>
60–75 | 1000 mg Q12H | 1000 mg Q24H | 1000 mg Q48H | 1000 mg, then redose by level<sup>†</sup>
75–90 | 1250 mg Q12H | 1250 mg Q24H | 1250 mg Q48H | 1250 mg, then redose by level<sup>†</sup>
90–110 | 1500 mg Q12H | 1500 mg Q24H | 1500 mg Q48H | 1500 mg, then redose by level<sup>†</sup>
110–125 | 1750 mg Q12H | 1750 mg Q24H | 1750 mg Q48H | 1750 mg, then redose by level<sup>†</sup>
125–140 | 2000 mg Q12H | 2000 mg Q24H | 2000 mg Q48H | 2000 mg, then redose by level<sup>†</sup>
>140 | Consult Pharmacy

<sup>†</sup>For patients with CrCl <15 mL/min and not receiving hemodialysis redose when random level <15–20 mcg/mL.

DOSING IN RENAL REPLACEMENT THERAPY
Dosing is dependent on type of renal replacement therapy.

**Intermittent Hemodialysis (iHD)**
- **Initial dose:** 15-20 mg/kg once
- Patients should be re-dosed based on serum levels drawn around the dialysis session. Consider redosing at 5-10 mg/kg.
• Pre-dialysis level (preferred): <25 mcg/mL (for meningitis consider re-dosing if <30 mcg/mL)
• Post-dialysis level: <20 mcg/mL

Note: must wait 3–6 hours after the end of the dialysis to account for redistribution of tissue and plasma levels
• For patients with ESRD on a stable HD schedule, a regimen should be established that coincides with HD (e.g. 500 mg qHD). Once weekly serum levels can be drawn to monitor for accumulation.

**Continuous Renal Replacement Therapy (e.g. CVVHD)**
• **Loading dose:** 25-30 mg/kg once
• **Maintenance:** 15-20 mg/kg q24h (assuming no interruption in CRRT, e.g. line clotting)
• Note: Dialysis flow rates >2.5 L/h - consult pharmacy
• **Monitoring:**
  • Patients with changing dialysis flow rates or dialysis held for >4 hours may need more frequent monitoring (consult pharmacy)
  • Patients on stable dialysis flow rates should have trough level checked prior to 4th dose

**Peritoneal Dialysis (PD)**
• **Initial dose:** 15-20 mg/kg once
• Consult pharmacy for recommendations for re-dosing and monitoring serum levels.

**THERAPEUTIC DRUG MONITORING (LEVELS)**
• **Trough levels** are the most accurate and practical method for monitoring Vancomycin effectiveness and toxicity.
• **Peak levels** should NOT be obtained.

Measuring serum Vancomycin levels
• Trough levels should be obtained within 30 minutes of the next dose at steady-state conditions (approximately before the 4th dose).
• In patients with ESRD on hemodialysis, it is preferable to obtain a pre-hemodialysis level with the routine laboratory venipuncture on the morning of hemodialysis. In the event a pre-hemodialysis level is not obtained, a post-hemodialysis level may be drawn at least six hours after the dialysis session.
• Trough levels should be considered in patients with any the following circumstances:
  • Receiving aggressive dosing (>1500 mg Q12H) or Q8H interval
  • Serious infections such as meningitis, endocarditis, osteomyelitis, and MRSA pneumonia.
  • Unstable renal function (change in SCr of 0.5 mg/dL or 50% from baseline) or dialysis
Concurrent therapy with nephrotoxic agents (e.g. aminoglycosides, Colistin, Amphotericin B)
- Prolonged courses (≥5 days) of therapy.

- Frequency of monitoring Vancomycin trough levels:
  - Once-weekly monitoring is recommended for patients with stable renal function who have achieved desired trough levels.
  - More frequent monitoring is recommended for patients who are hemodynamically unstable and/or with changing renal function.

Desired Vancomycin trough levels
- Pneumonia, osteomyelitis, endocarditis, bacteremia: 15-20 mcg/mL
- CNS infections: 20 mcg/mL
- Neutropenic fever, skin and skin-structure infections: 10-15 mcg/mL
- Minimum serum trough concentrations >10 mcg/mL should always be maintained to avoid development of resistance.

Monitoring for Toxicity
- Serum creatinine should be measured at least every other day initially, then weekly if patient’s renal function remains stable.
- Limited data suggest a direct causal relationship between nephrotoxicity and higher serum trough concentrations (>15-20 mcg/mL). Monitor Vancomycin trough levels (see above for frequency and indications).
- Formal audiology testing is not recommended for patients receiving Vancomycin, unless signs and symptoms of ototoxicity became apparent.

References:
### Recommendations for monitoring patients receiving long-term antimicrobial therapy

- Long term defined as ≥ 1 week, except for aminoglycosides and Amphotericin B (see below)
- For use once initial dosing and serum levels have been established
- These monitoring recommendations and monitoring for agents not listed should be individualized, based on each patient’s clinical features, including general health status, age, underlying conditions and organ dysfunction, concomitant medications, drug treatment history, type of infection, and type and dose of antibiotic

<table>
<thead>
<tr>
<th>Antimicrobial agent(s)</th>
<th>Test</th>
<th>Frequency</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides (Amikacin, Gentamicin, Tobramycin, Streptomycin)</td>
<td>CBC, BUN, Creatinine</td>
<td>Weekly</td>
<td>Clinical monitoring and patient education for hearing/vestibular dysfunction at each visit (see p. 149 for vestibular screening method)</td>
</tr>
<tr>
<td></td>
<td>Aminoglycoside level – trough (see dosing section p. 145)</td>
<td>Twice weekly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amphotericin B, AmBisome®</td>
<td>Weekly (twice weekly, if increased risk)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BUN, Creatinine, K, Mg, Phos</td>
<td>Twice weekly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CBC, AST, ALT</td>
<td>1–2 weeks</td>
<td></td>
</tr>
<tr>
<td>β-lactams (Aztreonam, carbapenems, cephalosporins, penicillins)</td>
<td>CBC, BUN, Creatinine</td>
<td>Weekly</td>
<td></td>
</tr>
<tr>
<td>Oxacinil, Naftilin, carbapenems, Penicillin G potassium</td>
<td>add AST/ALT/bilirubin</td>
<td>Weekly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>add K</td>
<td>Weekly</td>
<td></td>
</tr>
<tr>
<td>Micafungin</td>
<td>AST/ALT/bilirubin</td>
<td>Weekly</td>
<td></td>
</tr>
<tr>
<td>Colistin</td>
<td>BUN, Creatinine</td>
<td>Weekly (twice weekly, if increased risk)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(see dosing section p. 150)</td>
<td>Clinical monitoring for neurotoxicity (dizziness, paresthesia, vertigo, confusion, visual disturbances, ataxia)</td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>CBC, BUN, Creatinine, CPK</td>
<td>Weekly</td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>CBC</td>
<td>Weekly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(see dosing section p. 150)</td>
<td>Clinical monitoring for peripheral neuropathy and optic neuritis</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>CBC, AST/ALT/bilirubin</td>
<td>Weekly</td>
<td></td>
</tr>
<tr>
<td>Voriconazole /Posaconazole</td>
<td>CBC, AST/ALT/bilirubin</td>
<td>1–2 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(see dosing section p. 150)</td>
<td>Drug interactions (monitor start of any new medication), visual changes</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Normal renal function: CBC, BUN, Creatinine</td>
<td>Weekly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vancomycin level – trough (see dosing section p. 150)</td>
<td>Weekly, unless change in creatinine (if 50% from baseline), then twice weekly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dialysis: Vancomycin level (see dosing section p. 150)</td>
<td>At each dialysis session</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(see dosing section p. 150)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Oral antimicrobial use in hospitalized patients

When using an agent that is considered to be bioequivalent (no significant difference in rate and extent of absorption of the therapeutic ingredient) via the parenteral and oral route, the oral formulation is preferred if the patient does not have the contraindications listed below.

Contraindications to oral therapy
- NPO (including medications)
- Inability to take other oral medications OR not tolerating a liquid diet/tube feeds
- Hemodynamic instability
- Receiving continuous NG suctioning
- Severe nausea, vomiting, diarrhea, GI obstruction, dysmotility, mucositis
- A malabsorption syndrome
- A concomitant disease state that contraindicates the use of oral medications

NOTE: There are only a limited number of agents that can be used orally for bacteremia or fungemia; these are noted in the table below.

Bioavailability of oral antimicrobials

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>% Oral absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Should NOT be used orally for bacteremia</strong></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>74 – 90%</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanate (Augmentin®)</td>
<td>74 – 90%</td>
</tr>
<tr>
<td>Azithromycin*</td>
<td>38 – 83%</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>90%</td>
</tr>
<tr>
<td>Cefpodoxime*</td>
<td>41 – 50%</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>90%</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>90 – 100%</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>75 – 80%</td>
</tr>
<tr>
<td><strong>Can be used orally for bacteremia or fungemia</strong></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin*</td>
<td>65 – 85%</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Linezolid†</td>
<td>100%</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>100%</td>
</tr>
<tr>
<td>Moxifloxacin*</td>
<td>90%</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole†</td>
<td>100%</td>
</tr>
<tr>
<td>Voriconazole‡</td>
<td>60 – 96%</td>
</tr>
</tbody>
</table>

* Oral absorption is enhanced in presence of food
† Should not be used for *S. aureus* bacteremia
‡ Oral absorption is decreased in presence of food
¶ Inter-patient variability
Ⅷ Do not use with continuous tube feeds (IV preferred). Patients with cyclic tube feeds: separate oral fluoroquinolone by 2 hours before and 6 hours after tube feeds.
Antimicrobial dosing in renal insufficiency

Dosing recommendations can vary according to indication and patient-specific parameters. All dosage adjustments are based on creatinine clearance calculated by Cockcroft-Gault equation.

\[
\text{CrCl} = \frac{(140 - \text{age} \times \text{weight in kg})}{72} \times 0.85 \text{ (if female)}
\]

*For patients with low muscle, some advocate using a minimum of 1 to avoid overestimation of CrCl.

†If patient is on hemodialysis (HD) schedule administration so that patient receives daily dose immediately AFTER dialysis. For assistance with dosage adjustments for patients receiving CVVHD or CVVHDF, please call pharmacy.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical dose (may vary)</th>
<th>CrCl (mL/min)</th>
<th>Dose adjustment for renal insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir IV</td>
<td>5–10 mg/kg Q8H</td>
<td>&gt;50</td>
<td>5–10 mg/kg Q8H</td>
</tr>
<tr>
<td></td>
<td>25–50</td>
<td>25–50</td>
<td>5–10 mg/kg Q12H</td>
</tr>
<tr>
<td></td>
<td>10–24</td>
<td>10–24</td>
<td>5–10 mg/kg Q24H</td>
</tr>
<tr>
<td></td>
<td>&lt;10 or HD†</td>
<td>2.5–5 mg/kg Q24H</td>
<td></td>
</tr>
<tr>
<td>Acyclovir PO (Genital herpes)</td>
<td>200 mg 5x daily</td>
<td>&gt;10</td>
<td>200 mg 5x daily</td>
</tr>
<tr>
<td></td>
<td>&lt;10</td>
<td>200 mg Q12H</td>
<td></td>
</tr>
<tr>
<td>Acyclovir PO (Herpes Zoster)</td>
<td>800 mg 5x daily</td>
<td>&gt;25</td>
<td>800 mg 5x daily</td>
</tr>
<tr>
<td></td>
<td>10–25</td>
<td>800 mg Q8H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;10 or HD†</td>
<td>800 mg Q12H</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin (pneumonia)</td>
<td>500–1000 mg Q12H</td>
<td>&gt;30</td>
<td>500–1000 mg Q12H</td>
</tr>
<tr>
<td></td>
<td>10–30</td>
<td>250–875 mg Q12H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;10 or HD†</td>
<td>250–875 mg Q24H</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin/ clavulanate</td>
<td>1 g Q8H</td>
<td>&gt;30</td>
<td>1 g Q8H</td>
</tr>
<tr>
<td></td>
<td>10–30</td>
<td>1 g Q12H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;10 or HD†</td>
<td>1 g Q24H</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>500–1000 mg Q12H</td>
<td>&gt;30</td>
<td>500–1000 mg Q12H</td>
</tr>
<tr>
<td></td>
<td>10–30</td>
<td>250–500 mg Q12H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;10 or HD†</td>
<td>250–500 mg Q24H</td>
<td></td>
</tr>
<tr>
<td>AmBisome®</td>
<td>0.7–1 mg/kg Q24H</td>
<td>–</td>
<td>No dosage adjustment</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>3–5 mg/kg Q24H</td>
<td>–</td>
<td>No dosage adjustment</td>
</tr>
<tr>
<td>Ampicillin/ sulbactam</td>
<td>1.5–3 g Q6H</td>
<td>&gt;50</td>
<td>1–2 g Q4–6H</td>
</tr>
<tr>
<td></td>
<td>10–50</td>
<td>1–2 g Q6–8H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;10 or HD†</td>
<td>1–2 g Q8H</td>
<td></td>
</tr>
<tr>
<td>Ampicillin/ sulbactam (for Acinetobacter, E. faecalis)</td>
<td>3 g Q4H</td>
<td>≥50</td>
<td>3 g Q4H</td>
</tr>
<tr>
<td></td>
<td>10–50</td>
<td>3 g Q6H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥14 or HD†</td>
<td>3 g Q8H</td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>250–500 mg Q24H</td>
<td>–</td>
<td>No dosage adjustment</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>1–2 g Q8H</td>
<td>≥30</td>
<td>1–2 g Q8H</td>
</tr>
<tr>
<td></td>
<td>10–29</td>
<td>1–2 g Q12H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;10 or HD†</td>
<td>1–2 g Q24H</td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>1–2 g Q8H</td>
<td>≥35</td>
<td>2 g Q HD, if HD in 2 days OR 3 g Q HD, if HD in 3 days</td>
</tr>
<tr>
<td></td>
<td>11–34</td>
<td>2 g Q HD, if HD in 3 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;10 or HD†</td>
<td>2 g Q HD, if HD in 2 days OR 3 g Q HD, if HD in 3 days</td>
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E. Antimicrobial dosing in renal failure insufficiency
<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical dose (may vary)</th>
<th>CrCl (mL/min)</th>
<th>Dose adjustment for renal insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefdinir</td>
<td>300 mg Q12H</td>
<td>≥30</td>
<td>300 mg Q12H</td>
</tr>
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<td></td>
<td></td>
<td>&lt;30</td>
<td>300 mg Q24H</td>
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<td></td>
<td></td>
<td>HD†</td>
<td>300 mg QHD</td>
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<tr>
<td>Cefepime</td>
<td>1 g Q8H</td>
<td>&gt;60</td>
<td>1 g Q8H</td>
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<td></td>
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<td>30–60</td>
<td>1 g Q12H</td>
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<tr>
<td></td>
<td></td>
<td>&lt;29 or HD†</td>
<td>1 g Q24H</td>
</tr>
<tr>
<td>Cefepime (Central nervous system infections or Pseudomonas)</td>
<td>2 g Q8H</td>
<td>&gt;60</td>
<td>2 g Q8H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30–60</td>
<td>1 g Q12H</td>
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<td></td>
<td></td>
<td>11–29</td>
<td>1 g Q24H</td>
</tr>
<tr>
<td>Cefotetan</td>
<td>1–2 g Q12H</td>
<td>≥30</td>
<td>1–2 g Q12H</td>
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<td>10–29</td>
<td>1–2 g Q24H</td>
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<tr>
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<td></td>
<td>&lt;10 or HD†</td>
<td>500 mg Q24H</td>
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<td>Cefpodoxime</td>
<td>100–400 mg Q12H</td>
<td>≥30</td>
<td>100–400 mg Q12H</td>
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<td>100–400 mg Q24H</td>
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<td></td>
<td></td>
<td>HD†</td>
<td>100–400 mg three times/week</td>
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<tr>
<td>Ceftaroline</td>
<td>600 mg Q12H</td>
<td>&gt;50</td>
<td>600 mg Q12H</td>
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<td>30–50</td>
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<td>15–29</td>
<td>300 mg Q12H</td>
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<td></td>
<td>&lt;15 or HD†</td>
<td>200 mg Q12H</td>
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<td>Ceftaroline for MRSA</td>
<td>600 mg Q8H</td>
<td>&gt;50</td>
<td>600 mg Q8H</td>
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<td>15–29</td>
<td>300 mg Q8H</td>
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<tr>
<td></td>
<td></td>
<td>&lt;15 or HD†</td>
<td>200 mg Q12H</td>
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<tr>
<td>Ceftazidime</td>
<td>1–2 g Q8H</td>
<td>&gt;50</td>
<td>1–2 g Q8H</td>
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<td>For Pseudomonas</td>
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<td>30–50</td>
<td>1–2 g Q12H</td>
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<td>15–29</td>
<td>1–2 g Q24H</td>
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<td></td>
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<td>&lt;15 or HD†</td>
<td>1 g Q24H</td>
</tr>
<tr>
<td>Ceftolozane/tazobactam</td>
<td>1.5 g Q8H</td>
<td>&gt;50</td>
<td>1.5 g Q8H</td>
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<td>30–50</td>
<td>750 mg Q8H</td>
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<td>15–29</td>
<td>375 mg Q8H</td>
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<td></td>
<td>&lt;29 or HD†</td>
<td>Load with 750 mg, then 150 mg Q8H</td>
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<tr>
<td>Ceftolozane/tazobactam (Serious Infections)</td>
<td>3 g Q8H</td>
<td>&gt;50</td>
<td>3 g Q8H</td>
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<td>30–50</td>
<td>1.5 g Q8H</td>
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<td></td>
<td>15–29</td>
<td>750 mg Q8H</td>
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<tr>
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<td></td>
<td>&lt;29 or HD†</td>
<td>Load with 1.5 g, then 375 mg Q8H</td>
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<tr>
<td>Ceftriaxone</td>
<td>1–2 g Q24H</td>
<td>–</td>
<td>No dosage adjustment</td>
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<tr>
<td>Ceftriaxone (Central nervous system infections)</td>
<td>2 g Q12H</td>
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<td>No dosage adjustment</td>
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<tr>
<td>Cephalexin</td>
<td>500 mg PO Q6H</td>
<td>&gt;50</td>
<td>500 mg Q6H</td>
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<td></td>
<td>10–50</td>
<td>500 mg Q8H</td>
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<td>&lt;10 or HD†</td>
<td>500 mg Q12H</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>5 mg/kg Q week for 2 weeks, then every other week</td>
<td>≤55 or Cr&gt;1.5</td>
<td>Not recommended</td>
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<tr>
<td>Ciprofloxacin IV</td>
<td>400 mg Q8–12H</td>
<td>≥30</td>
<td>400 mg Q8–12H</td>
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<td>&lt;30 or HD†</td>
<td>400 mg Q24H</td>
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<tr>
<td>Ciprofloxacin PO</td>
<td>250–750 mg Q12H</td>
<td>≥30</td>
<td>250–750 mg Q12H</td>
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<td>&lt;30 or HD†</td>
<td>250–500 mg Q24H</td>
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<td>Clarithromycin</td>
<td>250–500 mg Q12H</td>
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<td></td>
<td>&lt;30</td>
<td>250–500 mg Q24H</td>
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<td>Clindamycin</td>
<td>PO: 300 mg Q8H IV: 600 mg Q8H</td>
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<td>No dosage adjustment</td>
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<tr>
<td>Colistin (Colistimethate)</td>
<td>2.5 mg/kg Q12H</td>
<td>≥50</td>
<td>2.5 mg/kg Q12H</td>
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<td></td>
<td></td>
<td>20–50</td>
<td>2.5 mg/kg Q24H</td>
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<td></td>
<td>&lt;20 or HD†</td>
<td>1.25 mg/kg Q24H</td>
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<td>Drug</td>
<td>Typical dose (may vary)</td>
<td>CrCl (mL/min)</td>
<td>Dose adjustment for renal insufficiency</td>
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<tr>
<td>Daptomycin for endocarditis/bacteremia</td>
<td>6–10 mg/kg Q24H</td>
<td>≥30</td>
<td>6–10 mg/kg Q24H</td>
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<td></td>
<td></td>
<td>&lt;30</td>
<td>6–10 mg/kg Q48H</td>
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<td>HD†</td>
<td>6–10 mg/kg Q48H</td>
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<td>Dicloxacillin</td>
<td>250–500 mg Q6H</td>
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<td>No dosage adjustment</td>
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<td>Doxycycline</td>
<td>100 mg Q12H</td>
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<td>No dosage adjustment</td>
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<td>Ertapenem</td>
<td>1 g Q24H</td>
<td>≥30</td>
<td>1 g Q24H</td>
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<td></td>
<td>&lt;30 or HD†</td>
<td>500 mg Q24H</td>
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<tr>
<td>Ethambutol</td>
<td>15–25 mg/kg Q24H</td>
<td>≥10</td>
<td>Normal dose Q24H</td>
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<td>&lt;10</td>
<td>Normal dose Q48H</td>
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<td>HD†</td>
<td>Normal dose QHD session</td>
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<tr>
<td>Fluconazole</td>
<td>200–800 mg Q24H</td>
<td>≥50</td>
<td>Normal dose (e.g. 100, 400, 800 mg) Q24H</td>
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<td>&lt;50 or HD†</td>
<td>Load w/normal dose, then 50% of normal dose Q24H</td>
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<tr>
<td>Flucytosine (5–FC)</td>
<td>12.5–25 mg/kg Q6H</td>
<td>&gt;40</td>
<td>12.5–25 mg/kg Q6H</td>
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<td>20–40</td>
<td>12.5–25 mg/kg Q12H</td>
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<td>10–19</td>
<td>12.5–25 mg/kg Q24H</td>
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<td></td>
<td>&lt;10 or HD†</td>
<td>12.5–25 mg/kg Q24–48H</td>
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<tr>
<td>Ganciclovir (Induction dose)</td>
<td>5 mg/kg Q12H</td>
<td>≥70</td>
<td>5 mg/kg Q12H</td>
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<td></td>
<td></td>
<td>50–69</td>
<td>2.5 mg/kg Q12H</td>
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<td>25–49</td>
<td>2.5 mg/kg Q24H</td>
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<td>10–24</td>
<td>1.25 mg/kg Q24H</td>
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<tr>
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<td>&lt;10 or HD†</td>
<td>1.25 mg/kg three times/week, administer after HD</td>
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<tr>
<td>Ganciclovir (Maintenance dose)</td>
<td>5 mg/kg Q24H</td>
<td>≥70</td>
<td>5 mg/kg Q24H</td>
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<td>50–69</td>
<td>2.5 mg/kg Q24H</td>
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<td>2.5 mg/kg Q24H</td>
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<td>10–24</td>
<td>0.625 mg/kg Q24H</td>
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<td></td>
<td>&lt;10 or HD†</td>
<td>0.625 mg/kg three times/week, administer after HD</td>
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<td>Gentamicin</td>
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<td>–</td>
<td>See section on aminoglycoside dosing</td>
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<tr>
<td>Isoniazid</td>
<td>300 mg Q24H</td>
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<td>No dosage adjustment</td>
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<tr>
<td>Linezolid</td>
<td>600 mg Q12H</td>
<td>–</td>
<td>No dosage adjustment</td>
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<tr>
<td>Meropenem</td>
<td>1 g Q8H</td>
<td>&gt;51</td>
<td>1 g Q8H</td>
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<td></td>
<td></td>
<td>26–50</td>
<td>1 g Q12H</td>
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<td></td>
<td></td>
<td>10–25</td>
<td>500 mg Q12H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;10 or HD†</td>
<td>500 mg Q24H</td>
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<tr>
<td>Meropenem (Meningitis, CRE infections)</td>
<td>2 g Q8H</td>
<td>&gt;51</td>
<td>2 g Q8H</td>
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<tr>
<td></td>
<td></td>
<td>26–50</td>
<td>1 g Q8H</td>
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<td>10–25</td>
<td>1 g Q12H</td>
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<td></td>
<td>&lt;10 or HD†</td>
<td>1 g Q24H</td>
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<tr>
<td>Metronidazole</td>
<td>500 mg Q8H</td>
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<td>No dosage adjustment</td>
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<tr>
<td>Micafungin</td>
<td>100–150 mg Q24H</td>
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<td>No dosage adjustment</td>
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<tr>
<td>Moxifloxacin</td>
<td>400 mg Q24H</td>
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<td>No dosage adjustment</td>
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<tr>
<td>Nitrofurantoin (Macrobid®)</td>
<td>100 mg Q12H</td>
<td>≥50</td>
<td>100 mg Q12H</td>
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<td>&lt;50</td>
<td>Not recommended</td>
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<td>Oseltamivir (Treatment)</td>
<td>75 mg Q12H</td>
<td>&gt;60</td>
<td>75 mg Q12H</td>
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<td>30–60</td>
<td>75 mg Q24H</td>
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<td>10–29</td>
<td>30 mg Q24H</td>
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<td>&lt;10 or HD†</td>
<td>30 mg QHD session</td>
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<td>Oseltamivir (Prophylaxis)</td>
<td>75 mg Q24H</td>
<td>&gt;60</td>
<td>75 mg Q24H</td>
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<td>30 mg Q48H</td>
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<td>&lt;10 or HD†</td>
<td>30 mg every other HD session</td>
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<td>Oxacillin</td>
<td>1–2 g Q4–6H</td>
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<td>No dosage adjustment</td>
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<td>Penicillin G</td>
<td>3–4 million units Q4H</td>
<td>≥50</td>
<td>3–4 million units Q4H</td>
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<td>10–49</td>
<td>1.5 million units Q4H</td>
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<td></td>
<td>&lt;10 or HD†</td>
<td>1.5 million units Q6H</td>
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<tr>
<td>Drug</td>
<td>Typical dose (may vary)</td>
<td>CrCl (mL/min)</td>
<td>Dose adjustment for renal insufficiency</td>
</tr>
<tr>
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<tr>
<td>Piperacillin/tazobactam</td>
<td>3.375–4.5 g Q6H</td>
<td>&gt;40</td>
<td>3.375 g Q6H (4.5 g Q6H for <em>Pseudomonas</em>)</td>
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<td></td>
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<td>20–40</td>
<td>2.25 g Q6H (3.25 g Q6H for <em>Pseudomonas</em>)</td>
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<td></td>
<td></td>
<td>&lt;20</td>
<td>2.25 g Q8H (2.25 g Q6H for <em>Pseudomonas</em>)</td>
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<td></td>
<td>HD†</td>
<td>2.25 g Q12H (2.25 g Q8H for <em>Pseudomonas</em>)</td>
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<tr>
<td>Posaconazole</td>
<td>See Posaconazole guidelines p. 18</td>
<td>–</td>
<td>No dosage adjustment</td>
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<tr>
<td>Pyrazinamide</td>
<td>15–30 mg/kg Q24H</td>
<td>≥10</td>
<td>15–30 mg/kg Q24H</td>
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<tr>
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<td></td>
<td>&lt;10</td>
<td>12–20 mg/kg Q24H</td>
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<td></td>
<td>HD†</td>
<td>25–30 mg/kg QHD session</td>
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<tr>
<td>Quinupristin/dalfopristin</td>
<td>7.5 mg/kg Q8H</td>
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<td>No dosage adjustment</td>
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<tr>
<td>Rifampin (TB)</td>
<td>600 mg Q24H</td>
<td>–</td>
<td>No dosage adjustment</td>
</tr>
<tr>
<td>Rifampin</td>
<td>300 mg Q8–12H</td>
<td>–</td>
<td>No dosage adjustment</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>100 mg once, then 50 mg Q12H</td>
<td></td>
<td>No dosage adjustment</td>
</tr>
<tr>
<td><strong>UTIs or cellulitis</strong></td>
<td><strong>PO: 1–2 DS tab Q12H IV: 160–320 mg Q12H (Dosing is based on TMP component)</strong></td>
<td>≥30</td>
<td>1–2 DS tab Q12 or 160–320 mg IV Q12H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;30 or HD†</td>
<td>1–2 DS tab Q24H or 160–320 mg IV Q24H</td>
</tr>
<tr>
<td><strong>PCP or serious systemic infections</strong></td>
<td><strong>5 mg/kg Q6–8H</strong></td>
<td>≥30</td>
<td>5 mg/kg Q6–8H</td>
</tr>
<tr>
<td>Valacyclovir (Genital herpes)</td>
<td>500–1000 mg Q12H</td>
<td>≥30</td>
<td>500–1000 mg Q12H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10–29</td>
<td>500–1000 mg Q24H</td>
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<tr>
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<td></td>
<td>&lt;10 or HD†</td>
<td>500 mg Q24H</td>
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<tr>
<td>Valacyclovir (Herpes Zoster)</td>
<td>1 g Q8H</td>
<td>≥50</td>
<td>1 g Q8H</td>
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<td></td>
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<td>30–49</td>
<td>1 g Q12H</td>
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<td>10–29</td>
<td>1 g Q24H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;10 or HD†</td>
<td>500 mg Q24H</td>
</tr>
<tr>
<td>Valganciclovir (Induction dose)</td>
<td>900 mg Q12H</td>
<td>≥60</td>
<td>900 mg Q12H</td>
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<td>40–59</td>
<td>450 mg Q12H</td>
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<td>25–39</td>
<td>450 mg Q24H</td>
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<td>10–24</td>
<td>450 mg Q48H</td>
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<tr>
<td></td>
<td></td>
<td>&lt;10 or HD†</td>
<td>450 mg twice weekly Not recommended</td>
</tr>
<tr>
<td>Valganciclovir (Maintenance dose)</td>
<td>900 mg Q24H</td>
<td>≥60</td>
<td>900 mg Q24H</td>
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<td></td>
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<td>40–59</td>
<td>450 mg Q24H</td>
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<td>25–39</td>
<td>450 mg Q48H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10–24</td>
<td>450 mg twice weekly Not recommended</td>
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<tr>
<td>Vancomycin</td>
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<td>See section on vancomycin dosing</td>
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<tr>
<td>Voriconazole</td>
<td>See Voriconazole guidelines p. 19</td>
<td>–</td>
<td>No dosage adjustment is necessary for PO, IV should not be administered to patients with CrCl ≤50 mL/min due to accumulation of the vehicle.</td>
</tr>
</tbody>
</table>

† If patient is on hemodialysis (HD) schedule administration so that patient receives daily dose immediately AFTER dialysis. For assistance with dosage adjustments for patients receiving CVVHD or CVVHDF, please call pharmacy.
Index

~A~

Abdominal infections
Biliary tract infections .... 39-40
Diverticulitis ...................... 40
Pancreatitis ...................... 41-42
Peritonitis, peritoneal
dialysis-related ................ 45
Peritonitis/GI perforation . 42-45
SBP .................................. 42-43

Acute bacterial
rhinosinusitis .................. 78-79
Allergy, penicillin .............. 137
Anaerobes ....................... 24-25

Amikacin
See Aminoglycosides

Aminoglycosides
Gram-negative infection
dosing ...............................146
Gram-positive synergy
dosing ...............................148
Mycobacterial infection
dosing ...............................147
SICU/WICU dosing ............. 148
UTI dosing ......................... 147

Amphotericin B, lipid ............. 16
Antibiotic lock therapy .......... 63

Antibiogram ..................... 37-38

Antimicrobial dosing
Aminoglycosides
See Aminoglycosides
CNS infections ................... 73
Renal insufficiency .......... 155-158
Surgical prophylaxis .... 121-124

Vancomycin
See Vancomycin

Aspergillosis ..................... 133
Aspiration pneumonia .... 84, 88
Azole drug interactions .... 21-22

Biliary tract infections ....... 39-40
Bloodstream infections
Catheter-related .......... 60-64
Candida .................. 117, 134
Enterococcus spp .......... 62
Gram-negative rods ......... 62
S. aureus ......................... 61
Staph, coagulase-negative . 61
Brain abscess ................. 76

~C~

Candidemia ..................... 117-118
Candidiasis
Hematologic patient .... 134-136
Non-neutropenic host .... 115-120
Candiduria ....................... 115-116
Catheter-related
bloodstream infections .... 60-64
Cellulitis ......................... 100-101
Ceftaroline ....................... 8
Ceftolozane/tazobactam .... 8-9

Central nervous system (CNS)
infections
Antibiotic dosing ............. 77
Brain abscess ................. 76-77
Encephalitis ..................... 75
Meningitis ....................... 73-75
Shunt infection ............... 76-77
Cholangitis ...................... 39-40
Cholecystitis ................... 39-40
Clostridium difficile
infections ......................... 47-50
Colistin ......................... 47-50
Communicable diseases,
reporting ...................... 140
Community-acquired pneumonia
Empiric therapy .............. 83-84
Pathogen-specific therapy . 85-86
COPD exacerbations ........ 82
Cost of antimicrobials .... 159-160
Cystic fibrosis .................. 91-92

~D~

Daptomycin .................. 10-11
Diarrhea ........................................ 51-53
Diabetic foot infections ......................... 103-105
Diverticulitis .................................. 40
Dosing, antimicrobials
  See Antimicrobial dosing

~E~
Encephalitis .................................... 75
Endocarditis ................................... 65-70
  Treatment
  Culture-negative ......................... 68
  Diagnosis .............................. 69-70
  Fungal .................................. 119-120
  Pathogen-specific therapy .......... 65-69
  Prosthetic valve ....................... 68-69
  Prophylaxis ............................ 125
Endomyometritis .............................. 56
Epidural abscess ............................. 108-109
Ertapenem .................................... 11

~F~
Febrile neutropenia .......................... 129-130
Formulary ..................................... 7
Fosfomycin ................................... 11-12
Fungal infections
  Candida spp ............................ 115-120, 134-136
  Filamentous fungi ...................... 133-134
  Prophylaxis, SICU/WICU .......... 120
Fusarium ..................................... 133

~G~
Gentamicin
  See Aminoglycosides
GI perforation .............................. 45
Gonococcal urethritis, cervicitis, proctitis .......... 57-58
Gynecologic infections
  Endomyometritis ....................... 56
  Pelvic inflammatory disease .......... 56

~H~
Healthcare-acquired pneumonia (not VAP) ........ 87-88
H. pylori infection ....................... 54-55

~I~
ICD infection ............................... 71-72
ID approval
  Antimicrobials .......................... 7
  Pager .................................... 6
Infection control ....................... 139-144
Infectious diarrhea ..................... 51-53
Influenza ................................... 93-94
Isolation precautions .................... 141

~L~
Linezolid .................................... 12-13
Long-term antimicrobial therapy ................. 153

~M~
Meningitis, bacterial ....................... 73-75
  Antimicrobial dosing ................. 77
  Empiric therapy ....................... 73
  Pathogen-specific therapy ......... 74
MDR Gram-negative organisms ............ 28-30
Micafungin .................................. 17-18
Microbiology .............................. 31-35
MRSA
  Decolonization ......................... 102-103
  Soft-tissue infections .............. 100-101
  Surveillance ......................... 142-143

~N~
Necrotizing fasciitis ..................... 107-108
Neutropenic fever ...................... 129-130
Nosocomial pneumonia ............. 87-88

~O~
Oncology
  Neutropenic fever .......... 129-130
Oral antimicrobials ..................................154
Orbital cellulitis ..................................80-81

~P~
P. acnes infection .........................25-26
Pacemaker infection ....................71-72
Pancreatitis ....................................41-42
Parasites ........................................53
Pelvic inflammatory disease ............56
Penicillin allergy ...........................137
Peritonitis/GI perforation ..............42-45
Peritoneal dialysis-related ............45
Spontaneous bacterial infection .......42-43
Post-op / post-procedure infections ...105-107
Pneumonia
  Community-acquired ..........83-84
  Healthcare-acquired ..........87-88
  Ventilator-associated ......88-90
Pneumococcal vaccine .................23
Posaconazole ..................................18-19
Pre-operative prophylaxis 121-124
Price of antimicrobials ..............159-160
Prophylactic use of antimicrobials
  Endocarditis .........................125
  Fluconazole in ICUs .................120
  Hematologic malignancy ..........131-132
  Pre-op / pre-procedure 121-124
  Solid organ .........................126-128

~R~
Renal insufficiency
  Antimicrobial dosing ..........155-158
Reported diseases .....................140
Resistant Gram-negative infections ...28-30
Respiratory viruses ....................93-94
Restricted antimicrobials ............7

~S~
SBP .............................................42-43
Sepsis .......................................99
Sexually transmitted diseases .......57-59
Shunt infection .........................76-77
Sinusitis ....................................78-79
Skin, soft-tissue and bone infections
  Cellulitis .........................100-101
  Cutaneous abscess ..........101-102
  Diabetic foot infection ........103-105
  Necrotizing fasciitis ......107-108
  Post-op infections ............105-107
  Recurrent MRSA .............102-103
  Surgical-site infections ....105-107
  Vertebral osteomyelitis,
    diskitis, epidural abscess ....108-109
  Streptococci ......................24-25
  Surgical prophylaxis .........121-124
  Surgical-site infections ...105-107
  Surveillance
    CRE ..................................142
    MRSA .........................142-143
    VRE ................................144
  Susceptibility testing ...........31-32
  Syphilis ............................58-59

~T~
Therapeutic monitoring
  Aminoglycosides ..............145-149
  Vancomycin .....................150-152
  Outpatient long-term antimicrobial therapy ....153
  Tigecycline .......................13
  Tobramycin
    See Aminoglycosides
Transplant
  Antimicrobial prophylaxis
    Hematologic malignancy ....131-132
    Solid organ ..................126-128
Trichomoniasis ......................... 57
Trimethoprim/
sulfamethoxazole ..........14-15
Tuberculosis .........................95-98

~U~
Urinary tract infections
    Bacterial
        Cystitis ......................... 110
        Pyelonephritis ..................111
        Urosepsis .......................111
    Catheter-related ........... 113-114
    Fungal ......................... 115-116

~V~
Vancomycin

Dosing ....................... 150-152
Monitoring .................. 151-152
Ventilator-associated
    pneumonia (VAP) ........... 88-90
Vertebral osteomyelitis, diskitis,
    epidural abscess ........ 108-109
Voriconazole ..................... 19-20
VRE Surveillance ............. 144

~W~
Wound infections,
    post-op ...................... 105-107
Important Phone Numbers

THE JOHNS HOPKINS HOSPITAL

Antibiotic Approval: ....... PING “JHH Antibiotic Approval Pager”
Antimicrobial Stewardship Program: ................................. 7-4570
Infectious Diseases Consults: .... PING “JHH Infectious Diseases”
Oncology/Transplant Service (Transplant ID) .... PING “Transplant/
Infectious Diseases”

Adult Inpatient Pharmacy (Zayed 7000): ...................... 5-6150
Critical Care and Surgery Pharmacy (Zayed 3121): .......... 5-6505
Weinberg Pharmacy: ............................................... 5-8998
Microbiology Lab: .................................................. 5-6510
Hospital Epidemiology & Infection Control: .................... 5-8384
HEIC Emergency Beeper: ........................................... 3-3855

JOHNS HOPKINS BAYVIEW MEDICAL CENTER

Antibiotic Approval: ........ PING “Bayview Antibiotic Approval”
Infectious Disease Consults: . PING “Bayview Infectious Diseases”
Bayview Inpatient Pharmacy: .................................. 0-0958
Microbiology Lab: ................................................ 5-6510
Hospital Epidemiology & Infection Control: .................... 0-0515

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Antimicrobial Stewardship in the Emergency Department and Guidelines for Development

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1. The Centers for Disease Control and Prevention Get Smart for Healthcare Program maintains a list of resources that provides guidance for implementation of antimicrobial stewardship programs. This campaign for inpatient stewardship has useful resources for ED clinicians, including patient educational brochures on antimicrobial resistance and guidelines to change clinician behavior which can be downloaded freely at http://www.cdc.gov/getsmart/. The CDC viral prescription pad is a simple, useful tool for patient education and discharge instruction: http://www.cdc.gov/getsmart/campaign-materials/print-materials/ViralRxPad.html

2. Local antimicrobial recommendations based on national guidelines and institution specific data can be created. Examples include the Johns Hopkins Hospital Antibiotic Guidelines (www.hopkinsmedicine.org/amp) and the University of Pennsylvania Medical Center Guidelines for Antimicrobial Therapy (http://www.uphs.upenn.edu/bugdrug/antibioticmanual/table%20of%20contents.htm)

3. While most antimicrobial order forms are restrictive forms geared at inpatients, there are some examples that may be tailored to the ED setting (see Appendix 1): http://hfhs-formslibrary.org/forms/HFH-78-7049MR-0409%20antimicrobial.pdf


Templates for the treatment of uncomplicated infections available in pdf format can be viewed electronically, printed, or directly integrated into an Electronic Health Record. Appendices 2 and 3 serve as examples.
Abstract

Antimicrobial resistance is a mounting public health concern. Emergency departments (EDs) represent a particularly important setting for addressing inappropriate antimicrobial prescribing practices, given the frequent use of antibiotics in this setting that sits at the interface of the community and the hospital. This article outlines the importance of antimicrobial stewardship in the ED setting and provides practical recommendations drawn from existing evidence for the application of various strategies and tools that could be implemented in the ED including advancement of clinical guidelines, clinical decision support systems, rapid diagnostics, and expansion of ED pharmacist programs.

Background

Antimicrobial resistance is a mounting public health concern. Antibiotic-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and extended spectrum beta lactamase – producing organisms (ESBL) have emerged and expanded their presence from healthcare settings to the community.\(^1\)\(^2\)\(^3\) Inappropriate antimicrobial use has been described as the most important preventable cause of drug resistance in both hospital and community settings.\(^4\)\(^5\)\(^6\)\(^7\) Estimated rates of inappropriate and unnecessary antibiotic use among office-based practitioners range from 25 to 63%.\(^8\) Infections with resistant pathogens are associated with increased morbidity, mortality, and rising health care costs.\(^1\) In addition, inappropriate antibiotic use is an important patient safety issue. An estimated 142,500 ED visits each year are for adverse events associated with systemic antibiotics, with nearly 80% due to allergic reactions.\(^9\)

Antimicrobial stewardship is a collection of strategies – including policies, guidelines, surveillance, data transparency, education, and evaluation – that collectively results in optimization of antibiotic prescribing practices.\(^1\)\(^10\)\(^11\) When implemented and monitored effectively, antimicrobial stewardship programs (ASPs) have been demonstrated to deliver a measurable impact in multiple clinical settings.\(^12\)\(^13\) Antimicrobial stewardship has been found to reduce overall and inappropriate antimicrobial use, lower drug costs, decrease treatment duration, decrease adverse events to antibiotics\(^14\), and reduce resistance locally.\(^15\) However, to date, ASPs have been targeted primarily to the inpatient setting, and there is a paucity of literature regarding ED antimicrobial stewardship strategies.

The 2010 United States’ Patient Protection and Affordable Care Act (PPACA) provides an important opportunity to focus on the quality of emergency care, given the expected increase in the population who will seek care in the ED.\(^16\) Judicious use of antimicrobial agents in both the inpatient and ED settings will likely receive increased emphasis given recent PPACA provisions to eliminate payments for hospital-acquired infections.\(^17\) According to the Surviving Sepsis campaign, the initial choice of antibiotic in the ED is arguably the most important dose the patient receives for patients who are admitted with serious infections and should be based not only on the suspected infection but also host factors and prior antibiotic exposure.\(^18\)\(^19\) The antibiotic choice made by the ED also has a significant influence on what therapy is continued in the inpatient setting, thus representing an important opportunity for antimicrobial stewardship and collaboration with other specialties. This principle applies to both admitted patients and ED outpatients. In addition to making the decision regarding first antibiotic dose for inpatients, ED clinicians play a vital role in obtaining relevant cultures.
prior to administration of antibiotics that allows for tailoring or stopping of antibiotic therapy during hospitalization.

**Importance**

Emergency Departments (EDs) represent a critical setting for initiating interventions that could reduce inappropriate antibiotic prescribing. As ED clinicians, we routinely prescribe antimicrobials to patients for a variety of conditions, including skin and soft-tissue infections (SSTIs), urinary tract infections (UTIs), blood-stream infections (BSIs), and upper and lower respiratory tract infections (URI, LRI). Since EDs sit at the interface of the inpatient and outpatient settings, ED practitioners have the unique opportunity to impact antimicrobial stewardship in both locations with important downstream implications. As an example, two recent ED observational studies report significant rates of overprescribing for acute bronchitis, with more than 75% of prescriptions being for broad spectrum antibiotics.\(^{20,21}\)

While pilot ED based interventional studies have been implemented,\(^{22}\) challenges remain with substantial antibiotic overuse despite improvements after the intervention.

Reducing unnecessary antimicrobial use is imperative not only for decreasing rates of antimicrobial resistance in the community but also for individual patient safety, given the high rate of adverse events to antibiotics, including allergic reactions and development of secondary antibiotic associated infections such as *C. difficile* infection.\(^{23}\)

While EDs may not be included in all hospital antimicrobial stewardship programs, strategies, some of which can be extrapolated from successes in other settings, may help reduce unnecessary antimicrobial prescribing in the ED.

**Challenges to Antimicrobial Stewardship in the ED setting**

There are a set of distinct challenges associated with providing systematic education and oversight for antimicrobial stewardship in the ED setting. These include high rates of ED overcrowding,\(^{24}\) rapid rate of patient turnover, the need for quick decision making usually without consultation, and importantly the large and varied mix of providers who work in a shift based scheduling format, with relatively high rates of staff turnover versus other clinical settings.\(^{25}\)

Specific barriers to implementing other public health measures in the ED have been previously described and include perceived lack of efficacy, concerns regarding reimbursement and resource availability, and potential interference with ED operational efficiency.\(^{26,27}\)

Further, medical liability concerns, including the failure to diagnose and treat and requirements to satisfy local or national externally monitored quality measures have been shown to be associated with overuse of antibiotics and other medications, due to insufficient time to hone in on a definitive diagnosis.\(^{29}\)

Further, clinicians’ desire to maintain patient satisfaction has been demonstrated to be an important factor in antibiotic prescribing practice in the ED setting.\(^{30}\)

Previous studies have shown that provision of antibiotic prescriptions is associated with increased satisfaction for ED visits for acute respiratory tract infection,\(^{31}\) and physicians are more likely to prescribe antibiotics if they perceive patients want them.\(^{32}\)

Despite these challenges, potential strategies described in this paper provide an important starting point for tackling this significant public health challenge.

**ED Approaches to Antimicrobial Stewardship**

In this concept paper, we review antimicrobial stewardship strategies, lessons learned from the literature in other settings, and existing clinical practice guidelines. The discussion includes critical interpretation of the findings or recommendations in relation to ED practice...
and is followed by a general set of recommendations for decreasing unnecessary antibiotic use in ED settings. The factors important in translating antimicrobial stewardship interventions to the ED are drawn both from critical evaluation of the literature, and the authorship team’s collective experience with infectious disease research in emergency settings and antimicrobial stewardship efforts in both inpatient and ED settings.

Broadly speaking support for the importance of antimicrobial stewardship programs in the ED is driven by recognition of the responsibility of front line practitioners in addressing the public health epidemic of rising rates of antimicrobial resistance. Antimicrobial stewardship in the ED, however, is nuanced by the fact that broad spectrum antibiotic use is often the most appropriate initial regimen for life-threatening infections, and ensuring the most appropriate empiric treatment is thus a major focus of stewardship interventions in that setting.

Many hospitals have existing antimicrobial stewardship programs, which are most often organized by leaders in hospital epidemiology and infection control. The simplest mechanism for EDs to engage in an antimicrobial stewardship program is to have an ED clinician volunteer to sit on the antimicrobial stewardship committee, which will provide opportunity for engaging with other professionals. Collaborative efforts between ED clinicians, pharmacists, microbiologists, and primary care and infectious disease colleagues are likely to be the most fruitful in yielding long-term successes, including reduced use of inappropriate empiric antimicrobial therapy. The most effective strategies include measurement of processes and specific outcomes; interventions optimally include a comprehensive multidisciplinary antibiotic management strategy, and outcome measures to carefully track antimicrobial utilization and resistance patterns. Various antimicrobial stewardship strategies are described below and summarized in Table 1.

Education of ED clinicians

Antimicrobial stewardship programs that have been shown to be the most effective are those that include active educational programs, such as seminars or roundtable discussions, as they promote dialogue and increase likelihood of clinician engagement which is fundamental to practice change. Clinical practice guidelines promulgated by the Infectious Disease Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) recommend education as an essential element of a stewardship program, which should be incorporated with other strategies to increase acceptance of other stewardship activities. It is noted however that these programs alone are unlikely to lead to enduring practice changes, as they require coupling with complementary strategies to reinforce practice change. For example, while a cluster randomized study of 16 EDs showed that multifaceted interventions could successfully reduce antibiotic use for the treatment of upper respiratory tract infections, substantial overuse remained even after the intervention, suggesting that education alone is insufficient for sustained practice change. Use of educational messaging for the ED should be tailored to existing practice patterns and the particular challenges of the ED environment. Inclusion of infectious disease topics in departmental grand rounds and inter-specialty conferences and meetings may facilitate improved antibiotic use in the ED but engagement of thought leaders from the ED is essential to tailor the content of the message and ensure optimal engagement of all members of the practice group.

Development of ED-specific guidelines

Clinical practice guidelines, typically developed by professional societies, provide an opportunity to improve evidence based practice, including appropriate empiric antibiotic therapy. While guidelines for infectious diseases are typically promulgated from a broader
scope, definitions for appropriate and inappropriate antimicrobial use and guidelines for meeting ED standards may not be explicitly defined. Guidelines can be developed at the state or local level, but ideally should be adapted to the individual facility ED; optimally, they should be based on local susceptibilities and formulary.\textsuperscript{36} For example, guideline committee recommendations for use of trimethoprim-sulfamethoxazole (TMP-SMX) for treatment of uncomplicated cystitis have been based on local patterns showing < 20% resistance.\textsuperscript{37} Consideration should also be given to provide guidance that helps clinicians decide when NOT to treat with an antibiotic; this is particularly relevant for non-antibiotic responsive upper respiratory tract infections such as bronchitis and sinusitis which are known to be overtreated in the ED.\textsuperscript{20,21} The IDSA/SHEA guidelines recommend multidisciplinary development of guidelines that incorporate local susceptibilities and facilitating these guidelines through provider education and feedback on antibiotic use.\textsuperscript{34} Recognizing that guidelines are affected by a variety of issues that impact uptake and sustained use, deliberate development using a team of invested partners and experts followed by systematic dissemination, implementation, and evaluation can help maximize clinical impact and address barriers to implementation in order to be most effective.\textsuperscript{38,39,40} Critical pathways may help address appropriate antibiotic use and decrease admission in low risk patients.\textsuperscript{41} Ultimately, a well thought out process for implementation will be most likely to foster the development of ED-specific recommendations alongside nationally developed measures for evaluating outcomes of antimicrobial stewardship.

**ED pharmacist**

Initial therapy decisions made in the ED are critical for ensuring positive patient outcomes. Several recent publications have reported the potential impact of inclusion of an ED pharmacist (EPh) as a key component of the clinical care team to facilitate appropriate prescribing in the ED, yet fewer than 5% of EDs have a dedicated EPh.\textsuperscript{42,43} While the EPh coverage recommended or supported by different programs varies, it is clear that the EPh offers added value for the ED across multiple roles, including continuous clinician education, real-time feedback and consultation regarding prescribing practices, provision of culture and susceptibility report follow-up, development of continuity of care programs, medication distribution and reconciliation, identification of drug interactions, and support for non-infectious disease programs including resuscitation management and trauma care. Studies have already demonstrated that an EPh in the ED can reduce duration of treatment and overall cost of care and plays an important role in reducing medication errors.\textsuperscript{44} The EPh may also play another important role in defining ASP outcome measures. Although direct demonstration of decreased antimicrobial resistance as an outcome of the ASP remains challenging, common surrogate outcomes which an ED pharmacist (or a hospital pharmacist focused on infectious diseases and antimicrobial stewardship) can evaluate and document include effect of the ASP on length of stay, antibiotic use, and compliance with guidelines, via a quality assurance program.

**Clinical decision support systems (CDSS)**

Clinical decision support systems use health information technology to deliver information to the clinician at the point of care. The use of CDSS to assist with antimicrobial prescribing has been shown to be successful in a variety of other clinical care settings,\textsuperscript{45,46} and could be applied to the ED. For example, the use of handheld CDSS was found to reduce antibiotic usage and length of stay in patients in the ICU setting.\textsuperscript{47} In the outpatient setting, CDSS has been successful in reducing unnecessary antibiotic use for upper respiratory infection in the community.\textsuperscript{48} The IDSA/SHEA guidelines recognize that CDSS can improve prescribing practices; however, widespread implementation of CDSS has been slow, likely because many institutions lack the IT infrastructure and systems required for implementation. In
order to be practically feasible in the ED, streamlined CDSS can be designed specifically to help avoid information overload. However, it is important to recognize that CDSS may lead to over-reliance on automation. An ideal CDSS system for use in the ED would incorporate patient data at the time of electronic antimicrobial prescribing, including laboratory results (e.g. culture if available, patient’s renal function), patient medical history and allergies, in addition to local recommendations, then deliver “suggestions” to the ED prescriber. With a trend toward wider spread implementation of electronic health records (EHRs) nationwide, CDSS may provide important high impact opportunities to facilitate antimicrobial stewardship in the ED.

**Antimicrobial order forms**

One of the earliest methods developed to reduce unnecessary antibiotic use is the use of antimicrobial order forms, which can be paper or electronic based and require clinician completion of a form, with subsequent approval by pharmacy or an infectious disease physician. Order forms have been advocated as a method to facilitate implementation of clinical practice guidelines. Published studies evaluating the impact of antibiotic order forms in reducing unnecessary antibiotic use report mixed results in different settings. For example, while they have been used successfully in reducing inappropriate surgical prophylaxis, they have not been shown to be useful in reducing vancomycin in pediatric inpatients. In the critical care setting, restrictions on antibiotic use have resulted in reducing selected antimicrobial agents, though that success has been offset in some studies by increasing use of other broad-spectrum agents. The most notable challenge with order forms which has been described is their practical inconvenience and undue time requirements; accordingly, future evaluation of the utility and impact of antibiotic order forms in ED should attend to streamlining methods for integrating them into EDs and will require further study. An example of an antimicrobial order form may be found in Appendix 1.

**Post-prescription review**

A common approach to stewardship among inpatients is to perform review of antimicrobial use 48 to 72 hours after antibiotics are started with the goals of stopping or streamlining therapy based on the patient’s clinical course as well as imaging and microbiology data which become available. ED providers can make significant contributions to these efforts by obtaining adequate culture specimens prior to the first dose of antibiotics so that the admitting physician will have pathogen identification and susceptibility results on which to de-escalate to targeted antibiotics.

Post-prescription review of patients discharged from the ED has not traditionally been performed by ED personnel due to lack of resources. However, with the expected increase in home health services advanced through health care reform, enhanced patient follow-up and care coordination presents a unique opportunity for culture follow-up and switching to narrow spectrum antibiotics. Telephone follow-up is already being conducted in many EDs for purposes of patient satisfaction (Press Ganey), and could be leveraged for decreasing unnecessary use of antibiotics in the ED. Patient satisfaction in the ED has been found to be related to better understanding of illness rather than receipt of antibiotics for upper respiratory infection. Techniques to enhance patient education include giving patients a prescription to fill in the event of a positive test (for example, for streptococcal pharyngitis), and use of the Centers for Disease Control and Prevention (CDC) viral prescription pad as an innovative patient education tool, which provides patient education on viral illness and recommendations for symptomatic treatment. Furthermore, follow-up phone calls can be used to assess medication compliance and identify adverse events. A systems based approach should be in place to assist with patient follow up and coordination of care, such as
a quality improvement program or staff nurse coordinator, in order to reduce the burden on ED clinicians.\textsuperscript{57} ED outpatients with viral infections present a unique opportunity for patient education and reduction of unnecessary antibiotics; for example, clinical practice guidelines recommend a “watch and wait” approach to the treatment of most cases of otitis media.\textsuperscript{58} Telephone follow-up for patients with these less severe infections represents an important opportunity for addressing patient or parent concerns and further education, while striving towards the goal of patient satisfaction.

\textbf{Rapid diagnostics}

Improving access to rapid diagnostics is one of the cornerstones of the IDSA strategy to curb resistance.\textsuperscript{59} Expanded laboratory capacity is beginning to play an important role in antimicrobial stewardship programs and the clinical microbiology laboratory has an important role in providing patient specific culture and susceptibility data.\textsuperscript{34,60} The recent availability of rapid molecular diagnostic tests can provide accurate pathogen identification including resistance markers with short turn-around-times of approximately one hour. The use of rapid molecular diagnostics in the inpatient setting has already been shown to lead to more targeted use of narrow spectrum antibiotics, earlier switch in therapy, and a decrease overall antibiotic use.\textsuperscript{61,62} There is a growing arsenal of rapid diagnostic tests which could have potential utility in the ED setting to improve antimicrobial prescribing and patient outcomes.\textsuperscript{63} Many of these tests are already or could be made available at or near the point of care, such as rapid streptococcal antigen tests and newly emerging rapid molecular tests (e.g. molecular based screening for \textit{S. aureus} colonization and infection, \textit{C. difficile}, and viral respiratory pathogens including influenza, RSV, and pneumococcus among others). Limitations to uptake and integration of molecular tests in the ED include false negative and positive results, challenges to simultaneous identification of multiple organisms, and logistical and regulatory constraints associated with integration of these tests in the ED.\textsuperscript{64} Nonetheless, expansion and further development of automated molecular platforms (such as the Cepheid GeneXpert\textsuperscript{R} and BDGeneOhm\textsuperscript{R}) as point of care tests for the ED setting could prove to be a critical component of a strategy directed toward decreasing antimicrobial resistance.\textsuperscript{65} Further study is required to assess performance and cost, relative to traditional testing or empiric therapy before widespread consideration is realized.

\textbf{Efforts to shorten duration of therapy}

Antibiotic guidelines which recommend reducing the duration of therapy have the potential to reduce selection pressure for resistant pathogens without compromising individual patient outcomes.\textsuperscript{66} Duration of antimicrobial therapy for community acquired pneumonia is now measured by the Centers for Medicare and Medicaid Services (CMS) as a core performance measure. Antimicrobial stewardship strategies that involve provider education and prospective feedback have already been found to reduce treatment duration from 10 to 7 days in non-ED settings.\textsuperscript{67} Similar models of educational interventions could be advanced in the ED but await ED advocates and/or formal investigation. Examples of shortened treatment regimens for various uncomplicated infections in ED patients treated as outpatients are shown in Table 2.

\textbf{Dose optimization}

Dose optimization relies on the principles of pharmacokinetics and pharmacodynamics and patient (age, weight, renal function) and infection specific factors (pathogen, site of infection) in antibiotic selection. Examples include prolonged beta lactam infusion and higher doses of fluoroquinolones for coverage of \textit{S. pneumo} in patients with community-acquired pneumonia. Dose optimization is most applicable for admitted patients that have
prolonged ED length of stay awaiting admission and can be undertaken with input from pharmacist colleagues.33,34

Streamlining or de-escalation of therapy—The goal of de-escalation is to transition patients from empiric broad spectrum antibiotics to targeted narrow spectrum therapy as soon as possible. In de-escalation strategies, laboratory reporting of the causative agent triggers antimicrobial switch therapy to the narrowest possible spectrum. Laboratory results are reviewed by a pharmacist or infectious disease physician, and recommendations are provided to the clinician for adjusting therapy.1,10 This strategy, while more commonly used in inpatient settings, could be applied to ED outpatients as well, in the context of a robust program for follow up and coordination of care. Streamlining aims to minimize a patient’s antibiotic exposure. For example, a pharmacy system can identify those patients on two or more antibiotics, triggering an alert for the pharmacist to contact the medical provider to determine clinical indication and provide alternatives, eliminating redundancy.68

ED antibiogram development
An antibiogram is a comprehensive picture of the susceptibility of microbial species to a select antimicrobial agent specific for an individual facility. While antibiograms are often reported for outpatient isolates, they may be limited in that they bias high risk cases or treatment failures where cultures are sent by the ED clinician. These antibiograms therefore may overestimate antimicrobial resistance, which could lead to inappropriate use of broad spectrum antibiotics unless that bias is taken into consideration. Hospital antibiograms may not always provide susceptibilities broken down by unit or source of isolate, which would be useful for helping guide ED clinicians in their choices for empiric therapy. According to the IDSA/SHEA guidelines, local antibiograms with pathogen-specific susceptibility data should be updated no less than once yearly and consideration should be given to providing ward specific data and outpatient data to facilitate clinical decision-making in those settings.34 ED-based antibiograms could be incorporated into CDSS platforms to provide ED physicians with a comprehensive resource for clinical decision-making, especially with the development of more rapid molecular based testing for drug resistance. Educational interventions would aid ED clinicians in appropriate interpretation and use. Dissemination of local antibiograms based on ED patient isolates would also be useful to establish uniform measures for tracking resistance and developing ED specific quality control initiatives.

Conclusions
Globally, clinicians practicing in ED settings must acknowledge and address the increasing problem of antimicrobial resistance stewardship, which require EDs take an active role in designing and systematically studying strategies to improve antimicrobial stewardship in these settings. Since not all antimicrobial stewardship strategies are applicable to the ED, programs must be developed through partnership between the ED and other key stakeholders, including local communities, outpatient physicians, hospital administrators, pharmacists, and infectious disease specialists. It is time to incorporate ED antimicrobial stewardship into these policies and other directives, as calls for its broad application continues to expand from leadership at the CDC, National Institutes of Health (NIH), IDSA, SHEA, and Centers for Medicare and Medicaid Services (CMS). While some have begun this process, there remains a large gap in the literature evaluating ED based antimicrobial stewardship strategies. Accordingly a strong need exists for research to define appropriate metrics for measuring ASP outcomes in EDs. In addition, research is needed to determine which of multiple ASP strategies (e.g. clinical practice guidelines, use of rapid diagnostics) are most appropriate for the ED, by assessing feasibility and relative impact for key outcome measures as well as acceptability to ED stakeholders. There is an important role for...
researchers and advocates to disseminate findings for evidence based public health interventions, identify local barriers to implementation, adapt measures to local context and advocate for legislation, regulation and incentives outside of the ED to strengthen these ED based interventions.69 Ultimately, however, it is the practicing ED clinician who has the greatest potential to impact outcomes for patients and their community through careful antimicrobial prescribing decision-making.

Acknowledgments

Grants and Financial Support:

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References


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Appendices: Templates for ED Antimicrobial Stewardship

**Prototypes developed by Larissa May and Sara Cosgrove. Templates are provided as examples only and are not intended to replace clinical judgment.**

**Appendix 1**
Sample Antimicrobial Order Form for Empiric Vancomycin in the ED

<table>
<thead>
<tr>
<th>Please check criteria met below in order to justify use of empiric vancomycin therapy for this patient:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Serious infection suspected to be caused by beta-lactam-resistant gram-positive microorganism</td>
</tr>
<tr>
<td>• Infection suspected to be caused by gram-positive microorganisms in patient who has a serious allergy to beta-lactams.</td>
</tr>
<tr>
<td>• History of MRSA or Coagulase negative S. aureus positive culture + suspected infection</td>
</tr>
<tr>
<td>• Bacterial Meningitis (suspected S. pneumonia)</td>
</tr>
<tr>
<td>• Prophylaxis for endocarditis following certain procedures in patients at high risk for endocarditis or with suspected S. aureus infection, per American Heart Association Guidelines.</td>
</tr>
<tr>
<td>• Respiratory tract, skin or musculoskeletal procedure Y/N</td>
</tr>
<tr>
<td>• Patient at risk of endocarditis Y/N</td>
</tr>
<tr>
<td>• Oral vancomycin: Patient with severe Clostridium difficile infection or failure to respond to metronidazole therapy</td>
</tr>
<tr>
<td>• If criteria above not met, please enter alternate explanation for use and call the pharmacy for notification.</td>
</tr>
<tr>
<td>• Send clinical specimen (blood, wound, sputum, urine, body fluids) to microbiology for culture and sensitivity</td>
</tr>
<tr>
<td>• Vancomycin use should be re-evaluated by the infectious disease pharmacy team at 48 hours for consideration of discontinuation if criteria are no longer met</td>
</tr>
</tbody>
</table>

**Appendix 2**
Template for Clinician Guidance for Treatment of SSTI

<table>
<thead>
<tr>
<th>Suspected Infection</th>
<th>Likely Pathogens</th>
<th>Empiric Therapy</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purulent SSTI</td>
<td><em>S. aureus</em></td>
<td>Cephalexin, dicloxacillin, clindamycin</td>
<td>5–10 days</td>
</tr>
<tr>
<td><em>Cutaneous abscess, uncomplicated</em></td>
<td><em>S. aureus</em> (MRSA, MSSA)</td>
<td>I and D first line</td>
<td></td>
</tr>
<tr>
<td><em>Cutaneous abscess, complicated (e.g. comorbidities, immune</em></td>
<td><em>S. aureus</em> (MRSA, MSSA)</td>
<td>TMP-SMX, clindamycin (outpatients) Vancomycin, linezolid, daptomycin (hospitalized patients)</td>
<td>7–10 days Consider admission</td>
</tr>
</tbody>
</table>

Ann Emerg Med. Author manuscript; available in PMC 2014 July 01.
<table>
<thead>
<tr>
<th>Suspected Infection</th>
<th>Likely Pathogens</th>
<th>Empiric Therapy</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suppression, failing outpatient treatment, area difficult to drain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis uncomplicated</td>
<td>Streptococcus sp., S. aureus</td>
<td>Cephalexin, dicloxacillin, clindamycin</td>
<td>5–7 days</td>
</tr>
<tr>
<td>Diabetic Foot Infection (not osteomyelitis)</td>
<td>polymicrobial</td>
<td>Broad spectrum penicillin, cephalosporin, quinolone + antimicrobial coverage</td>
<td>14 days Hospital admission</td>
</tr>
</tbody>
</table>

- Where possible, base empiric therapy on prior culture results, patient medical history, local antibiograms, taking into account any serious allergies or prior adverse events. While targeted spectrum antibiotics are ideal, cost, patient compliance and duration of treatment may be factors in clinical decision-making.

- Weblink to clinical practice guidelines: click here:
  - SSTI: http://cid.oxfordjournals.org/content/early/2011/01/04/cid.ciq146.full.pdf

**Appendix 3**

Template for Clinician Guidance for Empiric Treatment of Suspected UTI

<table>
<thead>
<tr>
<th>Suspected infection</th>
<th>Laboratory Results</th>
<th>Recommendation</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic Bacteriuria</td>
<td>Bacteria +/- pyuria</td>
<td>Do not treat unless pregnant. Consider telephone follow up for outpatients.</td>
<td>N/A</td>
</tr>
<tr>
<td>Cystitis</td>
<td></td>
<td>TMP-SMX where resistance rates &lt; 20% Nitrofurantoin</td>
<td>3 days for TMP-SMX or Fluoroquinolones, 7 days for nitrofurantoin</td>
</tr>
<tr>
<td>Uncomplicated Pyelonephritis</td>
<td></td>
<td>Ciprofloxacin or other quinolone Extended spectrum penicillin or cephalosporin in children/ pregnant females Send urine culture Consider telephone follow up for patients discharged home</td>
<td>7 days</td>
</tr>
<tr>
<td>Complicated UTI (diabetes, male, indwelling catheter)</td>
<td></td>
<td>Quinolone where resistance rates does not exceed 10% Consider Fosfomycin Send urine for culture and sensitivity</td>
<td>7–10 days Consider admission</td>
</tr>
</tbody>
</table>

- Where possible, base empiric therapy on prior culture results, patient medical history, local antibiograms, and taking into account any serious allergies or prior adverse events. While targeted spectrum antibiotics are ideal, cost, patient compliance and duration of treatment may be factors in clinical decision-making.

- Links to clinical practice guidelines: click here:
### Table 1

Summary of types of programs that may support antimicrobial stewardship in the ED

<table>
<thead>
<tr>
<th>Approaches</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td>Defined as an essential element of ASPs combined with implementation of active interventions to produce results. The type of education provided to clinicians and patients can take a variety of forms. The Centers for Disease Control and Prevention’s (CDC) Get Smart program is one prototype educational program that targets both physicians and patients.</td>
</tr>
<tr>
<td>Guidelines and clinical pathways</td>
<td>Assists physicians in the diagnosis and treatment of diseases with the goal of producing high quality care. Treatment algorithms are also identified to assist with decision-making before culture or susceptibility data are available.</td>
</tr>
<tr>
<td>ED Pharmacist</td>
<td>Facilitates selection of appropriate empiric antibiotic therapy and education on antimicrobial prescribing at the point of care; critical role of a dedicated pharmacist as part of a multidisciplinary team to address antibiotic use in the ED.</td>
</tr>
<tr>
<td>Clinical Decision Support Systems (CDSS)</td>
<td>Provides physicians with real-time feedback related to individual patients, including choices for antimicrobial therapy and side effects. There is a range of computer-assisted programs available in the United States, and some hospitals are actively using them with success.</td>
</tr>
<tr>
<td>Antimicrobial Order Forms</td>
<td>Actively engages physicians, by requiring completion of antimicrobial request forms, which require clinical justification for use of individual agents. Pre-written forms commonly include automatic stop orders to cease therapy after a defined period of time, and require a renewal process that includes empirical data driven decisions coupled with clinical judgment.</td>
</tr>
<tr>
<td>Post Prescription Review</td>
<td>Involves patient follow up and transition to the outpatient care setting. Examples include: phone follow up of patients with uncomplicated pyelonephritis to ensure appropriate antibiotic treatment was prescribed based on final susceptibilities, and delayed antimicrobial prescribing for patients with cutaneous abscesses, pharyngitis, and acute otitis media.</td>
</tr>
<tr>
<td>Rapid diagnostic testing</td>
<td>Evolving and key strategy for promoting ASPs. The capability of new rapid diagnostics to distinguish pathogens has been demonstrated to improve clinical decision-making and ensures rapid and appropriate initiation of antimicrobial therapy; this strategy helps eliminate antibiotic use in the case of viral pathogens and reduces use of broad-spectrum agents when a narrow-spectrum option is available.</td>
</tr>
<tr>
<td>Shortening duration of therapy</td>
<td>Current guidelines are more specifically defining the duration of antimicrobial therapy recommended; shorter therapeutic duration has been shown to reduce selective pressure for resistant bacteria without compromising patient outcomes.</td>
</tr>
<tr>
<td>Dose optimization</td>
<td>Involves defining individualized antibiotic dosing based on patient characteristics (age, weight), pathogen characteristics, site of infection, and the pharmacokinetic and pharmacodynamic properties of the medication. This strategy is most applicable in the ED for patients awaiting admission to a hospital bed.</td>
</tr>
<tr>
<td>Streamlining or de-escalation of therapy</td>
<td>Facilitates early transition from broad to narrow spectrum antibiotics. Laboratory reporting of the causative agent triggers antimicrobial switch therapy to the narrowest possible spectrum. Laboratory results are reviewed by a pharmacist or infectious disease physician, and recommendations are provided to the clinician for adjusting therapy. This strategy is most applicable to admitted patients but could be applied to ED outpatients as well, in the context of a robust program for follow up and coordination of care.</td>
</tr>
<tr>
<td>ED Antibiogram Development</td>
<td>Development of ED specific charts of pathogen susceptibility. In order to be representative of ED outpatients, hospital resources to facilitate sending routine cultures as a quality improvement intervention could be considered; antibiograms are most useful when broken down by inpatient versus outpatient status, by unit (ED), and by infection type and pathogen; inclusion of outpatient prescriptions (not just inpatient formulary) susceptibilities adds to fidelity of the guidelines.</td>
</tr>
</tbody>
</table>
Table 2
Examples of empiric antibiotic therapy and treatment duration for uncomplicated infections in ED outpatients based on IDSA guidelines

<table>
<thead>
<tr>
<th>Infection</th>
<th>Empiric Antibiotic</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community acquired pneumonia</td>
<td>Macrolide Fluoroquinolone Doxycycline</td>
<td>5–7 days</td>
</tr>
<tr>
<td>Uncomplicated cystitis in women</td>
<td>• Nitrofurantoin&lt;br&gt;• Trimethoprim-sulfamethoxazole (where local resistance &lt;20%)&lt;br&gt;• Ciprofloxacin or levaquin (where nitrofurantoin and TMP-SMX cannot be used)</td>
<td>5 days&lt;br&gt;3 days&lt;br&gt;3 days</td>
</tr>
<tr>
<td>Uncomplicated pyelonephritis</td>
<td>Ciprofloxacin Levofloxacin TMP-SMX (only if pathogen known to be susceptible)&lt;br&gt;Beta lactam (less effective)</td>
<td>7 days&lt;br&gt;5 days&lt;br&gt;14 days&lt;br&gt;10–14 days Dose of IV ceftriaxone in ED recommended if fluoroquinolone resistance &gt;10% or if using beta lactam or TMP-SMX empirically</td>
</tr>
<tr>
<td>Cutaneous abscess</td>
<td>Incision and Drainage +/- coverage for MRSA (clindamycin, TMP-SMX, doxycycline)</td>
<td>Antibiotic avoidance for uncomplicated abscesses 5 days</td>
</tr>
<tr>
<td>Uncomplicated cellulitis</td>
<td>Dicloxacillin Cephalexin</td>
<td>5 days</td>
</tr>
</tbody>
</table>

*Ann Emerg Med. Author manuscript; available in PMC 2014 July 01.*
Core Elements of Hospital Antibiotic Stewardship Programs From the Centers for Disease Control and Prevention

Loria A. Pollack and Arjun Srinivasan
Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia

The proven benefits of antibiotic stewardship programs (ASPs) for optimizing antibiotic use and minimizing adverse events, such as *Clostridium difficile* and antibiotic resistance, have prompted the Centers for Disease Control and Prevention (CDC) to recommend that all hospitals have an ASP. This article summarizes *Core Elements of Hospital Antibiotic Stewardship Programs*, a recently released CDC document focused on defining the infrastructure and practices of coordinated multidisciplinary programs to improve antibiotic use and patient care in US hospitals.

**Keywords.** antibacterial agents/therapeutic use; drug utilization; hospitals; practice guidelines as topic; program development.

Improving the use of antibiotics is an important patient safety and public health issue, and was identified by the Centers for Disease Control and Prevention (CDC) as a key strategy to address antibiotic resistance [1]. Hospital-based programs dedicated to improving antibiotic use, commonly referred to as antibiotic stewardship programs (ASPs), can increase the frequency of appropriate prescribing, optimize the treatment of infections, and minimize adverse events associated with antibiotic use, including *Clostridium difficile* infections (CDIs) [2]. Recent national data from the CDC highlighted that more than half of all hospital patients receive an antibiotic; antibiotic use rates among similar patient-care locations differ by up to 3-fold, and many opportunities exist to improve prescribing in common clinical scenarios [3]. In recognition of the urgent need to improve antibiotic use in hospitals and the benefits of ASPs, the CDC recommends that all acute care hospitals implement ASPs [3]. To support this recommendation, the CDC recently released *Core Elements of Hospital Antibiotic Stewardship Programs*, a document to assist hospitals in effectively implementing antibiotic stewardship [4]. The document complements existing antimicrobial stewardship guidelines from various organizations [5,6]. Elements common to successful stewardship programs are summarized in Table 1. We will outline those elements and provide suggestions on how they might be implemented, while recognizing that variability in the size, staffing, and type of care among US hospitals requires flexibility in implementation. The goal of this article is to briefly summarize the contents of *Core Elements of Hospital Antibiotic Stewardship Programs*.

**LEADERSHIP COMMITMENT, ACCOUNTABILITY, AND DRUG EXPERTISE**

Facility leadership support is critical to the success of ASPs. Formal statements of support for antibiotic stewardship should be accompanied by stewardship-related duties in job descriptions and ensuring that staff from relevant departments is given sufficient time to contribute to stewardship activities. Financial support greatly augments the capacity and impact of a stewardship program; these programs will often pay for themselves, through savings in both antibiotic expenditures and...
indirect costs [7–11]. To ensure accountability, facilities should identify a single leader responsible for coordinating and reporting on the needs and outcomes of the program to an executive-level or patient quality–focused hospital committee. Physicians have been highly effective in this role. In addition, because drug expertise is needed, a pharmacist should be involved. A pharmacist may also be an appropriate program leader. Formal training in infectious diseases and/or antibiotic stewardship benefits stewardship program leaders. Larger facilities have achieved success by hiring full-time staff to develop and manage stewardship programs, while some smaller facilities have reported other arrangements including use of part-time, off-site expertise and hospitalists [12]. Hospitalists can be ideal physician leaders for efforts to improve antibiotic use, given their increasing presence in inpatient care, the frequency with which they use antibiotics, and their commitment to quality improvement [13, 14]. The Pharmacy and Therapeutics Committee should not be considered the stewardship team within a hospital if it is only performing the traditional duties of managing the formulary and monitoring drug-related patient safety, although in some smaller facilities this committee has an expanded role to assess and improve antibiotic use [15].

The work of stewardship program leaders is greatly enhanced by the support of other key groups in hospitals in which they are available: Clinicians and department heads can provide input for policies and interventions; laboratory staff can guide the proper use of tests and empiric therapy by creating and interpreting facility antibiotic resistance reports; hospital epidemiologists and infection preventionists can provide surveillance data on multidrug-resistant organisms and CDIs to inform priorities or impact of ASPs [16]; nurses can review medications and prompt discussions of antibiotic treatment; and information technology staff can integrate stewardship protocols and relevant information into electronic medical records and ordering systems at the point of care [17].

### ACTIONS TO IMPROVE ANTIBIOTIC PRESCRIBING

Actions to improve prescribing include both institution-wide policies related to antibiotic use and disease state management as well as patient-specific interventions. These actions should be implemented in ways that do not delay the timely initiation of antibiotics for management of severe sepsis and septic shock [18]. Policies that support optimal antibiotic prescribing practices include documentation of the dose, duration, and indication for all prescriptions to inform future decisions to modify and/or discontinue antibiotics, and facility-specific treatment recommendations based on national guidelines and local susceptibilities, particularly for common indications for antibiotic use such as community-acquired pneumonia, urinary tract infections, intra-abdominal infections, skin and soft tissue infections, and surgical prophylaxis. However, policies alone do not translate into action and must be accompanied by interventions chosen based on the needs of the facility as well as the availability of resources. Programs should be careful not to implement too many interventions at once. Examples of stewardship interventions presented in the CDC’s Core Elements of Hospital Antibiotic Stewardship Programs are summarized below.

- **Broad interventions** generally focus on formally reviewing the need, choice, and duration of antibiotics. Prior approval or prescription preauthorization are reviews conducted at or shortly after prescribing to ensure selected drugs are used optimally. This approach should never limit prompt treatment of suspected sepsis. Another approach is to formally reassess the continued need for and choice of antibiotics after 48 hours when the patient’s clinical status is clearer and more diagnostic information is available. These reviews can be performed by the attending physician or treating team, referred to as an antibiotic “time out,” or by staff other than the treating team such as ASP staff (ie, prospective audit and feedback). The effectiveness of

<table>
<thead>
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<th>Leadership commitment</th>
<th>Dedicating necessary human, financial, and information technology resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accountability</td>
<td>Appointing a single leader responsible for program outcomes and accountable to an executive-level or patient quality–focused hospital committee. Experience with successful programs shows that a physician or pharmacist leader is effective</td>
</tr>
<tr>
<td>Drug expertise</td>
<td>Appointing a single pharmacist leader responsible for working to improve antibiotic use</td>
</tr>
<tr>
<td>Action</td>
<td>Implementing at least 1 recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (ie, antibiotic “time-out” after 48 h)</td>
</tr>
<tr>
<td>Tracking</td>
<td>Monitoring process measures (eg, adherence to facility-specific guidelines, time to initiation or de-escalation), impact on patients (eg, <em>Clostridium difficile</em> infections, antibiotic-related adverse effects and toxicity), antibiotic use and resistance</td>
</tr>
<tr>
<td>Reporting</td>
<td>Regular reporting of the above information to doctors, nurses, and relevant staff</td>
</tr>
<tr>
<td>Education</td>
<td>Educating clinicians about disease state management, resistance, and optimal prescribing</td>
</tr>
</tbody>
</table>

Source: Centers for Disease Control and Prevention [4].

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</tbody>
</table>

Source: Centers for Disease Control and Prevention [4].

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**Table 1. Core Elements of Hospital Antibiotic Stewardship Programs**

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</tr>
</tbody>
</table>

Source: Centers for Disease Control and Prevention [4].
prospective audit and feedback has been shown in multiple studies, but the scalability of this intervention is dependent on the capacity of the ASP [5, 19]. Some smaller facilities have shown success by engaging external experts to assist in performing such reviews [12]. The antibiotic “time out” approach may be more feasible for facilities that have ASPs with limited staffing and capacity.

- **Staff-pharmacy interventions** include automatic changes from intravenous to oral antibiotic therapy when appropriate; dose adjustments and optimization; therapeutic monitoring; automatic alerts in situations in which therapy might be unnecessarily duplicative; duration-specific stop orders; and detection of antibiotic-related drug–drug interactions. Pharmacists also often play critical roles in other types of interventions, such as reviewing clinical information for antibiotic time-outs, prospective audits, or disease-stage management, and giving direct feedback to prescribers.

- **Infection- and syndrome-specific interventions** can focus on the diagnostic evaluation, optimal empiric treatment, and re-evaluation of the need for and choice of prescribed antibiotic(s) for defined infections, such as community-acquired pneumonia, urinary tract infections, skin and soft tissue infections, and methicillin-resistant *Staphylococcus aureus* infections, as well as the discontinuation of unnecessary antibiotics in patients diagnosed with CDI and the timely modification of empiric treatment to culture and susceptibility results. Interventions to minimize the misuse of antibiotics in noninfectious syndromes such as asymptomatic bacteriuria and blood culture contamination are equally important.

**TRACKING AND REPORTING ANTIBIOTIC USE AND OUTCOMES**

Measurement may involve the evaluation of processes, such as whether prescribers documented treatment indications, adhered to facility-specific treatment guidelines, obtained appropriate diagnostic tests, and modified antibiotic choices to microbiological findings. Ideally, measurement should focus on patient outcomes to assess the impact of interventions, identify potential areas for improvement, and provide feedback to clinicians. Improving antibiotic use has a significant impact on rates of hospital-onset CDI, thus making CDI in hospitals an important patient-centered target for stewardship programs [7, 20, 21]. Reducing antibiotic resistance is another important goal of antibiotic stewardship and presents an option for measurement, particularly for specific patient care locations with active stewardship interventions.

Tracking actual antibiotic use is an objective indicator of prescribing practices. Hospital ASPs should measure overall use of antibiotics as well as conduct focused analyses on specific antibiotic(s) and hospital locations where stewardship actions are implemented. For example, the assessment of an intervention to improve the treatment of community-acquired pneumonia would be expected to impact the use of specific antibiotic agents on medical wards, rather than surgical wards. As part of the National Healthcare Safety Network surveillance system, the CDC has developed an Antibiotic Use Option that electronically collects and reports monthly antibiotic use data, which can be analyzed in aggregate and by specific agents and patient care locations [22]. As more facilities enroll in the Antibiotic Use Option, the CDC will begin to establish risk-adjusted facility benchmarks for antibiotic use. Antibiotic use rates, however, do not necessarily reflect appropriateness of use, and further work is needed to explore the factors associated with high and low use [23].

**EDUCATION**

ASP.s should provide regular updates on antibiotic prescribing, antibiotic resistance, and infectious diseases management that address both national and local issues [24]. Sharing facility-specific information on antibiotic use is a tool to motivate improved prescribing, particularly if wide variations in the patterns of use exist among similar patient care locations [25]. Reviewing deidentified cases with providers in which changes in antibiotic therapy could have been made is another useful approach. A variety of Web-based educational resources are available that can help facilities develop educational content [26]. Education has been found to be most effective when paired with corresponding interventions and measurement of outcomes [5].

**FUTURE DIRECTIONS**

The integration of information technology into the clinical data presentation and decision making for antibiotic use will expand with increased uptake and capabilities of electronic health records. The use of rapid diagnostic tests is an area of great interest, and further research is needed to determine how they can be best be applied to stewardship efforts. As more facilities engage in efforts to optimize antibiotic use, future work is needed to evaluate which interventions or antibiotic targets yield the greatest benefit in improving patient care, reducing patient risk of CDI and other adverse events, and combating antibiotic resistance.

**CONCLUSIONS**

ASP.s directed at improving antibiotic use can be implemented in a variety of ways that are feasible in any US hospital. In general, success is dependent on defined leadership and a coordinated multidisciplinary approach to implement improvement strategies, monitor antibiotic prescribing, and educate. The
proven benefits of ASPs, combined with the urgent need to address *C. difficile* and antibiotic resistance, have prompted the CDC to recommend that all hospitals have an ASP. The CDC’s *Core Elements of Hospital Antibiotic Stewardship Programs*, as well as a variety of resources available on the Get Smart for Healthcare Web site, is designed to assist hospitals in both starting and expanding ASPs [4, 27].

**Notes**

**Disclaimer.** The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

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**References**


How to educate prescribers in antimicrobial stewardship practices

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How to educate prescribers in antimicrobial stewardship practices

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Keywords: antibiotic prescribing, antimicrobial stewardship, antibiotic policies, undergraduate curriculum, postgraduate education, clinical practice guidelines, intervention strategies, implementation

Abbreviations: BSAC, British Society of Antimicrobial Chemotherapy; CDC, Centers for Disease Control and Prevention; DOTS, Doctors Online Training System; ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; ECDC, European Centre for Disease Prevention and Control; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; ESGAP, European Society of Clinical Microbiology and Infectious Diseases Study Group for Antibiotic Policies; EU, European Union; GMC, General Medical Council; GPs, general practitioners; GRACE, Genomics to combat resistance against antibiotics in community-acquired lower respiratory tract infections in Europe; ICAAC, Interscience Conference on Antimicrobial Agents and Chemotherapy; ICU, intensive care unit; ID, infectious diseases; IDSA, Infectious Diseases Society of America; IHII, Institute for Healthcare Improvement; MRSA, methicillin-resistant Staphylococcus aureus; NES, NHS Education for Scotland; NHS, National Health Service; PAUSE, Prudent Antibiotic User website; PK/PD, pharmacokinetics and -dynamics; SACAR, Specialist Advisory Committee on Antimicrobial Resistance; SAPG, Scottish Antimicrobial Prescribing Group; SHEA, Society for Healthcare Epidemiology of America; SMC, Scottish Medicines Consortium; UK, United Kingdom; US, United States of America

Widespread antimicrobial use has compromised its value, leading to a crisis of antimicrobial resistance. A major cause of misuse is insufficient knowledge of prescribing of antimicrobials in many categories of professionals. An important principle of antimicrobial stewardship is avoiding selection pressure in the patient, both on pathogen and commensal by avoiding unnecessary use, choosing the least broad-spectrum antibiotic, adequate doses, a good timing and the shortest possible duration. Up to now, most educational efforts have been targeted at professionals (mostly medical doctors) after their training and at the adult public. In the past few years, progress has been made in educating children. It is now crucial that academia and ministries of Health and Education jointly focus on an adapted undergraduate medical/professional curriculum that teaches all necessary principles of microbiology, infectious diseases and clinical pharmacology, with emphasis on the principles of prudent prescribing.

Background

Antimicrobial drugs are a precious but finite resource, different from other drugs. They are the only drugs that do not directly affect the patient but instead affect the growth, and ecology of invading pathogens and commensal microorganisms. Antimicrobial therapy is not only based on the characteristics of the pathogen and the drug, but also on the characteristics of the patient and the drug, the pathogen(s) and colonizing microflora. As is shown in the pyramid (Fig. 1), the choice of the appropriate antimicrobial therapy is a complex decision, depending on the knowledge of many different aspects of infectious diseases: immunological and genetic host factors, microbial virulence, pharmacokinetics and -dynamics (PK/PD) of drugs.

Prescribers of antimicrobial drugs have dual, somewhat contradictory responsibilities. On the one hand they want to offer optimal therapy for the individual patient under their care; on the other hand they have a responsibility to the same and other patients in the future and to public health to preserve the efficacy of antibiotics and minimize the development of resistance. The former responsibility tends to promote overtreatment; the latter is usually overlooked. Among antimicrobial drugs, those targeting bacteria, i.e., antibiotics, are most extensively developed and prescribed. Misuse of antibiotics, i.e., unnecessary prescriptions as well as inappropriate use (inadequate dosing, wrong duration) is frequent; up to half of the antibiotic prescriptions both in the community and in hospitals are considered unjustified.1,2 Bacterial resistance to antibiotics is a serious threat to patients that is increasing rapidly. With few new antibiotics in the research and development pipeline, particularly in the Gram-negative spectrum,3 and “old” useful antibiotics, which are not...
marketed anymore in some countries, prudent antibiotic use is the only option to delay the emergence of resistance.

The quantity and quality of antibiotic prescribing differs greatly between countries. This has become clear in international comparative studies on antibiotic prescribing in a quantitative and qualitative fashion. For instance, the amount of antibiotics used in southern European countries is about three times higher than in Scandinavian countries or the Netherlands. In general, these differences in use are reflected by the magnitude of the antimicrobial resistance problems: the more (broad-spectrum) antibiotics are used, the greater the prevalence of resistant microorganisms leading to a spiral of escalating broad-spectrum use.

As early as in 1993, the British Society of Antimicrobial Chemotherapy (BSAC) Working Party on Antimicrobial Use considered training in infectious diseases (ID) and knowledge of prescribing of antimicrobial drugs insufficient in clinicians, which is one of the major causes of misuse. According to a recent policy paper by the Infectious Diseases Society of America (IDSA), clinician training and continuing education in appropriate antimicrobial use in the United States (US) is “highly variable, non standardized, infrequent, and highly prone to bias, especially when conveyed or sponsored by pharmaceutical firms or their agents. Apart from initial training and, to a limited extent, in preparation for board recertification examinations, there is little if any compulsory training or education of physicians in antimicrobial stewardship.” Conversely, focus on prescribing older, narrow-spectrum drugs in targeted therapy has been taught in medical schools and has been common practice in northern European countries such as Scandinavia and the Netherlands for several decades.

National and international authorities have repeatedly recommended multifaceted strategies to promote prudent antibiotic use for the control of antibiotic resistance. One of these strategies is to optimize education of all healthcare professionals who prescribe antibiotics. Because patients have an increasingly participative role in their treatment, education of the public is also of the utmost importance. Until recently the public’s knowledge on antibiotics—appropriateness, side effects and limitations—was poor in the European Union (EU). In the last decade, national and regional campaigns have been conducted to educate the public worldwide; e.g., in the US the Centers for Disease Control and Prevention (CDC)’s Get Smart about Antibiotics (www.cdc.gov/getsmart/), in Canada Do Bugs Need Drugs? (www.dobugsneeddrugs.org) and across Europe the European Centre for Disease Prevention and Control (ECDC)’s annual European Antibiotic Awareness Day (http://ecdc.europa.eu/en/eaad/Pages/Home.aspx), launched on 18 November 2008. Huttner et al. identified and reviewed the characteristics and outcomes of 22 campaigns done at a national or regional level in high-income countries between 1990 and 2007. In France yearly public antibiotic campaigns have been conducted since 2002. During its first 3 years, the French public campaign accelerated a pre-existing decrease in ambulatory antibiotic prescriptions. However, the decrease in consultation rates suggests that altered illness behavior of patients may have contributed to the observed decline.

Because of the major deficiencies found in elementary knowledge on antibiotics in surveys of adults throughout Europe (e.g., “antibiotics are useful for colds”), educating children on this topic might be a good idea. Three major initiatives have been directed to the education of children. The first program, Do Bugs Need Drugs? started as a small six-month pilot in Alberta, Canada in 1998. It contained a kids’ section dealing with handwashing and responsible use of antibiotics in a playful way. The program evolved into a larger provincial program in Alberta and British
A lack of knowledge of infectious disease and antibiotics may seriously hamper the quality of prescription. In this situation, the prescribing physician may prefer to err on the safe side, i.e., prescribing maximal broad-spectrum treatment, instead of making a well-informed guess. A negative attitude, based on a lack of agreement with protocols or guidelines, will also affect prescribing. Likewise, a lack of self-efficacy, a lack of outcome expectancy and inertia may lead to poor prescribing. Based on the available international recommendations for antimicrobial stewardship policies and on the literature, Table 1 presents the main principles for education in prudent antibiotic prescribing. These elements have to be translated into topics, concepts, disciplines, learning outcomes and competencies both for the undergraduate core curriculum of medical doctors and other healthcare professionals, the internship/foundation year and specialty/professional training.

Who are the Prescribers of Antibiotics?

Unlike many other drugs, for which prescribing is kept within a specialty (for example neuroleptic drugs), antibiotics are prescribed universally by all medical doctors and dentists in the community. In Europe, over the counter use by the public is low except for a few southern countries (e.g., Spain and Greece). But even in the case of over the counter purchases, health professionals have a major responsibility as patients copy their prescribing habits. In some countries (for example the United Kingdom (UK) or France), midwives, clinical pharmacists or nurses (“physician assistants,” in the UK, Netherlands and Belgium) can also prescribe some antibiotics in selected clinical situations. Pharmacists also play a key role in the process, by dispensing the drugs and giving advice to the patients. Therefore, all healthcare professionals in contact with the patient must be educated with respect to knowledge on antimicrobial resistance, (lack of) evidence of benefit of antibiotics in different conditions and related beliefs, knowledge of management of symptoms and the use of microbiology laboratory tests to guide antibiotic treatment. Education on management of demanding patients is also required.

Antibiotic management requires effective teamwork between all health professions, regardless of who writes the prescription. It is therefore crucial to educate not only prescribers, but all other healthcare professionals in contact with the patients who are prescribed an antibiotic (e.g., nurses, midwives and pharmacists), since patients should receive consistent messages on correct and prudent antibiotic use when taking antibiotics. Therefore, all these healthcare professionals must receive continuous training in prudent antibiotic prescribing.

In hospitals, only patients with complicated or severe infections will be referred to infectious diseases departments or medical microbiologists or infectious diseases teams for consultation, the majority being treated for their infection by other physicians, mostly organ specialists. On average, one patient out of three is treated with antibiotics during his hospital stay. In the recent national English Point Prevalence Survey on healthcare-associated infections and antimicrobial use report, the prevalence

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**Antimicrobial Stewardship Principles**

According to the IDSA definition of antimicrobial stewardship it includes: optimizing the indication, selection, dosing, route of administration and duration of antimicrobial therapy to maximize clinical cure or prevention of infection while limiting the collateral damage of antimicrobial use, including toxicity, selection of pathogenic organisms (such as _Clostridium difficile_) and emergence of resistance. An important principle is avoiding selection pressure of the antibiotic in the patient, both on pathogen and commensal (Fig. 1) by choosing the least broad-spectrum antibiotic, adequate doses, a good timing and the shortest possible duration. With resistance increasing worldwide, additional uncertainty arises on the optimal breadth of spectrum needed for empirical therapy. The level of in vitro resistance that should guide the abandonment of an antibiotic and the shift to a broad-spectrum agent is not known. Antibiotic choices for empirical therapy should be decided upon at local level, guided by local antibiograms and patient outcome data. However, in settings with a well-developed microbiology laboratory system, it is possible to adapt the empirical therapy to a targeted therapy when culture results become available; streamlining or de-escalating antimicrobial therapy has become more widely accepted since intensive care physicians have adopted it as their strategy. Targeted therapy decreases unnecessary antimicrobial exposure and contains costs. De-escalation may also include dis-continuation of empirical antimicrobial therapy based on clinical criteria and negative culture results.1
<table>
<thead>
<tr>
<th>Topic</th>
<th>Concept, understanding</th>
<th>Field, discipline</th>
<th>Principles, learning outcomes, competencies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial resistance</strong></td>
<td>Selection, mutation</td>
<td>(Micro) biology, genetics</td>
<td>• Extent, causes of bacterial resistance in pathogens (low antibiotic concentration, longtime exposure of microorganisms to antibiotics is driving resistance)</td>
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<tr>
<td></td>
<td>Epidemiology</td>
<td></td>
<td>• Extent, causes of bacterial resistance in commensals and the phenomenon of overgrowth (e.g., <em>Clostridium difficile</em> infection, yeast infection)</td>
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<td></td>
<td>Hygiene</td>
<td>Infection control—mostly microbiology</td>
<td>• Epidemiology of resistance, accounting for local variations and importance of surveillance (differences between wards, countries...)</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td>Mechanisms of action of antibiotics/resistance</td>
<td>Pharmacology</td>
<td>• Broad vs. narrow-spectrum antibiotics, preferred choice of narrow-spectrum drugs</td>
</tr>
<tr>
<td></td>
<td>Toxin</td>
<td></td>
<td>• Combination therapy (synergy, limiting emergence of resistance, broaden the spectrum)</td>
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<tr>
<td></td>
<td>Costs</td>
<td>Ethics, public health, pharmacology</td>
<td>• Collateral damage of antibiotic use (toxicity, cost)</td>
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<td></td>
<td></td>
<td></td>
<td>• Consequences of bacterial resistance</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Lack of development of new antibiotics (limited arsenal)</td>
</tr>
<tr>
<td><strong>Diagnosis of infection</strong></td>
<td>Infection/inflammation</td>
<td>Physiology/microbiology/infectious diseases</td>
<td>• Interpretation of clinical and laboratory biological markers</td>
</tr>
<tr>
<td></td>
<td>Isolation, identification of bacteria, viruses and fungi</td>
<td>(Micro) biology</td>
<td>• Fever and C-Reactive Protein (CRP) elevation are also a sign of inflammation, not per se of an infection</td>
</tr>
<tr>
<td></td>
<td>Susceptibility to antibiotics</td>
<td>Microbiology/infectious diseases</td>
<td>• Practical use of point-of-care tests (e.g., urine dipstick, streptococcal rapid antigen diagnostic test in tonsillitis...)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Importance of taking microbiological samples for culture before starting antibiotic therapy</td>
</tr>
<tr>
<td><strong>Treatment of infection</strong></td>
<td>Indication for antimicrobials</td>
<td>Clinical microbiology/infectious diseases</td>
<td>• Definitions and indications of empiric/directed therapy vs. prophylaxis</td>
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<tr>
<td></td>
<td></td>
<td>Organ specialty</td>
<td>• Clinical situations when not to prescribe an antibiotic:</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Colonization vs. infection (e.g., asymptomatic bacteriuria)</td>
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<td></td>
<td>• Viral infections (e.g., acute bronchitis)</td>
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<td></td>
<td></td>
<td></td>
<td>• Inflammation vs. infection (e.g., fever without a definite diagnosis in a patient with no severity criteria)</td>
</tr>
<tr>
<td><strong>Prevention of infection</strong></td>
<td></td>
<td>Pharmaotherapy, surgery, anesthesiology, clinical microbiology/infectious diseases</td>
<td>• Surgical antibiotic prophylaxis: indication, choice, duration (short), timing</td>
</tr>
<tr>
<td><strong>Medical record keeping</strong></td>
<td>Choice</td>
<td>Clinical medicine</td>
<td>• Documentation of antimicrobial indication in clinical notes</td>
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<tr>
<td></td>
<td>Duration</td>
<td></td>
<td>• Recording (planned) duration or stop date</td>
</tr>
<tr>
<td></td>
<td>Timing</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prescribing antibiotics: initially</strong></td>
<td>Empiric therapy (local guide, antibiotic booklet...) Diagnostic uncertainty</td>
<td>Clinical microbiology/infectious diseases/organ specialists Clinical pharmacology</td>
<td>• Best bacteriological guess for empiric therapy</td>
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<td></td>
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<td></td>
<td>• Choice in case of prior use of antibiotics when selecting an antibiotic for empiric therapy</td>
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<td></td>
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<td></td>
<td>• Choosing the dose and interval of administration (basic principles of PK/PD)</td>
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<td></td>
<td></td>
<td></td>
<td>• Estimating the shortest possible adequate duration</td>
</tr>
<tr>
<td><strong>Prescribing antibiotics: targeted therapy</strong></td>
<td>Communication with the microbiology laboratory Value of specialist consultation in infectious diseases or microbiology</td>
<td>Clinical microbiology/infectious diseases/organ specialists Hospital pharmacy</td>
<td>• Reassessment of the antibiotic prescription around day 3</td>
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<td></td>
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<td></td>
<td>• Streamlining/de-escalation once microbiological results are known</td>
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<td></td>
<td></td>
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<td>• IV-oral switch (bioavailability of antibiotics)</td>
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<td></td>
<td></td>
<td></td>
<td>• Therapeutic drug monitoring to ensure adequate drug levels (e.g., vancomycin)</td>
</tr>
</tbody>
</table>

*A competency is a quality or characteristic of a person that is related to effective performance. Competencies can be described as a combination of knowledge skills, motives and personal traits.*

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**Table 1. Elements of education on prudent antibiotic prescribing**

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[22] A competency is a quality or characteristic of a person that is related to effective performance. Competencies can be described as a combination of knowledge skills, motives and personal traits.
Table 1. Elements of education on prudent antibiotic prescribing (continued)

<table>
<thead>
<tr>
<th>Prescribing antibiotics: standard of care</th>
<th>The importance of guidelines in clinical practice</th>
<th>Clinical medicine, organ specialists</th>
<th>• Prescribing antibiotic therapy according to national/local practice guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality indicators of antibiotic use</td>
<td>Quality institute</td>
<td>• Audit and feedback assessing prescribing practice using quality indicators</td>
<td></td>
</tr>
<tr>
<td>Communication skills</td>
<td>Discussion techniques</td>
<td>Psychology, clinical medicine</td>
<td>• Explaining to the patient the absence of an antibiotic prescription (comply with the doctors’ prescription, no self-medication...)</td>
</tr>
</tbody>
</table>

*A competency is a quality or characteristic of a person that is related to effective performance. Competencies can be described as a combination of knowledge skills, motives and personal traits.*

of national antimicrobial use was 34.7%. It was greatest in the intensive care units (ICUs) (60.8%) and antimicrobial use prevalence in surgery was 36%. Junior doctors of all specialties often prescribe the antibiotics under the supervision of their seniors. Therefore, both senior and junior doctors must be educated in order to change practice.

Finally, we must also consider the antibiotic prescriptions for animals and agriculture, made by the veterinarians. Although there are similarities of antimicrobial stewardship for companion animals and the human sector, antibiotic use in livestock animals is further complicated by economic issues. An enormous challenge is awaiting those wanting to introduce antibiotic stewardship in the undergraduate veterinarian curriculum.

**When Should Antimicrobial Stewardship Education Start?**

Figure 2 shows the timeline of education on prudent antibiotic use of both the patients and the prescribers of antimicrobials. As mentioned above, in the past few years a lot of progress has been made in teaching of children. Education at the primary and secondary level will prepare the individual who later might become a patient or more importantly, the anxious parent of a sick toddler with, for example, otitis media. In addition, it provides the basic education of the future professional. Not much is known about the content, volume and quality of medical curricula teaching antimicrobial stewardship principles and resistance in terms of knowledge, attitude and behavior to medical students, and more specifically, their timeline in Europe. One survey was done by the British Society for Antimicrobial Chemotherapy. The authors pleaded for inclusion of antimicrobial chemotherapy in the undergraduate curriculum, as most doctors regularly treat infections. European national medical undergraduate curricula can either be quite detailed such as the Raamplan Artsopleiding 2009 in the Netherlands in which general learning outcomes with keywords are specified such as: prevention of infections and spread, aspects of guidelines and protocols and development of antibiotics. Other learning outcomes of university curricula such as the University of Leuven on websites (http://med.kuleuven.be/Faculteit_Geneeskunde/english/studies/medicine) are very robust and transparent framework for curriculum development at all stages. Subsequently, the learning outcomes could be translated into competencies by the appropriate bodies. Prescribing is included as a component of the undergraduate program in the UK, and the importance of undergraduate training in prescribing is reflected in aspects of the General Medical Council’s (GMC’s) Tomorrow’s Doctors. The GMC has now endorsed the report entitled A single competency framework for all prescribers, as in the UK nurses are allowed to prescribe antibiotics. Doctors should...
be able to prescribe on registration. In the UK, this competency is subjected to the standards for supervision for doctors in training set out in The Trainee Doctor report. Statement competency examples are: (1) Competency 1: Knowledge. Has up-to-date clinical, pharmacological and pharmaceutical knowledge relevant to own area of practice. Nr 11: Understands antimicrobial resistance and the roles of infection prevention, control and antimicrobial stewardship measures; (2) Competency 7: The Healthcare system. Understands and works within local and national policies, processes and systems that impact on prescribing practice. Sees how own prescribing impacts on the wider healthcare community, Nr 59: Understands and works within local frameworks for medicines use as appropriate (e.g., local formularies, care pathways, protocols and guidelines). More specific learning outcomes or competencies can be developed departing from this list.

Re-examining the principles and learning outcomes in Table 1, it is clear that much emphasis is needed on the transfer of basic science knowledge at an early stage. Just as optimal periods and subjects have been identified to guarantee maximal exposure to children, the undergraduate curriculum and internship/foundation year seem optimal stages to build a solid knowledge base for later practice. For example: surgeons will have a much higher acceptance of prophylaxis guidelines if they have been exposed to the principles of guideline development and antibiotic prophylaxis taught as core competencies in the third year of medical school. Conversely, a plethora of literature is available on the difficult task of changing the behavior of trained medical practitioners, the barriers being multiple, cultural among others.

Who Should Educate/Teach/Train?

As all doctors prescribe antibiotics, a strong input is needed from academia to transfer the knowledge in the undergraduate curriculum. As depicted in Table 1, the curriculum is expected to deliver knowledge and shape the right attitude and behavior regarding the basic principles of antimicrobial stewardship. In most settings the organ specialist hardly covers this topic. A wide variety of disciplines must be involved, including epidemiology, ethics and communication skills (working with guidelines, communicating with the patient). To link the undergraduate and postgraduate programs, in particular in the period of internship/foundation training, close collaboration between healthcare providers and academicians and between hospitals and medical schools is needed.

In the postgraduate training track most medical and surgical specialties are anatomically defined, but all have to deal with infections. In practice, each specialty thus has a certain degree of “claim” over antimicrobial prescribing in their field. Again, as depicted in Table 1, the input of many disciplines is required to train a junior prescriber at the bedside, and the
organ specialist (e.g., urologist) may not have the full required background for implementing the general principles of prudent antibiotic prescribing in the microbiological diagnostic and therapeutic management of urological patients. With worldwide increasing resistance data, multidisciplinary guideline development of national and local guidelines becomes of the utmost importance. The ADAPTE framework (www.adapte.org) can be used to minimize barriers to the development and acceptance of guidelines.17 In particular, guidelines must be evidence-based and developed by a multidisciplinary group, involving all key stakeholders to foster acceptance and ownership. National or international guidelines should be adapted to the local context to ensure relevance for local practice and policies. Transparent reporting is essential to promote confidence in the recommendations of the adapted guideline and flexible, easily accessible formats must be used (booklet, poster, smartphone applications...). In Canada, the CanMEDS Physician Competency framework describes the knowledge, skills and abilities that specialist physicians need for better patient outcomes.57 This model has been adapted around the world in the health profession and other professions.

In the hospitals, a multidisciplinary core group, including infectious diseases specialists, microbiologists, (clinical) pharmacists and/or an antibiotic stewardship team must be involved in the development and implementation of a local educational program on prudent antibiotic prescribing. In the Netherlands, general practitioners (GPs) organize regional therapy focus groups where they discuss prescribing practices with pharmacists.

The teachers delivering the educational sessions must also be trained, both regarding the available educational strategies and the current literature on antimicrobial stewardship. As an example, the project “ABS International” implemented a training program for national antibiotic stewardship trainers in nine European countries, and offered them standard tools for implementing an antibiotic stewardship program in their hospitals (e.g., guidelines for treatment and surgical prophylaxis, organizational measures, tools to analyze consumption data...).18 Learning societies such as the ESCMID (European Society of Clinical Microbiology and Infectious Diseases) Study Group for Antibiotic Policies (ESGAP) have been organizing educational workshops on antibiotic stewardship for more than 10 years. Table 2 presents a selection of the main learning outcomes for such workshops. The format of these postgraduate educational courses is discussed in the next paragraph.

### How to Educate? Formats of Educational Curricula

**Undergraduate.** In the undergraduate curriculum, classical formal lectures are seldom considered as a successful means of transferring knowledge. Over the past decade, problem-based learning has been introduced in many universities. This type of education allows for alternative formats of interactive learning in smaller student groups. It is important to identify the topics or concepts that benefit from a disease- (e.g., acute bronchitis) or problem- (e.g., antimicrobial resistance) oriented rather than a pathogen- (e.g., MRSA, methicillin-resistant *Staphylococcus aureus*) oriented or a drug- (e.g., antibiotic classes) oriented approach.

Microbial resistance can be part of microbiology teaching, information on antibiotics part of pharmacology and managing the demands of patients in particular parents of young children integrated in communication skills sessions. However, targeted “antibiotic” sessions in the format of problem-based learning are absolutely necessary to integrate all aspects of the topic.23 Apart from formal lectures, interactive learning with case vignettes, PowerPoint presentations and role play can be particularly appropriate for this topic. Elective rather than core modules are particularly suitable for discussions in small groups. Potential topics are case studies, e.g., with questions and answer sessions, illustrating the evidence base of surgical prophylaxis. As an example, the University of Rotterdam (The Netherlands) has included a one-week module on several concepts of antimicrobial resistance, hygiene and prudent antibiotic prescribing in the core curriculum of the second year of medical school. The University of Nijmegen offers an additional elective, problem-based module.

### Table 2. Main learning outcomes used to design antibiotic stewardship workshops

| Measuring antibiotic use | • Identify sources of data and understand how to measure antimicrobial use in the community and in hospitals |
| • Select proper measurement units to describe the volume of antimicrobial use |
| • Interpret antimicrobial use data locally and within a multicenter network (benchmarking) |
| • Choose and apply a method to study the relationship between antimicrobial prescribing and bacterial resistance |

| Auditing antibiotic use | • Choose and apply an audit methodology for monitoring the quality of antimicrobial prescriptions |

| Improving antibiotic use | • Identify the steps and sources for evidence-based guideline development |
| • Describe the elements needed to launch a stewardship program in hospitals Identify barriers encountered in Antimicrobial Stewardship programs and how to overcome them |
| • Make sense of interpersonal aspects of implementing change |
| • Identify possible intervention strategies (and their relative advantages and disadvantages) which could be implemented in a hospital |
| • Identify the electronic antimicrobial drug prescribing aids and their advantages and disadvantages |
| • Build national and international support for Antimicrobial Stewardship programs |
| • Select a proper method to study the effect of interventions in hospitals |
| • Describe how an individual hospital can determine if its antimicrobial management program was economically successful and if it had an impact on bacterial resistance |
on antibiotic policy for third year students, treating the history of infectious diseases, hygiene and infection control, antibiotic guidelines, principles of prophylaxis and laboratory techniques among others.

In Scotland, for example, an extensive range of e-learning resources have been developed to train both undergraduate and postgraduate healthcare professionals on prudent antibiotic prescribing. Such training is mandatory for junior doctors. Also in the UK, the Prudent Antibiotic User (PAUSE, www.pause-online.org.uk) is a website of shared standardized teaching materials for prudent antimicrobial prescribing for use in the undergraduate medical curriculum. PAUSE provides standardized teaching aides for all educators of antibiotic prescribing based on patient-focused, reflective learning. Resources are designed to enable students to prepare for interactive sessions to compare standard patient vignettes with their own clinical experience. The structured preparation required of the students is a key to success. The interactive discussion sessions focus on learning prudent antibiotic prescribing through reflective practice. Prepared materials in relation to structure and content for each interactive session are available for tutors to use (in a PowerPoint format). These resources include patient histories, clinical signs, investigations and questions on diagnosis, assessing severity, appropriate prescribing, public health issues and patient management. Best practice statements and core resource lists are also available. In addition, guideline answers to the questions with feedback are provided, including inappropriate responses and the corresponding reasons. The materials may be shared, reproduced and modified as necessary. Another example is the educational work conducted by the Scottish Antimicrobial Prescribing Group (SAPG), hosted by the Scottish Medicines Consortium (SMC) in Scotland. The educational program is led by NHS Education for Scotland (NES) and involves scoping and development of training materials on antimicrobial stewardship both for undergraduate and postgraduate healthcare professionals. A range of online resources are available on the website (www.nes.scot.nhs.uk/education-and-training/by-theme-initiative/healthcare-associated-infections/training-resources/antimicrobials-in-clinical-practice.aspx). A framework of learning outcomes for antimicrobial stewardship that aligns with The Scottish Doctor report has been developed after broad consultation, and SAPG has recommended its adoption into the curricula of the five Scottish medical schools. The framework is also being evaluated by the two Schools of Pharmacy in Scotland to ensure that those learning outcomes applicable to pharmacists are covered by their undergraduate curricula. Such training is mandatory for junior doctors.

Internship, foundation year training (UK). Recently, the training programs of graduated doctors into primary care or specialty have been the subjects of reforms in many countries. In Scotland, the Doctors Online Training System (DOTS), a mandatory web-based education resource for all foundation training doctors, was revised to highlight current issues in prudent antibiotic prescribing in 2009. Access to the DOTS program has been extended to allow other medical staff, pharmacists and non-medical prescribers to participate in the training, and a primary care module has also been added. An induction pack for junior doctors and other new clinical staff has been produced and made available for antimicrobial management teams and other staff involved in training. This endeavor has been developed and taught by NES (www.nes.scot.nhs.uk/education-and-training/by-theme-initiative/healthcare-associated-infections/training-resources/antimicrobials-in-clinical-practice.aspx).

Specialist training. The format of internship/specialist training of medical doctors is very variable both regarding the onset of exposure to patients, the duration, type of training and responsibilities within Europe and the world which renders standardization of learning outcomes very difficult. This period is extremely crucial for shaping behavior, as juniors start to copy the behavior of their supervisors within the first weeks in the hospital. The same principles used for undergraduates apply, and competencies and learning outcomes must be clearly defined. The impact of learning sessions can be enhanced by measurement of current practice, and the use of quality improvement strategies.

Strong political support is necessary for a curriculum program to be successfully implemented. As an example, in the UK, the General Medical Council requested in 2009 that all postgraduate deans and Royal Colleges ensure infection prevention and control and antimicrobial prescribing become standard practice implemented in all clinical settings, and that they are strongly emphasized in undergraduate and postgraduate medical training.

Postgraduate level. Up to now, most initiatives on education in antimicrobial stewardship have been deployed in the postgraduate setting. A considerable effort has been put into education in hospitals. Many interventional programs to optimize antibiotic use have been conducted worldwide, and to a lesser extent in primary care. Intervention strategies have been categorized as educational, restrictive and supportive (Table 3). A multifaceted approach is favored to improve antibiotic use. Education is an essential element of any hospital program designed to influence antibiotic prescribing behavior. Educational measures are usually more popular among clinicians than restrictive measures. However, passive education alone (lectures, educational events, leaflets and handouts), without incorporation of active intervention, has been shown only marginally effective in changing antimicrobial prescribing practices and has not demonstrated a sustained impact. In many places the limited success of in-hospital education may be partly due to the rapid turnover of junior staff and the difficulty in maintaining a local continuous educational program. Printed educational materials and educational conferences alone also have had little effect on changing prescribing practices for antibiotics or other medications in the outpatient setting. Face-to-face and one-on-one educational sessions provided by physicians are based on established principles of behavioral science and market research and communications theory. This type of education has been used intensively and successfully by the pharmaceutical industry. The approach in antimicrobial stewardship has proved to be a practical, effective and safe method for reducing excessive broad-spectrum antibiotic use, but it is costly and labor-intensive. Clinical pathways have successfully been used to implement prudent antibiotic strategies, such as...
the de-escalation pathway described by Singh et al. to curb inappropriate antibiotic use for pulmonary infiltrates in the intensive care unit in their hospital.46 Clinical pathways, audit and feedback and the development of practice guidelines are discussed more extensively in another part of this issue. In conclusion, according to the Cochrane review, a wide variety of interventions have been proven successful in changing antibiotic prescribing to hospital inpatients.45 Any interventions can work some of the time.45 Hospitals are complex institutions and what is effective in one setting may not be effective in another.

An open access curriculum has been developed in the context of the European Union funded research project “Genomics to combat resistance against antibiotics in community-acquired lower respiratory tract infections in Europe” (GRACE). It contains a series of postgraduate courses and workshops and permitted the creation of an open access e-Learning portal. A total of 153 presentations matching the topics within the curriculum, slide material, handouts and 104 webcasts are available through this portal. The website is a considerable source of knowledge, mainly on diagnostics and much less on therapy (www.gracedud.org/pages/default.aspx?id=1617).47

Also on a European level, the European Centre for Disease Prevention and Control (ECDC) chose the hospital prescribers as target for their European Antibiotic Awareness Day campaign in 2010. The aim of the toolkit was to support efforts at a national level to increase prudent use of antibiotics in hospitals through dissemination of evidence-based educational and information materials. The toolkit contains template materials and evidence-based key messages which may be adapted for use at national level, and suggests tactics for getting the messages regarding prudent use of antibiotics through to the target audiences. The template toolkit materials and more information about the European Antibiotic Awareness Day are available on the European Antibiotic Awareness Day website (http://ecdc.europa.eu/en/EAAD/Pages/Home.aspx/).

In the US, the CDC started its campaign “Get Smart for Healthcare” in the same year. It focuses on improving antibiotic use in inpatient healthcare facilities starting with hospitals and then expanding to long-term care facilities. The goal of the campaign is to optimize the use of antimicrobial agents in inpatient healthcare settings by focusing on strategies to help hospitals and other inpatient facilities implement interventions to improve antibiotic use. The CDC provides slides, fact sheets, and an annotated bibliography on the evidence base of outcomes among other tools on its website (www.cdc.gov.getsmart/healthcare/). The CDC also collaborates with the Society for Healthcare Epidemiology of America (SHEA) to develop simple implementation tools, and with the Institute for Healthcare Improvement (IHI) and SHEA to develop a driver diagram with practical antibiotic stewardship implementation strategies.

In view of training the trainers, multiple educational postgraduate courses and workshops have been organized in the past decade, targeting a multidisciplinary group of clinicians including infectious diseases specialists, clinical microbiologists, (ID) hospital pharmacists and hospital epidemiologists.

The ESCMID study group for Antibiogenic Policies (ESGAP, available at www.escmid.org/egap) has been conducting postgraduate international education courses “Antimicrobial Stewardship: Measuring, auditing and improving,” held biannually before the European Conference on Microbiology and Infectious Diseases (ECCMID). Up to now, seven courses have been organized, training over 400 medical doctors, scientists, and clinical pharmacists over the past decade. Another one-day course is conducted as a pre-ICAAC workshop (www.icaac.org/workshops). ESGAP has also published its efforts in making an inventory of antimicrobial stewardship websites.48

<table>
<thead>
<tr>
<th>Table 3. Main antimicrobial stewardship strategies recommended in the international literature to improve antibiotic use at the hospital level49</th>
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<tbody>
<tr>
<td><strong>Educational measures and active interventions</strong></td>
</tr>
<tr>
<td><strong>Passive educational measures</strong></td>
</tr>
<tr>
<td>• Developing/updating local antibiotic guidelines</td>
</tr>
<tr>
<td>• Educational sessions, workshops, local conferences</td>
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<tr>
<td><strong>Active interventions</strong></td>
</tr>
<tr>
<td>• Clinical rounds discussing cases</td>
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<tr>
<td>• Prospective audit with intervention and feedback</td>
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<tr>
<td>• Reassessment of antibiotic prescriptions, with streamlining</td>
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<tr>
<td>and de-escalation of therapy</td>
</tr>
<tr>
<td>• Academic detailing, educational outreach visits</td>
</tr>
<tr>
<td><strong>Restrictive measures</strong></td>
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<tr>
<td>• Limiting number of antibiotics on the hospital formulary</td>
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<tr>
<td>• Antibiotic order form (compulsory)</td>
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<tr>
<td>• Automatic stop order</td>
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<tr>
<td>• Formulary restriction and preauthorization</td>
</tr>
<tr>
<td>• Limiting reporting of susceptibilities by the microbiology</td>
</tr>
<tr>
<td>laboratory</td>
</tr>
<tr>
<td>• Regulating contacts with the pharmaceutical industry</td>
</tr>
<tr>
<td><strong>Supportive/supplemental measures</strong></td>
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<tr>
<td>• Multidisciplinary antimicrobial stewardship team</td>
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<tr>
<td>• Consultancy service (infectious diseases, pharmacy, microbiology)</td>
</tr>
<tr>
<td>• Computer-assisted management program</td>
</tr>
<tr>
<td>• Parenteral to oral conversion</td>
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<tr>
<td>• Therapeutic drug monitoring service</td>
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</tbody>
</table>
After 30 years of antibiotic policy activities trying to curb antibiotic resistance, some reflection is appropriate. Antimicrobial stewardship interventions have mainly been conducted at the postgraduate level, aiming at changing the behavior of professionals. This has proven extremely difficult and frustrating. Quite paradoxically, although a thorough analysis is of the situation is lacking, only minimal investment has been put in the antimicrobial stewardship education in the undergraduate curriculum in most countries. This is, in our opinion, a missed opportunity for the future. It seems obvious that antimicrobial stewardship is likely to be more successful when started much earlier, at the time when knowledge, attitude and behavior of professionals are being shaped.

Therefore, it is now crucial to focus on an adapted undergraduate medical/professional curriculum that teaches all necessary principles of microbiology, infectious diseases and clinical pharmacology, with emphasis on the principles of prudent prescribing in an adequate format. Appropriate curricula on antimicrobial stewardship are a joint responsibility of the academia and the ministries of Health and Education.

References


Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Conclusion

• Education on prudent antimicrobial prescribing should start early in the undergraduate curriculum, preferably in the third year of undergraduate training in medicine and correspondent level in non-medical curricula of pharmacy, dentistry, midwifery, nursing and veterinary medicine to reach all health professionals.

• This requires commitment from medical schools on a national level to agree that antimicrobial stewardship is among the necessary skills to practice.

• The teaching of principles preparing for antimicrobial stewardship should be guaranteed by the development of learning outcomes and competencies and the appropriate evaluation.

• Postgraduate education should then focus on implementation and measurement of practice, with additional supportive and restrictive measures.

Recommendations

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Virulence 201


Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America
Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship


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EXECUTIVE SUMMARY

This document presents guidelines for developing institutional programs to enhance antimicrobial stewardship, an activity that includes appropriate selection, dosing, route, and duration of antimicrobial therapy. The multifaceted nature of antimicrobial stewardship has led to collaborative review and support of these recommendations by the following organizations: American Academy of Pediatrics, American Society of Health-System Pharmacists, Infectious Diseases Society for Obstetrics and Gynecology, Pediatric Infectious Diseases Society, Society for Hospital Medicine, and Society of Infectious Diseases Pharmacists. The primary goal of antimicrobial stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms (such as *Clostridium difficile*), and the emergence of resistance. Thus, the appropriate use of antimicrobials is an essential part of patient safety and deserves careful oversight and guidance. Given the association between antimicrobial use and the selection of resistant pathogens, the frequency of inappropriate antimicrobial use is often used as a surrogate marker for the avoidable impact on antimicrobial resistance. The combination of effective antimicrobial stewardship with a comprehensive infection control program has been shown to limit the emergence and transmission of antimicrobial-resistant bacteria. A secondary goal of antimicrobial stewardship is to reduce health care costs without adversely impacting quality of care.

These guidelines focus on the development of effective hospital-based stewardship programs and do not include specific outpatient recommendations. Although judicious use of antimicrobials is important in outpatient clinics and long-term care facilities, there are very few data regarding effective interventions, and it is unclear which interventions are most responsible for improvement in these settings.

The population targeted by these guidelines includes all patients in acute care hospitals. Most of the evidence supporting the recommendations in these guidelines is derived from studies of interventions to improve antimicrobial use for hospitalized adults. Many of these studies have focused on adults in intensive care units. Only a handful of studies have focused on hospitalized newborns, children, and adolescents. Few studies have included substantial populations of severely immunocompromised patients, such as patients undergoing...
hematopoetic stem cell transplantation or receiving chemotherapy likely to cause prolonged neutropenia. Nonetheless, the recommendations in these guidelines are likely to be broadly applicable to all hospitalized patients.

The ratings of the practices recommended in this document reflect the likely impact of stewardship practices on improving antimicrobial use and, consequently, minimizing the emergence and spread of antimicrobial resistance. Each recommendation is rated on the basis of the strength of the recommendation and the quality of evidence supporting it, using the rating system of the Infectious Disease Society of America (IDSA), as shown in table 1 [1]. The ratings provided also reflect the likely ability of the recommendation to reduce health care costs. Some strategies to reduce resistance may actually result in an increase in drug acquisition costs as part of a more comprehensive plan to reduce overall costs, including the attributable costs of resistance. In situations in which the likely impact of a recommendation on appropriate use of antimicrobials and health care costs diverge or in which cost data are not available, separate ratings are given.

Effective antimicrobial stewardship programs can be financially self-supporting and improve patient care [2–7] (A-II). Comprehensive programs have consistently demonstrated a decrease in antimicrobial use (22%–36%), with annual savings of $200,000–$900,000 in both larger academic hospitals [2, 3, 5, 7, 8] and smaller community hospitals [4, 6]. Thus, health care facilities are encouraged to implement antimicrobial stewardship programs. A comprehensive evidence-based stewardship program to combat antimicrobial resistance includes elements chosen from among the following recommendations based on local antimicrobial use and resistance problems and on available resources that may differ, depending on the size of the institution or clinical setting.

1. Core members of a multidisciplinary antimicrobial stewardship team include an infectious diseases physician and a clinical pharmacist with infectious diseases training (A-II) who should be compensated for their time (A-III), with the inclusion of a clinical microbiologist, an information system specialist, an infection control professional, and hospital epidemiologist being optimal (A-III). Because antimicrobial stewardship, an important component of patient safety, is considered to be a medical staff function, the program is usually directed by an infectious diseases physician or codirected by an infectious diseases physician and a clinical pharmacist with infectious diseases training (A-III).

2. Collaboration between the antimicrobial stewardship team and the hospital infection control and pharmacy and therapeutics committees or their equivalents is essential (A-III).

3. The support and collaboration of hospital administration, medical staff leadership, and local providers in the development and maintenance of antimicrobial stewardship programs is essential (A-III). It is desirable that antimicrobial stewardship programs function under the auspices of quality assurance and patient safety (A-III).

4. The infectious diseases physician and the head of pharmacy, as appropriate, should negotiate with hospital administration to obtain adequate authority, compensation, and expected outcomes for the program (A-III).

5. Hospital administrative support for the necessary infrastructure to measure antimicrobial use and to track use on an ongoing basis is essential (A-III).

6. There are 2 core strategies, both proactive, that provide the foundation for an antimicrobial stewardship program. These strategies are not mutually exclusive.

A. **Prospective audit with intervention and feedback.**
Prospective audit of antimicrobial use with direct interaction and feedback to the prescriber, performed by either an infectious diseases physician or a clinical pharmacist with infectious diseases training, can result in reduced inappropriate use of antimicrobials (A-I).

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**Table 1. Infectious Diseases Society of America–United States Public Health Service grading system for ranking recommendations in clinical guidelines.**

<table>
<thead>
<tr>
<th>Category, grade</th>
<th>Definition</th>
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<tbody>
<tr>
<td><strong>Strength of recommendation</strong></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Good evidence to support a recommendation for use</td>
</tr>
<tr>
<td>B</td>
<td>Moderate evidence to support a recommendation for use</td>
</tr>
<tr>
<td>C</td>
<td>Poor evidence to support a recommendation for use</td>
</tr>
<tr>
<td><strong>Quality of evidence</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Evidence from ≥1 properly randomized, controlled trial</td>
</tr>
<tr>
<td>II</td>
<td>Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from ≥1 center); from multiple time-series; or from dramatic results from uncontrolled experiments</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees</td>
</tr>
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NOTE. Adapted from [1].
B. Formulary restriction and preauthorization. Formulary restriction and preauthorization requirements can lead to immediate and significant reductions in antimicrobial use and cost (A-II) and may be beneficial as part of a multifaceted response to a nosocomial outbreak of infection (B-II). The use of preauthorization requirements as a means of controlling antimicrobial resistance is less clear, because a long-term beneficial impact on resistance has not been established, and in some circumstances, use may simply shift to an alternative agent with resulting increased resistance (B-II). In institutions that use preauthorization to limit the use of selected antimicrobials, monitoring overall trends in antimicrobial use is necessary to assess and respond to such shifts in use (B-III).

7. The following elements may be considered and prioritized as supplements to the core active antimicrobial stewardship strategies based on local practice patterns and resources.

A. Education. Education is considered to be an essential element of any program designed to influence prescribing behavior and can provide a foundation of knowledge that will enhance and increase the acceptance of stewardship strategies (A-III). However, education alone, without incorporation of active intervention, is only marginally effective in changing antimicrobial prescribing practices and has not demonstrated a sustained impact (B-II).


C. Antimicrobial cycling. There are insufficient data to recommend the routine use of antimicrobial cycling as a means of preventing or reducing antimicrobial resistance over a prolonged period of time (C-II). Substituting one antimicrobial for another may transiently decrease selection pressure and reduce resistance to the restricted agent. Unless the resistance determinant has been eliminated from the bacterial population, however, reintroduction of the original antimicrobial is again likely to select for the expression of the resistance determinant in the exposed bacterial population.

D. Antimicrobial order forms. Antimicrobial order forms can be an effective component of antimicrobial stewardship (B-II) and can facilitate implementation of practice guidelines.

E. Combination therapy. There are insufficient data to recommend the routine use of combination therapy to prevent the emergence of resistance (C-II). Combination therapy does have a role in certain clinical contexts, including use for empirical therapy for critically ill patients at risk of infection with multidrug-resistant pathogens, to increase the breadth of coverage and the likelihood of adequate initial therapy (A-II).

F. Streamlining or de-escalation of therapy. Streamlining or de-escalation of empirical antimicrobial therapy on the basis of culture results and elimination of redundant combination therapy can more effectively target the causative pathogen, resulting in decreased antimicrobial exposure and substantial cost savings (A-II).

G. Dose optimization. Optimization of antimicrobial dosing based on individual patient characteristics, causative organism, site of infection, and pharmacokinetic and pharmacodynamic characteristics of the drug is an important part of antimicrobial stewardship (A-II).

H. Parenteral to oral conversion. A systematic plan for parenteral to oral conversion of antimicrobials with excellent bioavailability, when the patient’s condition allows, can decrease the length of hospital stay and health care costs (A-I). Development of clinical criteria and guidelines allowing switch to use of oral agents can facilitate implementation at the institutional level (A-III).

8. Health care information technology in the form of electronic medical records (A-III), computer physician order entry (B-II), and clinical decision support (B-II) can improve antimicrobial decisions through the incorporation of data on patient-specific microbiology cultures and susceptibilities, hepatic and renal function, drug-drug interactions, allergies, and cost. However, implementation of these features has been slow, and conformation of the technology to the clinical environment remains a challenge.

9. Computer-based surveillance can facilitate good stewardship by more efficient targeting of antimicrobial interventions, tracking of antimicrobial resistance patterns, and identification of nosocomial infections and adverse drug events (B-II).

10. The clinical microbiology laboratory plays a critical role in antimicrobial stewardship by providing patient-specific culture and susceptibility data to optimize individual antimicrobial management and by assisting infection control efforts in the surveillance of resistant organisms and in the molecular epidemiologic investigation of outbreaks (A-III).

11. Both process measures (did the intervention result in the desired change in antimicrobial use?) and outcome measures (did the process implemented reduce or prevent resistance or other unintended consequences of antimicrobial use?) are useful in determining the impact of antimicrobial stewardship on antimicrobial use and resistance patterns (B-III).

INTRODUCTION

Purpose. In recognition that antimicrobial resistance results in increased morbidity, mortality, and cost of health care, the IDSA initially published guidelines for improving the use of...
antimicrobial agents in hospitals in 1988 [9] and then jointly published guidelines with the Society for Healthcare Epidemiology of America in 1997 for the prevention of antimicrobial resistance in hospitals [10]. However, subsequent surveys of hospitals have found that practices to improve antimicrobial use are frequently inadequate and not routinely implemented [11–13]. The purpose of these guidelines is to build on the previous position statements, as well as to provide evidence-based recommendations for developing a program to enhance antimicrobial stewardship in the hospital setting to improve the quality of care. These guidelines are not a substitute for clinical judgment, and clinical discretion is required in the application of guidelines to individual patients.

Effective antimicrobial stewardship programs, also known as antimicrobial management programs, can be financially self-supporting and can improve patient care [2–7] (A-II). Antimicrobial stewardship includes not only limiting inappropriate use but also optimizing antimicrobial selection, dosing, route, and duration of therapy to maximize clinical cure or prevention of infection while limiting the unintended consequences, such as the emergence of resistance, adverse drug events, and cost. Given the emergence of multidrug-resistant pathogens and their impact on clinical care, appropriate use of antimicrobial agents has become a focus of patient safety and quality assurance along with medication errors, allergy identification, and drug-drug interactions [14]. The ultimate goal of antimicrobial stewardship is to improve patient care and health care outcomes.

From the institutional perspective, antimicrobials account for upwards of 30% of hospital pharmacy budgets [15]. It has been recognized for several decades that up to 50% of antimicrobial use is inappropriate, adding considerable cost to patient care [8, 9, 15–18]. In addition to direct pharmacy acquisition costs, numerous reports suggest that inappropriate and unnecessary antimicrobial use leads to increased selection of resistant pathogens (table 2). Once antimicrobial resistance emerges, it can have a significant impact on patient morbidity and mortality, as well as increased health care costs [32, 33]. Bacteremia [34, 35] and surgical site infections [36] due to methicillin-resistant Staphylococcus aureus (MRSA) have been associated with a higher mortality rate than similar infections due to methicillin-susceptible S. aureus, with the mean attributable cost of an MRSA infection ranging from $2975 to $13,901 [36, 37]. Similarly, compared with vancomycin-susceptible Enterococcus faecium infections, bloodstream infections due to vancomycin-resistant E. faecium (VRE) were associated with decreased survival (24% vs. 59%), increased length of hospital stay (34.8 vs. 16.7 days), and an attributable cost of $27,190 per episode [38, 39]. A meta-analysis of 9 studies of VRE bloodstream infections found an attributable excess mortality of 30%, compared with vancomycin-susceptible Enterococcus bloodstream infections [40]. Similar adverse outcomes have also been reported for infections with resistant gram-negative organisms, including Pseudomonas, Acinetobacter, and Enterobacter species and extended-spectrum β-lactamase-producing organisms [41]. A case-control study found that third-generation cephalosporin–resistant Enterobacter infections were associated with increased mortality (relative risk, 5.02), length of hospital stay (1.5-fold increase), and an attributable cost of $29,379 [42]. The emergence of infections with multidrug-resistant gram-negative organisms, combined with a paucity of new drug development, has unfortunately led to the resurgent use of colistin, a polymyxin antimicrobial previously abandoned because of its high rates of nephrotoxicity and neurotoxicity [43]. In 1998, the Institute of Medicine estimated that the annual cost of infections caused by antimicrobial-resistant bacteria was $4–$5 billion [44].

**Methods.** The recommendations in this guideline are based on a review of published studies identified through a search of the PubMed database (search terms used alone and in combination included “antimicrobial,” “antibiotic,” “stewardship,” “management,” “resistance,” “cost,” “education,” “guidelines,” “restriction,” “cycling,” “order forms,” and “combination therapy”) supplemented by review of references of relevant articles to identify additional reports. Committee members were also asked to cite additional relevant studies to support the recommendations. Because of the limited number of randomized, controlled trials, results from prospective cohort studies, case-control studies, longitudinal time series, and other descriptive studies are included in the review. The ratings of the practices recommended in this document reflect the likely impact of such practices on improving antimicrobial use and, ultimately, antimicrobial resistance. Given the association between antimicrobial use and the selection of resistant pathogens, rates of

**Table 2. Causal associations between antimicrobial use and the emergence of antimicrobial resistance.**

| Changes in antimicrobial use are paralleled by changes in the prevalence of resistance. |
| Antimicrobial resistance is more prevalent in healthcare–associated bacterial infections, compared with those from community-acquired infections. |
| Patients with healthcare–associated infections caused by resistant strains are more likely than control patients to have received prior antimicrobials. |
| Areas within hospitals that have the highest rates of antimicrobial resistance also have the highest rates of antimicrobial use. |
| Increasing duration of patient exposure to antimicrobials increases the likelihood of colonization with resistant organisms. |

**NOTE.** A causal association between antimicrobial use and the emergence of antimicrobial resistance has been reviewed elsewhere [9, 19–22] and is strongly suggested on the basis of several lines of evidence that are derived from patient and population levels of analysis, colonization and infection data, and retrospective and prospective studies [23–31]. Adapted from [10].
inappropriate antimicrobial use are considered as surrogate markers for the avoidable impact on antimicrobial resistance.

The strength of the recommendations and quality of evidence are rated using IDSA criteria (table 1) [1]. Individual studies were evaluated both for their impact on the targeted antimicrobial(s) or resistance problem and for any secondary impact on local antimicrobial use and resistance patterns. The ratings also reflect the likely ability of the recommendation to reduce health care costs. In situations in which the likely impact of a recommendation on appropriate use of antimicrobials and health care costs diverge or cost data are not available, separate ratings are given. Recommendations reflect a compilation of the studies in each section, as well as the opinions of the committee members.

GUIDELINES FOR DEVELOPING AN INSTITUTIONAL PROGRAM TO ENHANCE ANTIMICROBIAL STEWARDSHIP

THE ANTIMICROBIAL STEWARDSHIP TEAM AND ADMINISTRATIVE SUPPORT

It is essential that the antimicrobial stewardship team includes an infectious diseases physician and a clinical pharmacist with infectious diseases training and that both of these individuals are compensated appropriately for their time. Optimally, the team should include a clinical microbiologist who can provide surveillance data on antimicrobial resistance, as well as an information system specialist who can provide the computer support necessary for surveillance and implementation of recommendations. In addition, it is optimal that the team includes an infection control professional and hospital epidemiologist to coordinate efforts on improving antimicrobial use, because reduction of antimicrobial resistance is a common goal of these persons. Because antimicrobial stewardship, an important component of patient safety, is considered to be a medical staff function, the program is usually directed by an infectious diseases physician or codirected by an infectious diseases physician and a clinical pharmacist with infectious diseases training (A-III). Because antimicrobial stewardship, an important component of patient safety, is considered to be a medical staff function, the program is usually directed by an infectious diseases physician or codirected by an infectious diseases physician and a clinical pharmacist with infectious diseases training (A-III).

• Core members of a multidisciplinary antimicrobial stewardship team include an infectious diseases physician and a clinical pharmacist with infectious diseases training (A-II) who should be compensated for their time (A-III), with the inclusion of a clinical microbiologist, an information system specialist, an infection control professional, and hospital epidemiologist being optimal (A-III). Because antimicrobial stewardship, an important component of patient safety, is considered to be a medical staff function, the program is usually directed by an infectious diseases physician or codirected by an infectious diseases physician and a clinical pharmacist with infectious diseases training (A-III).

• Collaboration between the antimicrobial stewardship team and the hospital infection control and pharmacy and therapeutics committees, or their equivalents, is essential (A-III).

• The support and collaboration of hospital administration, medical staff leadership, and local providers in the development and maintenance of antimicrobial stewardship programs is essential (A-III). It is desirable that antimicrobial stewardship programs function under the auspices of quality assurance and patient safety (A-III).

• The infectious diseases physician and the head of pharmacy, as appropriate, should negotiate with hospital administration to obtain adequate authority, compensation, and expected outcomes for the program (A-III). It is essential that there be hospital administrative support for the necessary infrastructure, to measure antimicrobial use and to track use on an ongoing basis (A-III).

• Hospital administrative support for the necessary infrastructure to measure antimicrobial use and to track use on an ongoing basis is essential (A-III).

ELEMENTS OF AN ANTIMICROBIAL STEWARDSHIP PROGRAM

The best strategies for the prevention and containment of antimicrobial resistance are not definitively established, because there is a paucity of randomized, controlled trials in this field [45]. Often, multiple interventions have been made simultaneously, making it difficult to assess the benefit attributable to any one specific intervention. However, a comprehensive program that includes active monitoring of resistance, fostering of
appropriate antimicrobial use, and collaboration with an effective infection control program to minimize secondary spread of resistance [46, 47] is considered to be optimal [48]. A comprehensive evidence-based stewardship program to combat antimicrobial resistance includes elements chosen from among the following strategies, which are based on local antimicrobial use and resistance problems, and on available resources that may differ depending on the size of the institution or clinical setting.

**Active Antimicrobial Stewardship Strategies**

**Prospective audit with intervention and feedback.** Prospective audit of antimicrobial use with intervention and feedback to the prescriber have been demonstrated to improve antimicrobial use. In a large teaching hospital, house staff were randomized by the medical service to receive either no intervention or one-on-one education by a clinical specialist (academic detailing) on a patient-specific basis, emphasizing microbiologic data, local resistance patterns, and clinical literature, when the pharmacy received an order for either levofloxacin or ceftazidime. This resulted in a 37% reduction in the number of days of unnecessary levofloxacin or ceftazidime use by decreasing the duration of therapy, as well as reducing new starts, suggesting that house staff learned not to initiate unnecessary antibiotic treatment regimens [49]. At a 600-bed tertiary teaching hospital, inpatients receiving parenteral antimicrobials chosen by their primary care physician were randomized to an intervention group that received antimicrobial-related suggestions from an infectious diseases fellow and a clinical pharmacist versus no antimicrobial suggestions. Physicians in the intervention group received 74 suggestions for 62 of 127 patients, including suggestions on a more appropriate agent, route of administration, dosing, discontinuation of the drug, or toxicity monitoring. Eighty-five percent of the suggestions were implemented, resulting in 1.6 fewer days of parenteral therapy and a cost savings of $400 per patient, with no adverse impact on clinical response, compared with the control group [50]. There was a trend, however, toward increasing rates of readmission in the intervention group, emphasizing the need to monitor the impact of such interventions designed to decrease length of hospital stay.

Prospective audit and interventions by a clinical pharmacist and infectious diseases physician at a medium-sized community hospital resulted in a 22% decrease in the use of parenteral broad-spectrum antimicrobials, despite a 15% increase in patient acuity over a 7-year period [3]. They also demonstrated a decrease in rates of *C. difficile* infection and nosocomial infection caused by drug-resistant Enterobacteriaceae, compared with the preintervention period.

In hospitals where daily review of antimicrobial use is not feasible because of limited resources, a scaled-down model can still have a significant impact, as illustrated by a small, 120-bed community hospital that used an infectious diseases physician and clinical pharmacist 3 days per week to review patients receiving multiple, prolonged, or high-cost courses of antimicrobial therapy [4]. Sixty-nine percent of 488 recommendations were implemented, resulting in a 19% reduction in antimicrobial expenditures for an estimated annual savings of $177,000, compared with the preintervention period. In these studies, interventions were communicated to prescribers either verbally or in writing. Written communication was typically accomplished by using special, nonpermanent forms that were placed in the medical record or chart but were subsequently removed after the intervention or at the time of discharge from the hospital. Each intervention provides the opportunity for provider education.

Effective audit with intervention and feedback can be facilitated through computer surveillance of antimicrobial use, allowing the targeting of specific services or units where problems exist, as well as identification of patients receiving particular agents or combinations of agents that might benefit from intervention.

**Recommendation**

- Prospective audit of antimicrobial use with direct interaction and feedback to the prescriber, performed by either an infectious diseases physician or a clinical pharmacist with infectious diseases training, can result in reduced inappropriate use of antimicrobials (A-I).

**Formulary restriction and preauthorization requirements for specific agents.** Most hospitals have a pharmacy and therapeutics committee or an equivalent group that evaluates drugs for inclusion on the hospital formulary on the basis of considerations of therapeutic efficacy, toxicity, and cost while limiting redundant new agents with no significant additional benefit. Antimicrobial restriction—either through formulary limitation by this method or by the requirement of preauthorization and justification—is the most effective method of achieving the process goal of controlling antimicrobial use. Longitudinal studies implementing restrictive policies have demonstrated significant initial decreases in the use of the targeted antimicrobials, with annual antimicrobial cost savings ranging upwards of $800,000 [14, 51–57]. The achievement of the outcome goal of reducing antimicrobial resistance has not been as clear, as illustrated by the following studies.

Both formulary restriction [58] and preauthorization requirements for use of clindamycin [59] during nosocomial epidemics of *C. difficile* infection have led to prompt cessation of the outbreaks, whereas preapproval restriction of broad-spectrum antimicrobials has led to short-term increased susceptibilities among gram-negative pathogens, such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Enterobacter*
cloacae, during a 6–12-month period [57, 60]. Restriction of vancomycin and third-generation cephalosporins in response to increasing rates of VRE has demonstrated mixed results [61–63]. Fecal VRE colonization rates of 47% (despite barrier precautions) led one center to restrict vancomycin and cefotaxime use while encouraging the replacement of third-generation cephalosporins with β-lactam/β-lactamase inhibitor combinations. This led to a reduction in the rates of monthly use of vancomycin, cefotaxime, and ceftazidime by 34%, 84%, and 55%, respectively, and of ampicillin-sulbactam and piperacillin-tazobactam use increased. This was accompanied by a decrease in the fecal VRE point prevalence from 47% to 15% during 6 months [59]. In contrast, in another study, the prevalence of VRE increased from 17% to 30%, despite the restriction on the use of vancomycin and third-generation cephalosporins during a 10-year period [64]. The interpretation of these study results is often confounded by concomitant changes in infection control practices and by the influence of nonrestricted antimicrobial agents on gut flora.

Studies of antibiotic-restriction policies among pediatric patients have demonstrated inconsistent results. A crossover study of 2 neonatal intensive care units (ICUs) compared 2 approaches for empirical treatment of early- and late-onset suspected sepsis—a “broad-spectrum” regimen consisting of ampicillin and cefotaxime versus a “narrow-spectrum” regimen consisting of penicillin and tobramycin—on the prevalence of colonization with bacteria resistant to each of the regimens [65]. The narrow-spectrum regimen was associated with a markedly lower prevalence of colonization with resistant gram-negative bacilli. In contrast, a quasi experimental study from a pediatric ICU of a policy to restrict ceftazidime use (piperacillin-tazobactam was the preferred regimen) found no change in the incidence of colonization with ceftazidime-resistant gram-negative bacilli, although there was a decrease in the prevalence of colonization with specific species of gram-negative bacilli that commonly harbor inducible AmpC β-lactamases (e.g., E. cloacae, Serratia marcesens, Citrobacter freundii, and P. aeruginosa) [66].

The effectiveness of a preauthorization program depends on who is making the recommendations. Restriction of cefotaxime use through a program requiring approval from a chief resident or attending physician had no impact on its use [67]. Recommendations from an antimicrobial management team consisting of a pharmacist and an infectious diseases physician resulted in increased antimicrobial appropriateness, increased clinical cure, and a trend towards improved economic outcome, compared with recommendations made by infectious diseases fellows [68].

The challenge of antimicrobial restriction and its effect on antimicrobial resistance is exemplified in a study by Rahal et al. [27]. In response to an increasing incidence of cephalosporin-resistant Klebsiella, a preapproval policy was implemented for cephalosporins. This resulted in an 80% reduction in hospital-wide cephalosporin use and a subsequent 44% reduction in the incidence of ceftazidime-resistant Klebsiella throughout the medical center, as well as a 71% reduction in the ICUs. Concomitantly, however, imipenem use increased 141%, accompanied by a 69% increase in the incidence of imipenem-resistant P. aeruginosa. This untoward restrictive effect of “squeezing the balloon” may counteract the originally sought benefits [69]. Furthermore, restricting use of a single drug to prevent or reverse antimicrobial resistance may be ineffective, because multiple antimicrobials may be associated with changes in susceptibility to other drugs for a given pathogen [70].

Recommendation
• Formulary restriction and preauthorization requirements can lead to immediate and significant reductions in antimicrobial use and cost (A-II) and may be beneficial as part of a multifaceted response to a nosocomial outbreak of infection (B-II). The use of preauthorization requirements as a means of controlling antimicrobial resistance is less clear, because a long-term beneficial impact on resistance has not been established, and in some circumstances, may simply shift to an alternative agent with resulting increased resistance (B-II). In institutions that use preauthorization to limit the use of selected antimicrobials, monitoring overall trends in antimicrobial use is necessary to assess and respond to such shifts in use (B-III).

Supplemental Antimicrobial Stewardship Strategies

Education. Education is the most frequently employed intervention and is considered to be an essential element of any program designed to influence prescribing behavior. Educational efforts include passive activities, such as conference presentations, student and house staff teaching sessions, and provision of written guidelines or e-mail alerts. However, education alone, without incorporation of active intervention, is only marginally effective and has not demonstrated a sustained impact [71–73].

Step-wise implementation of an antimicrobial stewardship program initially with passive strategies, such as education and order forms, followed by an active strategy with prospective audit and intervention demonstrated progressive decreases in antimicrobial consumption, resulting in a savings of $913,236 over 18 months. During the period of active intervention, 25% of antimicrobial orders were modified (86% resulted in less expensive therapy, and 47% resulted in use of a drug with a narrower spectrum of activity), resulting in a significant increase in microbiologically based prescribing (63% vs. 27%) [71].

In an attempt to improve adherence to recommendations for perioperative antimicrobial prophylaxis, a before-and-after...
study compared prescribing practices after distribution of an educational handbook with those after the introduction of an order form. The educational handbook led to a marginal improvement in compliance (from 11% to 18%), whereas introduction of the order form led to significantly improved compliance (from 17% to 78%) [73].

**Recommendation**

- Education is considered to be an essential element of any program designed to influence prescribing behavior and can provide a foundation of knowledge that will enhance and increase the acceptance of stewardship strategies (A-III). However, education alone, without incorporation of active intervention, is only marginally effective in changing antimicrobial prescribing practices and has not demonstrated a sustained impact (B-II).

**Guidelines and clinical pathways.** Clinical practice guidelines are being produced with increasing frequency, with the goal of ensuring high-quality care. However, the impact on provider behavior and improved clinical outcomes has been difficult to measure. Although physicians usually agree, in principle, with national guidelines, the absence of accompanying strategies for local implementation often presents a formidable barrier [74]. Antimicrobial stewardship programs can facilitate multidisciplinary development of evidence-based practice guidelines that incorporate local microbiology and resistance patterns.

Randomized implementation of a clinical pathway, compared with conventional management of community-acquired pneumonia, among 20 hospitals led to a 1.7-day decrease in the median length of hospital stay, an 18% decrease in the rate of admissions of low-risk patients, and 1.7 fewer mean days of intravenous therapy in the intervention group, without an increase in complications, readmissions, or mortality [75]. In another study, multidisciplinary development of practice guidelines based on evidence in the literature and local microbiology and resistance patterns and implementation in a surgical ICU led to a 77% reduction in antimicrobial use and cost, a 30% reduction in overall cost of care, decreased mortality among patients with infection, and a trend towards reduced length of ICU stay, compared with the preimplementation time period [76]. Importantly, both of these studies demonstrate that antimicrobial selection is only 1 component in improving the management of infectious diseases and cannot be done without recommendations for diagnosis and testing, admission criteria, nursing care, conversion to oral medication, and discharge planning. Whether the use of guidelines will lead to a long-term impact on antimicrobial resistance remains to be determined, but the following studies of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) suggest that improving antimicrobial use through the use of guidelines may decrease the emergence of resistant pathogens.

The increasing incidence of multidrug-resistant organisms in cases of HAP and VAP, the diagnostic challenge of these entities, and the mortality benefit associated with initial appropriate therapy [77] have led to an increased use of broad-spectrum antimicrobials, which must be balanced against further selection of resistant pathogens. Invasive diagnosis of VAP with quantitative bronchoscopy for diagnosis and antimicrobial guidance led to reduced mortality at 14 days and a decrease in antimicrobial use [78]. Another strategy to address the inappropriate use of antimicrobials in the ICU setting used an algorithm incorporating the clinical pulmonary infection score to identify patients with a low likelihood of pneumonia. Patients randomized to the intervention group who continued to have a low clinical pulmonary infection score (≤6) had their antimicrobial therapy discontinued at day 3, and the control group received the standard 10–21 days of therapy. This led to a significant decrease in duration of therapy (3 vs. 9.8 days) and antimicrobial cost ($400 per patient), with no difference in mortality. In addition, the development of antimicrobial resistance and/or superinfections was less common in the group receiving the short-course antimicrobial therapy (15% vs. 35%) [79]. A prospective before-and-after study of a clinical guideline for the management of VAP incorporated broad empirical therapy based on local microbiology with culture-driven de-escalation and a standard 7-day course of therapy. Implementation of the protocol led to increased initial administration of adequate antimicrobial therapy (94% vs. 48%), decreased duration of therapy (8.6 vs. 14.8 days), and decreased VAP recurrence (8% vs. 24%), without affecting patient mortality [80]. The efficacy of short-course therapy for VAP was subsequently confirmed in a randomized study of 8 versus 15 days of antimicrobial therapy in patients with VAP documented by quantitative culture of samples obtained by bronchoscopy. There was no difference in mortality or recurrent infection in patients who received the shorter course of therapy, but the short-course group did have more antimicrobial-free days (13.1 vs. 8.7) and a decreased rate of emergence of multidrug-resistant pathogens among those patients with recurrences of pulmonary infection (42% vs. 62%) [81]. These studies support the development and implementation of evidence-based guidelines for diagnosis and antimicrobial therapy for HAP and VAP.

A quasi experimental study in a pediatric hospital in Australia demonstrated similar results regarding the use of guidelines to improve therapy for common infections [82]. The investigators provided recommendations for the treatment of childhood infections on a laminated card that could be clipped to a hospital badge. When the 6-month period during implementation of the intervention (intervention period) was compared with the prior 6 months (baseline period), the intervention was asso-
associated with substantial increases in the percentage of prescriptions with the correct choice and dose of antimicrobial agents for 2 of 3 indicator infections (pneumonia and orbital/periorbital cellulitis). The cost of third-generation cephalosporins was reduced by more than one-half in the intervention period.

**Recommendation**
- Multidisciplinary development of evidence-based practice guidelines incorporating local microbiology and resistance patterns can improve antimicrobial utilization (A-I). Guideline implementation can be facilitated through provider education and feedback on antimicrobial use and patient outcomes (A-III).

**Antimicrobial cycling and scheduled antimicrobial switch.**

“Antimicrobial cycling” refers to the scheduled removal and substitution of a specific antimicrobial or antimicrobial class to prevent or reverse the development of antimicrobial resistance within an institution or specific unit. In true cycling, there is a return to the original antimicrobial after a defined time, as opposed to a simple switch of antimicrobials [83–86]. In many respects, cycling is an attempt at controlled heterogeneity of antimicrobial use to minimize antimicrobial selection pressures. Studies of true antimicrobial cycling are limited and vary in terms of antimicrobial class selection, duration of cycling, therapeutic options offered during cycling periods, and cycling by time period versus by patient. Concerns about allergies, adverse drug events, and conflicts with national guidelines have led to 10%–50% of patients in cycling programs to receive “off-cycle” antimicrobials, resulting in poor implementation of the intended process change, with multiple antimicrobials being used at the same time by different patients [85].

Driven by both increasing resistance among Enterobacteriaceae and pricing changes, the largest cycling experience has been reported for changes in aminoglycoside use—particularly, substituting amikacin for gentamicin. Such a switch in aminoglycoside use has been associated with a significant reduction in gentamicin resistance [87–93]; however, rapid reintroduction of gentamicin was accompanied by a rapid return of gentamicin resistance [89, 92]. In one institution with 10 years of experience, this led to an additional cycle of amikacin followed by a more gradual return of gentamicin, without an associated increase in resistance once the original gentamicin resistance plasmids could no longer be detected [92]. This last example highlights the importance of understanding and monitoring mechanisms of resistance over the long term when developing protocols for antimicrobial cycling. Once antimicrobial resistance emerges, it will often persist even in the absence of direct antimicrobial selection pressure, potentially minimizing the impact of antimicrobial removal strategies [21].

A switch from the empirical use of ceftazidime to ciprofloxacin for suspected gram-negative bacterial infection in a cardiothoracic ICU led to a decreased incidence of VAP due to multidrug-resistant, gram-negative bacteria (1% vs. 4%) [94]. Restriction of ceftazidime and ciprofloxacin in a medical ICU, combined with cycling of the preferred β-lactam agent at monthly intervals, led to a decreased incidence of VAP and improved susceptibilities for *P. aeruginosa.* Because these maneuvers, as well as de-escalation of therapy based on culture results, led to a 50% reduction in overall antimicrobial use, the benefit of cycling alone cannot be ascertained [95]. Quarterly rotation of empirical antimicrobial regimens in a surgical ICU for pneumonia and peritonitis/sepsis led to a decreased incidence of resistant bacterial infections and mortality due to infection [96]. However, significant patient population differences and the simultaneous changes in infection control, including institution of an antibiotic surveillance team and the introduction of alcohol gel dispensers, confounded interpretation of the results. In addition, only 62%–83% of patients received the “on-cycle” antimicrobial intended in the process change, resulting in antimicrobial mixing as opposed to time period–based cycling.

It should be noted that mathematical modeling suggests that true cycling is unlikely to reduce the evolution or spread of antimicrobial resistance. Rather, such modeling suggests that the simultaneous mixed use of different antimicrobial classes in a heterogeneous fashion may slow the spread of resistance [97, 98].

In an attempt to examine this hypothesis, a prospective cross-over study compared the effects of monthly cycling of antipseudomonal agents (cefeplime or ceftazidime, ciprofloxacin, imipenem or meropenem, or piperacillin-tazobactam) with the use of these agents in the same order by consecutive patients (i.e., mixing) [99]. During mixing, a significantly higher proportion of patients acquired a strain of *P. aeruginosa* that was resistant to ceftazidime (9% vs. 3%; *P* = .01). As in previous cycling studies, however, adherence to the cycling regimen was problematic, with scheduled antimicrobials never accounting for more than 45% of all antipseudomonal antimicrobials. Additional clinical studies to examine optimal cycling parameters and the role of antimicrobial diversity are needed.

**Recommendation**
- There are insufficient data to recommend the routine use of antimicrobial cycling as a means of preventing or reducing antimicrobial resistance over a prolonged period of time (C-II). Substituting one antimicrobial for another may transiently decrease selection pressure and reduce resistance to the restricted agent. Unless the resistance determinant has been eliminated from the bacterial population, however, reintroduction of the original antimicrobial is again likely to select for the expression of the resistance determinant in the exposed bacterial population.
Antimicrobial order forms. Antimicrobial order forms decrease antimicrobial consumption in longitudinal studies through the use of automatic stop orders and the requirement of physician justification [100, 101]. Prior to more recent studies further defining the optimal timing and duration of perioperative antimicrobial prophylaxis [102, 103], use of perioperative prophylactic order forms with automatic discontinuation at 2 days resulted in a decrease in the mean duration of antimicrobial prophylaxis (from 4.9 to 2.4 days) and a decrease in the percentage of patients receiving perioperative prophylaxis for ≥2 days (from 85% to 44%) [100]. The rate of inappropriate initiation of antimicrobial prophylaxis postoperatively decreased from 30% to 11% with use of the order form. The use of an order form for all inpatient antimicrobial orders in an 800-bed hospital that required clinical indication, as well as a defined duration before order renewal, led to a 30% decrease in antibiotic courses and a 2% decrease in the hospital pharmacy budget for parenteral antibiotics over a 25-month period, during which time most hospitals were experiencing an increase in expenditures [101]. Use of an antibiotic order form for vancomycin did not improve appropriate use of vancomycin in a pediatriic hospital [104]. Automatic stop orders should not replace clinical judgment, and renewal requirements must be clearly communicated to providers to avoid inappropriate treatment interruptions.

Recommendation

- Antimicrobial order forms can be an effective component of antimicrobial stewardship (B-II) and can facilitate implementation of practice guidelines.

Combination therapy: prevention of resistance versus redundant antimicrobial coverage. The rationale for combination antimicrobial therapy includes broad-spectrum empirical therapy for serious infections, improved clinical outcomes, and the prevention of resistance. Inadequate initial antimicrobial therapy was found to be an independent risk factor for mortality in nonurinary infections due to extended-spectrum β-lactamase–producing Escherichia coli and Klebsiella species [105]. Similarly, inadequate early antimicrobial coverage has been associated with increased mortality in patients with microbiologically confirmed severe sepsis (39% vs. 24%) [106] and critically ill ICU patients (42% vs. 18%) [55], leading to incorporation of empirical combination therapy for late-onset VAP in the recent IDSA–American Thoracic Society guidelines [107]. These studies highlight the need to assess risk factors for multidrug-resistant pathogens when selecting empirical antimicrobial therapy for critically ill patients.

However, in many situations, combination therapy is redundant and unnecessary. Evidence supporting the role of combination antimicrobial therapy for the prevention of resistance is limited to those situations in which there is a high organism load combined with a high frequency of mutational resistance during therapy. Classic examples are tuberculosis or HIV infection. There is often debate about the role of combination therapy in serious infections due to gram-negative organisms, such as Pseudomonas species, but clear evidence supporting a clinical benefit or resistance benefit is lacking [108–118]. A meta-analysis of randomized, controlled trials comparing a β-lactam plus an aminoglycoside as combination therapy with β-lactam monotherapy for the treatment of hospitalized patients with serious infections found no difference in the emergence of antimicrobial resistance. In fact, β-lactam monotherapy was associated with fewer superinfections [119].

Recommendation

- There are insufficient data to recommend the routine use of combination therapy to prevent the emergence of resistance (C-II). Combination therapy does have a role in certain clinical contexts, including use for empirical therapy for critically ill patients at risk of infection with multidrug-resistant pathogens, to increase the breadth of coverage and the likelihood of adequate initial therapy (A-II).

Streamlining or de-escalation of therapy. Good stewardship to optimize empirical initial antimicrobial therapy may conflict with good stewardship to promote judicious use, because continuing excessively broad therapy contributes to the selection of antimicrobial resistant pathogens [120]. This conflict can be resolved when culture results become available by streamlining or de-escalating antimicrobial therapy to more targeted therapy that decreases antimicrobial exposure and contains cost. De-escalation may also include discontinuation of empirical antimicrobial therapy based on clinical criteria and negative culture results as demonstrated in the management of suspected VAP [79, 107, 121]. Review by a pharmacist and an infectious diseases physician of 625 patients receiving combination antimicrobial therapy led to streamlining recommendations in 54% of antimicrobial courses over 7 months, resulting in a projected annual savings of $107,637 [122].

In another study, a computer query to mine the hospital pharmacy database followed by targeted review by an infectious diseases clinical pharmacist facilitated the identification of potentially redundant antimicrobial combinations in 16% of patients receiving ≥2 antimicrobials. Even after accepting the debatable “double gram-negative coverage,” 71% of the combinations were deemed to be inappropriate. Interestingly, half of the redundancy was due to physician prescribing error, whereas the other half was due to medication ordering and distribution system errors. The annualized potential savings from this intervention was estimated to be $60,000, and ∼3500 redundant inpatient antibiotic–days were avoided [123].

Recommendation

- Streamlining or de-escalation of empirical antimicrobial
therapy on the basis of culture results and elimination of redundant combination therapy can more effectively target the causative pathogen, resulting in decreased antimicrobial exposure and substantial cost savings (A-II).

**Dose optimization.** Optimization of antimicrobial dosing that accounts for individual patient characteristics (e.g., age, renal function, and weight), causative organism and site of infection (e.g., endocarditis, meningitis, and osteomyelitis), and pharmacokinetic and pharmacodynamic characteristics of the drug is an important part of antimicrobial stewardship. For instance, the bactericidal activity of β-lactams correlates with the percentage of time that the drug concentration remains greater than the MIC, whereas fluoroquinolones and aminoglycosides are concentration-dependent agents, with the ratio of the maximum concentration to the MIC or the ratio of the area under the curve to the MIC being important predictors of activity. Examples of these principles in practice include prolonged or continuous infusion of β-lactams [124], extended-interval dosing of aminoglycosides [125], and dosing of fluoroquinolones for *Streptococcus pneumoniae* in community-acquired pneumonia [126, 127] and for *Pseudomonas* in HAP and VAP [107]. The use of pharmacokinetic and pharmacodynamic principles is more likely to be in development of antimicrobial use guidelines than in individual patients’ care.

**Recommendation**

- Optimization of antimicrobial dosing based on individual patient characteristics, causative organism, site of infection, and pharmacokinetic and pharmacodynamic characteristics of the drug is an important part of antimicrobial stewardship (A-II).

**Conversion from parenteral to oral therapy.** Antimicrobial therapy for patients with serious infections requiring hospitalization is generally initiated with parenteral therapy. Enhanced oral bioavailability among certain antimicrobials—such as fluoroquinolones, oxazolidinones, metronidazole, clindamycin, trimethoprim-sulfamethoxazole, fluconazole, and voriconazole—allows conversion to oral therapy once a patient meets defined clinical criteria. This can result in reduced length of hospital stay, health care costs, and potential complications due to intravenous access.

Randomized studies evaluating early transition from parenteral to oral therapy in the management of adults with community-acquired pneumonia have demonstrated significant reductions in length of hospital stay and cost of care with no adverse effect on clinical outcomes [128–130]. A similar decrease in length of hospital stay, with a 52% reduction in total health care costs, was noted in the treatment of lower respiratory tract infections in children, compared with historical control subjects [131]. A pharmacist-initiated program utilizing predetermined clinical criteria for general conversion from parenteral to oral therapy decreased length of hospital stay by 1.53 days, with cost savings for drug acquisition and reduced length of hospital stay of $15,149 and $161,072, respectively, over 12 months [132].

A randomized study of oral linezolid versus intravenous vancomycin in patients with complicated skin and soft-tissue infections due to MRSA demonstrated a decreased mean length of hospital stay of 5 days for the linezolid group [133], and a switch from vancomycin to oral linezolid for early discharge from the hospital resulted in an annual savings of $294,750 [134]. The use of new agents, such as linezolid, in this manner must be done judiciously and with the direct oversight of an antimicrobial-management program to balance concerns about the development of resistance and added antimicrobial acquisition costs.

A systematic plan for switching from parenteral to oral treatment may have an added benefit of aiding in early hospital discharge planning, if needed, to provide surge capacity during local or national problems (e.g., epidemic influenza).

**Recommendation**

- A systematic plan for parenteral to oral conversion of antimicrobials with excellent bioavailability, when the patient’s condition allows, can decrease length of hospital stay and health care costs (A-I). Development of clinical criteria and guidelines allowing conversion to use of oral agents can facilitate implementation at the institutional level (A-III).

**Computer Surveillance and Decision Support**

Increased focus on medical errors and patient safety led to a series of reports by the Institute of Medicine’s National Roundtable on Health Care Quality to emphasize the role of information technology in the delivery of health care [135–137]. The Leapfrog Group has identified computer physician order entry (CPOE) as 1 of the 3 most important “leaps” that organizations can take to substantially improve patient safety. CPOE has the potential to incorporate clinical decision support and to facilitate quality monitoring [138]. Progress to this end, however, remains slow, with only 13% of US hospitals converting to electronic medical records and 5% implementing CPOE as of 2002 [139, 140].

The most well-described computer surveillance and decision-support system related to antimicrobial prescribing linked to electronic medical records is from LDS Hospital in Salt Lake City, Utah [141]. This program presents epidemiologic information with detailed recommendations and warnings regarding antimicrobial regimens and courses of therapy. Even if a physician overrides the recommendation for the antimicrobial and selects his or her own treatment plan, the computer still automatically reviews the patient’s allergies and potential drug-drug interactions, recommending a dosage and interval based...
on the patient’s renal and hepatic function. A prospective study of the use of this program in an ICU demonstrated significant reductions in orders for drugs to which the patients had reported allergies, excess drug dosages based on renal function, adverse drug events, antimicrobial-susceptibility mismatches, antimicrobial costs, and length of hospital stay [142]. Implementation of a computer-assisted antibiotic-dose monitor throughout the same hospital over a 12-month period identified 1974 (44%) of 4483 patients receiving excessive antimicrobial dosages (based on renal function), leading to more-appropriate dosing and fewer adverse drug events [143]. Incorporation of practice guidelines into the system increased the percentage of surgical patients who received their preoperative prophylactic antimicrobials within 2 h of incision from 40% to 99.1% [144, 145].

In addition to improving antimicrobial use and care of the individual patient, their system has facilitated the electronic surveillance of hospital-acquired infections and adverse drug events. Computer surveillance identified 90% of confirmed nosocomial infections, compared with 76% of such infections identified by manual surveillance, allowing infection control practitioners to reduce the time required for such activities by 65% [146]. Automated surveillance of 36,653 patients over 18 months using defined triggers identified 731 adverse drug events, whereas only 9 were reported through traditional voluntary incident reports [147].

This computer decision-support system was adapted for use in pediatric patients by Mullett et al. [148], and its effect was evaluated in a quasi experimental study. Dosing guidelines were adjusted for pediatric and neonatal populations, to ensure that treatment recommendations were appropriate for infections common in the pediatric population (e.g., bacterial meningitis), local antimicrobial resistance patterns (e.g., the prevalence of S. pneumoniae with reduced susceptibility to penicillin), special populations (e.g., children with cystic fibrosis), and children with renal insufficiency. Comparing a 6-month period after implementation (intervention period) with the prior 6 months (baseline period), the decision-support system was associated with a 59% decrease in the rate of pharmacy interventions for erroneous drug doses and 36% and 28% decreases in the rates of subtherapeutic and excessive antimicrobial dosing days, respectively. There was a 9% decrease in the cost of antimicrobial agents during the intervention period. The frequency of adverse drug events and antimicrobial-bacterial susceptibility mismatches were not significantly different during the intervention period—a finding likely attributable to the low frequency of these events in the baseline period. Clinicians using the system reported that they felt that the program improved their selection of antimicrobial agents, increased their awareness of impairments in renal function that affected drug dosing, and reduced the likelihood of adverse drug events. The lead investigator has subsequently developed a separate decision-support system for treatment of bloodstream infection in hospitalized children, although the system has not yet been evaluated prospectively [149].

A randomized study incorporating guidelines for vancomycin use into a hospital’s CPOE at the time of initial ordering and after 72 h of therapy led to 32% fewer vancomycin orders and a 36% reduction in the duration of vancomycin therapy. This resulted in a projected savings of $90,000 [150]. Simply adding antimicrobial cost information to antimicrobial susceptibility data resulted in decreased average monthly antimicrobial expenditures by $7636 (17%) in another hospital [151].

Despite these initial promising studies, matching the linear technology of CPOE with complex clinical management that can be subjective, interpretive, and reactive has been a challenge at other institutions [152]. Implementation of CPOE at a 750-bed teaching hospital to reduce medical errors was actually found to frequently facilitate medication errors [140]. Errors included inappropriate dose selection, double-dosing caused by separate order and discontinuation functions, and gaps in antimicrobial therapy resulting from automatic discontinuation orders. In large part, these errors reflected the difficulty of implementation rather than the concept of CPOE.

The Veterans Administration health care system has been a leader in the use of an electronic medical records and CPOE. Despite being a model for implementing CPOE, one Veterans Administration hospital found a continuing high rate of adverse drug events in the absence of decision support for drug selection, dosing, and monitoring [153]. Twenty-six percent of hospital admissions were associated with at least 1 adverse drug event, with medication errors contributing to 27% of these adverse events.

The lofty goal of merging the electronic records with CPOE and clinical decision support to optimize antimicrobial use is currently not attainable for most institutions on the basis of current technology. Depending on available resources, however, automated targeting of interventions to facilitate antimicrobial stewardship can be obtained through varying levels of complexity. Such targeting may include using pharmacy records to identify patients who are receiving broad-spectrum or expensive antimicrobials, use of simple computer programs that merge hospital pharmacy and microbiology databases, and use of more-complex, commercially available software to identify antimicrobial interventions.

**Recommendations**

- Health care information technology in the form of electronic medical records (A-III), CPOE (B-II), and clinical decision support (B-II) can improve antimicrobial decisions through the incorporation of data on patient-specific microbiology cultures and susceptibilities, hepatic and renal function, drug-drug interactions, allergies, and cost. However, im-
plementation of these features has been slow, and conformation of the technology to the clinical environment remains a challenge.

- Computer-based surveillance can facilitate good stewardship by more efficient targeting of antimicrobial interventions, tracking of antimicrobial resistance patterns, and identification of nosocomial infections and adverse drug events (B-II).

Microbiology Laboratory

The clinical microbiology laboratory plays a critical role in the timely identification of microbial pathogens and the performance of susceptibility testing [154, 155]. Susceptibility testing and reporting should be based on the guidelines developed by the Clinical and Laboratory Standards Institute (CLSI; formerly the NCCLS) [156]. Prioritization of tested antimicrobials and selective reporting of susceptibility profiles (e.g., not routinely reporting susceptibility of *S. aureus* to rifampin to prevent inadvertent monotherapy with rifampin) can aid in the prudent use of antimicrobials and direct appropriate therapy based on local guidelines. The advance of molecular diagnostics allows the identification of difficult-to-culture pathogens, potentially avoiding the need for extended courses of broad-spectrum empirical therapy.

In addition to routine susceptibility testing, the clinical microbiology laboratory should be actively involved in resistance surveillance. Local antibiograms with pathogen-specific susceptibility data should be updated at least annually, to optimize expert-based recommendations for empirical therapy [157]. Computerized surveillance can facilitate more-frequent monitoring of antimicrobial resistance trends, as well as provide ICU- or ward-specific data and inpatient versus outpatient data, recognizing that different parts of a health care institution can have very different patterns of antimicrobial use and resistance [157]. Besides qualitative determination of antimicrobial resistance or susceptibility, periodic review of MICs or zone diameters in disk-diffusion techniques can detect early trends of emerging resistance, even within the “susceptibility” cut-offs. Kirby-Bauer disk-diffusion methods can also be used to perform the D test for inducible clindamycin resistance for *S. aureus* [158], as well as provide quick screenings for extended-spectrum β-lactamase– and AmpC β-lactamase–containing organisms. Finally, the laboratory is an important partner with infection control in the identification and molecular epidemiologic investigation of local outbreaks of infection. The development of rapid resistance testing will facilitate the surveillance of organisms such as MRSA and VRE, allowing the more rapid implementation of infection control measures to prevent secondary spread [159, 160]. Clonal characterization of resistant strains through molecular typing can help focus appropriate interventions, leading to a reduction in nosocomial infections with associated cost savings [161]. If antimicrobial resistance is due to a clonal outbreak, antimicrobial interventions may be of limited value, compared with infection control interventions. If resistant strains are diverse, antimicrobial interventions may be required.

Recommendation

- The clinical microbiology laboratory plays a critical role in antimicrobial stewardship by providing patient-specific culture and susceptibility data to optimize individual antimicrobial management and by assisting infection control efforts in the surveillance of resistant organisms and in the molecular epidemiologic investigation of outbreaks (A-III).

Monitoring of Process and Outcome Measurements

In conjunction with developing local strategies for improving antimicrobial stewardship, programs must establish process and outcome measures to determine the impact of antimicrobial stewardship on antimicrobial use and resistance patterns. Furthermore, health care systems must invest in data systems to allow the evaluation of antimicrobial stewardship as a routine measure of quality improvement [162]. With antimicrobial stewardship, the “process goal” is often to change use of a specific antimicrobial or class of antimicrobials. The related “process measure” for this goal would determine the degree to which the intervention to change the use of an antimicrobial or class of antimicrobials has been successfully implemented, compared with baseline levels. The desired “outcome goal” of these process changes is to reduce or prevent resistance or other unintended consequences of antimicrobial use. “Outcome measurements” define the degree to which these outcomes are achieved, such as reduced antimicrobial resistance, adverse drug events, and cost, as well as unintended consequences, such as rates of *C. difficile* infection and the use of nontargeted antimicrobials as a result of the process change.

Antimicrobial use data based on pharmacy expenditure or dispensing reports often do not account for drug wastage, unused doses returned to pharmacy, or fluctuations in institutional price structures and discounts [163]. Drug use data can be standardized using the defined daily dose, calculated as the total number of grams of an antimicrobial agent divided by the number of grams in an average adult daily dose of the agent [164]. The World Health Organization publishes defined daily dose values for nearly all antimicrobials (http://www.whocc.no/atcddd/). The use of defined daily doses is recommended so that hospitals may compare their antimicrobial use with that of other similar hospitals, recognizing the challenges of interhospital comparisons and the potential need for “risk adjustment.” However, in populations with renal compromise (e.g., the elderly population) and for drugs that require...
renewal dose adjustment, the defined daily dose may be less accurate than measures of antimicrobial-days of therapy [165].

Recommendation
- Both process measures (did the intervention result in the desired change in antimicrobial use?) and outcome measures (did the process implemented reduce or prevent resistance or other unintended consequences of antimicrobial use?) are useful in determining the impact of antimicrobial stewardship on antimicrobial use and resistance patterns (B-III).

Comprehensive Multidisciplinary Antimicrobial Management Programs

Through the previous review of individual interventions directed at improving antimicrobial use, it is clear that effective antimicrobial stewardship requires a multidisciplinary team approach that incorporates many of these elements simultaneously. The core members of a comprehensive antimicrobial management program include an infectious diseases physician and a clinical pharmacist with infectious diseases training, with the inclusion of infection control professionals, the hospital epidemiologist, a clinical microbiologist, and an information system specialist, when possible [166–174]. The latter is critical for linking the patient’s medical record to the pharmacy and microbiology databases, to identify interventions and to perform surveillance activities. Program personnel should be included as active members on the hospital infection control and pharmacy and therapeutics committees or their equivalents.

Central to an effective program is a proactive strategy incorporating prospective audit with direct intervention and feedback to the provider and/or preauthorization requirements for antimicrobial use. On the basis of an understanding of local antimicrobial use and resistance problems and of available resources that may differ depending on the size of the institution, the core active strategies may be supplemented by education, guidelines and clinical pathways, antimicrobial order forms, adequate empirical therapy followed by de-escalation based on culture results, dose optimization, and a systematic plan for conversion from parenteral to oral therapy. Consensus building with the support of administration and local providers is essential, with the focus on collaborating in the safety and care of their patients rather than a policing role. Although reports describing the clinical and economic impacts of multidisciplinary antimicrobial management programs are limited to single-center longitudinal studies, they consistently demonstrate a decrease in antimicrobial use (22%-36%) and annual savings of $200,000–$900,000, which more than pays for the program in both larger academic hospitals [2, 3, 5, 7, 8, 69] and smaller community hospitals [4, 6]. Quantifying a long-term impact on antimicrobial resistance has been more challenging, and further studies are needed to determine the optimal processes by which the goals of improved clinical outcomes and containment of antimicrobial resistance can be achieved. However, given the strong association between antimicrobial use and antimicrobial resistance (table 2), improving antimicrobial stewardship is an important first step.

RESEARCH PRIORITIES AND FUTURE DIRECTIONS

Because of the limited number of randomized clinical studies addressing antimicrobial stewardship strategies, many of the recommendations in this guideline are based on level III evidence. Further research and evaluation through appropriately conducted clinical trials are necessary to determine the best strategies for the prevention and containment of antimicrobial resistance. Recommended topics for investigation are as follows:

1. Antimicrobial cycling at the patient, unit, and institutional level to determine whether cycling is effective and, if so, the optimal antimicrobials to be cycled, the optimal duration of the cycles, and the preferred order in which agents should be cycled.
2. Clinical validation of mathematical models suggesting that heterogeneous antimicrobial use slows the spread of resistance.
3. The long-term impact of formulary restriction and preauthorization requirements on antimicrobial use and resistance.
4. Evaluation of “bundled” approaches that incorporate many or all of the most effective strategies.
5. Examination of the effectiveness of these strategies in more detail in subpopulations of hospitalized patients, including neonates, infants, and children; elderly patients; and severely immunocompromised patients.
6. The ability of antimicrobials to cause “collateral damage” or unintended ecological resistance, to focus interventions.
7. The incremental role of antimicrobial stewardship combined with infection control practices, such as hand hygiene and isolation, designed to prevent secondary spread of resistant organisms.
8. Understanding the resistance gene pool through molecular epidemiology, to determine the relative impact of antimicrobial stewardship and infection control practices on specific resistant bacteria, to tailor an approach to local resistance issues.
10. Development of decision-support systems incorporating antimicrobial stewardship into CPOE.
11. Development and cost-effectiveness of more rapid and sensitive diagnostic tests, to identify patients with bacterial versus viral infections and to identify resistant bacterial organisms earlier.

12. Strategies to stimulate research and development of novel antimicrobials as outlined in the IDSA “Bad Bugs, No Drugs” campaign.

13. Education and training of infectious diseases fellows and pharmacists in the area of antimicrobial stewardship, including program implementation and management.

14. The influence of pharmaceutical industry and representatives on antimicrobial prescribing within the health care setting and effective strategies to counteract inappropriate detailing.

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Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America


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Evidence-based guidelines for implementation and measurement of antibiotic stewardship interventions in inpatient populations including long-term care were prepared by a multidisciplinary expert panel of the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. The panel included clinicians and investigators representing internal medicine, emergency medicine, microbiology, critical care, surgery, epidemiology, pharmacy, and adult and pediatric infectious diseases specialties. These recommendations address the best approaches for antibiotic stewardship programs to influence the optimal use of antibiotics.

Keywords. antibiotic stewardship; antibiotic stewardship programs; antibiotics; implementation.

EXECUTIVE SUMMARY

Antibiotic stewardship has been defined in a consensus statement from the Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS) as “coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration” [1]. The benefits of antibiotic stewardship include improved patient outcomes, reduced adverse events including Clostridium difficile infection (CDI), improvement in rates of antibiotic susceptibilities to targeted antibiotics, and optimization of resource utilization across the continuum of care. IDSA and SHEA strongly believe that antibiotic stewardship programs (ASPs) are best led by infectious disease physicians with additional stewardship training.

Summarized below are the IDSA/SHEA recommendations for implementing an ASP. The expert panel followed a process used in the development of other IDSA guidelines, which included a systematic weighting of the strength of recommendation and quality of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system (Figure 1) [2–5]. A detailed description of the methods, background, and evidence summaries that support each of the recommendations can be found online in the full text of the guidelines. For the purposes of this guideline, the term antibiotic will be used instead of antimicrobial and should be considered synonymous.

RECOMMENDATIONS FOR IMPLEMENTING AN ANTIBIOTIC STEWARDSHIP PROGRAM

Interventions

1. Does the Use of Preauthorization and/or Prospective Audit and Feedback Interventions by ASPs Improve Antibiotic Utilization and Patient Outcomes? Recommendation

We recommend preauthorization and/or prospective audit and feedback over no such interventions (strong recommendation, moderate-quality evidence).
Comment: Preauthorization and/or prospective audit and feedback improve antibiotic use and are a core component of any stewardship program. Programs should decide whether to include one strategy or a combination of both strategies based on the availability of facility-specific resources for consistent implementation, but some implementation is essential.

II. Is Didactic Education a Useful Antibiotic Stewardship Intervention for Reducing Inappropriate Antibiotic Use?

Recommendation

2. We suggest against relying solely on didactic educational materials for stewardship (weak recommendation, low-quality evidence).

Comment: Passive educational activities, such as lectures or informational pamphlets, should be used to complement other stewardship activities. Academic medical centers and teaching hospitals should integrate education on fundamental antibiotic stewardship principles into their preclinical and clinical curricula.

III. Should ASPs Develop and Implement Facility-Specific Clinical Practice Guidelines for Common Infectious Diseases Syndromes to Improve Antibiotic Utilization and Patient Outcomes?

Recommendation

3. We suggest ASPs develop facility-specific clinical practice guidelines coupled with a dissemination and implementation strategy (weak recommendation, low-quality evidence).

Comment: Facility-specific clinical practice guidelines and algorithms can be an effective way to standardize prescribing practices based on local epidemiology. ASPs should develop those guidelines, when feasible, for common infectious diseases syndromes. In addition, ASPs should be involved in writing clinical pathways, guidelines, and order sets that address antibiotic use and are developed within other departments at their facility.
IV. Should ASPs Implement Interventions to Improve Antibiotic Use and Clinical Outcomes That Target Patients With Specific Infectious Diseases Syndromes?

Recommendation

4. We suggest ASPs implement interventions to improve antibiotic use and clinical outcomes that target patients with specific infectious diseases syndromes (weak recommendation, low-quality evidence).

Comment: ASP interventions for patients with specific infectious diseases syndromes can be an effective way to improve prescribing because the message can be focused, clinical guidelines and algorithms reinforced, and sustainability improved. ASPs should regularly evaluate areas for which targeted interventions are needed and adapt their activities accordingly. This approach is most useful if the ASP has a reliable way to identify patients appropriate for review.

V. Should ASPs Implement Interventions Designed to Reduce the Use of Antibiotics Associated With a High Risk of CDI?

Recommendation

5. We recommend antibiotic stewardship interventions designed to reduce the use of antibiotics associated with a high risk of CDI compared with no such intervention (strong recommendation, moderate-quality evidence).

Comment: The goal of reducing CDI is a high priority for all ASPs and should be taken into consideration when crafting stewardship interventions.


Recommendation

6. We suggest the use of strategies (eg, antibiotic time-outs, stop orders) to encourage prescribers to perform routine review of antibiotic regimens to improve antibiotic prescribing (weak recommendation, low-quality evidence).

Comment: Published data on prescriber-led antibiotic review are limited, but successful programs appear to require a methodology that includes persuasive or enforced prompting. Without such a mechanism, these interventions are likely to have minimal impact.

VII. Should Computerized Clinical Decision Support Systems Integrated Into the Electronic Health Record at the Time of Prescribing be Incorporated as Part of ASPs to Improve Antibiotic Prescribing?

Recommendation

7. We suggest incorporation of computerized clinical decision support at the time of prescribing into ASPs (weak recommendation, moderate-quality evidence).

Comment: Computerized clinical decision support for prescribers should only be implemented if information technology resources are readily available. However, computerized surveillance systems that synthesize data from the electronic health record and other data sources can streamline the work of ASPs by identifying opportunities for interventions.

VIII. Should ASPs Implement Strategies That Promote Cycling or Mixing in Antibiotic Selection to Reduce Antibiotic Resistance?

Recommendation

8. We suggest against the use of antibiotic cycling as a stewardship strategy (weak recommendation, low-quality evidence).

Comment: Available data do not support the use of antibiotic cycling as an ASP strategy, and further research is unlikely to change that conclusion. Because clinical data are sparse for antibiotic mixing, we cannot give any recommendation about its utility.

Optimization

IX. In Hospitalized Patients Requiring Intravenous (IV) Antibiotics, Does a Dedicated Pharmacokinetic (PK) Monitoring and Adjustment Program Lead to Improved Clinical Outcomes and Reduced Costs?

Recommendations

9. We recommend that hospitals implement PK monitoring and adjustment programs for aminoglycosides (strong recommendation, moderate-quality evidence).

10. We suggest that hospitals implement PK monitoring and adjustment programs for vancomycin (weak recommendation, low-quality evidence).

Comment: PK monitoring and adjustment programs can reduce costs and decrease adverse effects. The ASP should encourage implementation and provide support for training and assessment of competencies. The conduct of those programs should be integrated into routine pharmacy activities.

X. In Hospitalized Patients, Should ASPs Advocate for Alternative Dosing Strategies Based on PK/Pharmacodynamic Principles to Improve Outcomes and Decrease Costs for Broad-Spectrum β-Lactams and Vancomycin?

Recommendation

11. In hospitalized patients, we suggest ASPs advocate for the use of alternative dosing strategies vs standard dosing for broad-spectrum β-lactams to decrease costs (weak recommendation, low-quality evidence).

Comment: Although data for improved outcomes for broad-spectrum β-lactam dosing with this approach are still limited, these interventions are associated with antibiotic cost savings. ASPs should consider implementation but must take into account logistical issues such as nursing and pharmacy education and need for dedicated IV access. Considering the limited evidence, we cannot give any...
recommendation about the utility of alternative dosing strategies for vancomycin.

XI. Should ASPs Implement Interventions to Increase Use of Oral Antibiotics as a Strategy to Improve Outcomes or Decrease Costs?

**Recommendation**

12. We recommend ASPs implement programs to increase both appropriate use of oral antibiotics for initial therapy and the timely transition of patients from IV to oral antibiotics *(strong recommendation, moderate-quality evidence).*

Comment: Programs to increase the appropriate use of oral antibiotics can reduce costs and length of hospital stay. IV-to-oral conversion of the same antibiotic is less complicated than other strategies and is applicable to many healthcare settings. The conduct of those programs should be integrated into routine pharmacy activities. ASPs should implement strategies to assess patients who can safely complete therapy with an oral regimen to reduce the need for IV catheters and to avoid outpatient parenteral therapy.

XII. In Patients With a Reported History of β-Lactam Allergy, Should ASPs Facilitate Initiatives to Implement Allergy Assessments With the Goal of Improved Use of First-Line Antibiotics?

**Recommendation**

13. In patients with a history of β-lactam allergy, we suggest that ASPs promote allergy assessments and penicillin (PCN) skin testing when appropriate *(weak recommendation, low-quality evidence).*

Comment: Allergy assessments and PCN skin testing can enhance use of first-line agents, but it is largely unstudied as a primary ASP intervention; however, ASPs should promote such assessments with providers. In facilities with appropriate resources for skin testing, the ASPs should actively work to develop testing and treatment strategies with allergists.

XIII. Should ASPs Implement Interventions to Reduce Antibiotic Therapy to the Shortest Effective Duration?

**Recommendation**

14. We recommend that ASPs implement guidelines and strategies to reduce antibiotic therapy to the shortest effective duration *(strong recommendation, moderate-quality evidence).*

Comment: Recommending a duration of therapy based on patient-specific factors is an important activity for ASPs. Suitable approaches include developing written guidelines with specific suggestions for duration, including duration of therapy recommendations as part of the preauthorization or prospective audit and feedback process, or specifying duration at the time of antibiotic ordering (eg, through an electronic order entry system).

Microbiology and Laboratory Diagnostics

XIV. Should ASPs Work With the Microbiology Laboratory to Develop Stratified antibiograms, Compared With Nonstratified antibiograms?

**Recommendation**

15. We suggest development of stratified antibiograms over solely relying on nonstratified antibiograms to assist ASPs in developing guidelines for empiric therapy *(weak recommendation, low-quality evidence).*

Comment: Although there is limited evidence at this time that stratified antibiograms (eg, by location or age) lead to improved empiric antibiotic therapy, stratification can expose important differences in susceptibility, which can help ASPs develop optimized treatment recommendations and guidelines.

XV. Should ASPs Work With the Microbiology Laboratory to Perform Selective or Cascade Reporting of Antibiotic Susceptibility Test Results?

**Recommendation**

16. We suggest selective and cascade reporting of antibiotics over reporting of all tested antibiotics *(weak recommendation, low-quality evidence).*

Comment: Although data are limited that demonstrate direct impact of those strategies on prescribing, some form of selective or cascaded reporting is reasonable. After implementation, ASPs should review prescribing to ensure there are no unintended consequences.

XVI. Should ASPs Advocate for Use of Rapid Viral Testing for Respiratory Pathogens to Reduce the Use of Inappropriate Antibiotics?

**Recommendation**

17. We suggest the use of rapid viral testing for respiratory pathogens to reduce the use of inappropriate antibiotics *(weak recommendation, low-quality evidence).*

Comment: Although rapid viral testing has the potential to reduce inappropriate use of antibiotics, results have been inconsistent. Few studies have been performed to assess whether active ASP intervention would improve those results.

XVII. Should ASPs Advocate for Rapid Diagnostic Testing on Blood Specimens to Optimize Antibiotic Therapy and Improve Clinical Outcomes?

**Recommendation**

18. We suggest rapid diagnostic testing in addition to conventional culture and routine reporting on blood specimens if combined with active ASP support and interpretation *(weak recommendation, moderate-quality evidence).*

Comment: Availability of rapid diagnostic tests is expected to increase; thus, ASPs must develop processes and interventions to assist clinicians in interpreting and responding appropriately to results.
XVIII. In Adults in Intensive Care Units (ICUs) With Suspected Infection, Should ASPs Advocate Procalcitonin (PCT) Testing as an Intervention to Decrease Antibiotic Use?

**Recommendation**

19. In adults in ICUs with suspected infection, we suggest the use of serial PCT measurements as an ASP intervention to decrease antibiotic use (weak recommendation, moderate-quality evidence).

*Comment:* Although randomized trials, primarily in Europe, have shown reduction in antibiotic use through implementation of PCT algorithms in the ICU, similar data are lacking for other regions including the United States where the patterns of antibiotic prescribing and approach to stewardship may differ. If implemented, each ASP must develop processes and guidelines to assist clinicians in interpreting and responding appropriately to results, and must determine if this intervention is the best use of its time and resources.

XIX. In Patients With Hematologic Malignancy, Should ASPs Advocate for Incorporation of Nonculture-Based Fungal Markers in Interventions to Optimize Antifungal Use?

**Recommendation**

20. In patients with hematologic malignancy at risk of contracting invasive fungal disease (IFD), we suggest incorporating nonculture-based fungal markers in ASP interventions to optimize antifungal use (weak recommendation, low-quality evidence).

*Comment:* ASPs with an existing intervention to optimize antifungal use in patients with hematologic malignancy can consider algorithms incorporating nonculture-based fungal markers. Those interventions must be done in close collaboration with the primary teams (eg, hematology-oncology). Antibiotic stewards must develop expertise in antifungal therapy and fungal diagnostics for the programs to be successful. The value of those markers for interventions in other populations has not been demonstrated.

XV. Which Overall Measures Best Reflect the Impact of ASPs and Interventions?

**Recommendation**

21. We suggest monitoring antibiotic use as measured by days of therapy (DOTs) in preference to defined daily dose (DDD) (weak recommendation, low-quality evidence).

*Comment:* Every ASP must measure antibiotic use, stratified by antibiotic. DOTs are preferred, but DDDs remain an alternative for sites that cannot obtain patient-level antibiotic use data. ASPs should consider measurement of appropriate antibiotic use within their own institutions by examining compliance with local or national guidelines, particularly when assessing results of a targeted intervention, and share that data with clinicians to help inform their practice. Although rates of CDI or antibiotic resistance may not reflect ASP impact (because those outcomes are affected by patient population, infection control, and other factors), those outcomes may also be used for measurement of targeted interventions.

XX. What is the Best Measure of Expenditures on Antibiotics to Assess the Impact of ASPs and Interventions?

**Recommendation**

22. We recommend measuring antibiotic costs based on prescriptions or administrations instead of purchasing data (good practice recommendation).

XXI. What Measures Best Reflect the Impact of Interventions to Improve Antibiotic Use and Clinical Outcomes in Patients With Specific Infectious Diseases Syndromes?

**Recommendation**

23. Measures that consider the goals and size of the syndrome-specific intervention should be used (good practice recommendation).

Special Populations

XXIII. Should ASPs Develop Facility-Specific Clinical Guidelines for Management of Fever and Neutropenia (F&N) in Hematology-Oncology Patients to Reduce Unnecessary Antibiotic Use and Improve Outcomes?

**Recommendation**

24. We suggest ASPs develop facility-specific guidelines for F&N management in hematology-oncology patients over no such approach (weak recommendation, low-quality evidence).

*Comment:* Clinical guidelines with an implementation and dissemination strategy can be successfully used in the care of cancer patients with F&N and are strongly encouraged.

XXIV. In Immunocompromised Patients Receiving Antifungal Therapy, do Interventions by ASPs Improve Utilization and Outcomes?

**Recommendation**

25. We suggest implementation of ASP interventions to improve the appropriate prescribing of antifungal treatment in immunocompromised patients (weak recommendation, low-quality evidence).

*Comment:* In facilities with large immunocompromised patient populations, ASP interventions targeting antifungal therapy can show benefit. Those interventions must be done in close collaboration with the primary teams (eg, hematology-oncology, solid organ transplant providers). Antibiotic stewards must develop expertise in antifungal therapy and fungal diagnostics for the programs to be successful.
XXV. In Residents of Nursing Homes and Skilled Nursing Facilities, do Antibiotic Stewardship Strategies Decrease Unnecessary Use of Antibiotics and Improve Clinical Outcomes?

Recommendation

26. In nursing homes and skilled nursing facilities, we suggest implementation of antibiotic stewardship strategies to decrease unnecessary use of antibiotics (good practice recommendation).

Comment: Implementing ASPs at nursing homes and skilled nursing facilities is important and must involve point-of-care providers to be successful. The traditional physician–pharmacist team may not be available on-site, and facilities might need to investigate other approaches to review and optimize antibiotic use, such as obtaining infectious diseases expertise through telemedicine consultation.

XXVI. In Neonatal Intensive Care Units (NICUs), do Antibiotic Stewardship Interventions Reduce Inappropriate Antibiotic Use and/or Resistance?

Recommendation

27. We suggest implementation of antibiotic stewardship interventions to reduce inappropriate antibiotic use and/or resistance in the NICU (good practice recommendation).

XXVII. Should ASPs Implement Interventions to Reduce Antibiotic Therapy in Terminally Ill Patients?

Recommendation

28. In terminally ill patients, we suggest ASPs provide support to clinical care providers in decisions related to antibiotic treatment (good practice recommendation).

INTRODUCTION

The discovery of antibiotics in the early 20th century transformed healthcare, dramatically reducing morbidity and mortality from infectious diseases and allowing for major advancements in medicine. The increase in organisms with resistance to antibiotics in our armamentarium, however, combined with the slow pace of development of new antibiotics threatens those gains. Approaches to optimize the use of both existing antibiotics and newly developed antibiotics are of critical importance to ensure that we continue to reap their benefits and provide the best care to patients.

The need for antibiotic stewardship across the spectrum of healthcare has been recognized in the National Action Plan for Combating Antibiotic-Resistant Bacteria issued by the White House in March 2015 [6]. This plan calls for establishment of ASPs in all acute care hospitals by 2020 and for the Centers for Medicare and Medicaid Services to issue a Condition of Participation that participating hospitals develop programs based on recommendations from the Centers for Disease Control and Prevention’s (CDC) Core Elements of Hospital Antibiotic Stewardship Programs [7]. Expansion of stewardship activities to ambulatory surgery centers, dialysis centers, nursing homes and other long-term care facilities, and emergency departments and outpatient settings is also recommended.

The purpose of this guideline is to comprehensively evaluate the wide range of interventions that can be implemented by ASPs in emergency department, acute inpatient, and long-term care settings as they determine the best approaches to influence the optimal use of antibiotics within their own institutional environments. In addition, this guideline addresses approaches to measure the success of these interventions. This guideline does not specifically address the structure of an ASP, which has been well outlined in a previous guideline [8] and in the CDC’s Core Elements of Hospital Antibiotic Stewardship Programs and Core Elements of Antibiotic Stewardship for Nursing Homes [7, 9]. These documents emphasize the importance of physician and pharmacist leadership for an ASP, the need for infectious diseases expertise, and the role of measurement and feedback as critical components of ASPs. This guideline does not address antibiotic stewardship in outpatient settings.

Although not all of the antibiotic stewardship interventions, optimization measures, diagnostic approaches, and program measurements described in this guideline have been implemented or evaluated in all populations or clinical settings, the majority could be considered for use in pediatrics, oncology, community hospitals, small hospitals, and nursing home and long-term care environments, and not limited to acute care facilities. Any antibiotic stewardship intervention must be customized based on local needs, prescriber behaviors, barriers, and resources. In contrast to other guidelines, this guideline provides comments that supplement the formal recommendations and contain practical input from the expert panel to better guide ASPs in determining which interventions to implement.

METHODS

Panel Composition

Led by Co-chairs Tamar Barlam and Sara Cosgrove, a panel of 18 multidisciplinary experts in the management of ASPs was convened per the IDSA Handbook on Clinical Practice Guideline Development [10] in 2012. In addition to members of IDSA and the SHEA, representatives from diverse geographic areas, pediatric and adult practitioners, and a wide breadth of specialties representing major medical societies were included among the panel’s membership (American College of Emergency Physicians [ACEP], American Society of Health-System Pharmacists [ASHP], American Society for Microbiology [ASM], PIDS, Society for Academic Emergency Medicine [SAEM], Society of Infectious Diseases Pharmacists [SIDP], and the Surgical Infection Society [SIS]). A guideline
methodologist and member of the GRADE Working Group and a medical writer were added to assist the panel.

**Literature Review and Analysis**

PubMed, which includes Medline (1946 to present), was searched to identify relevant studies for each of the antibiotic stewardship guideline PICO (population/patient, intervention/indicator, comparator/control, outcome) questions. Search strategies were developed and built by 2 independent health sciences librarians from the Health Sciences Library System, University of Pittsburgh. For each PICO question, the librarians developed the search strategies using PubMed’s command language and appropriate search fields. Medical Subject Headings terms and keywords were used for the main search concepts of each PICO question. A data supplement that includes search strings can be found following publication on the IDSA website [11]. Articles in all languages and all publication years were included. Initial searches were created and confirmed with input from the guideline committee chairs and group leaders from February through mid-July 2013. The searches were finalized and delivered between late July and September 2013. After the literature searches were performed, authors continued to review the literature and added relevant articles as needed.

**Process Overview**

To evaluate evidence, the panel followed a process consistent with other IDSA guidelines. The process for evaluating the evidence was based on the IDSA Handbook on Clinical Practice Guideline Development [10] and involved a systematic weighting of the quality of the evidence and the grade of recommendation using the GRADE system (Figure 1) [2–5]. Unless otherwise stated, each PICO comparator was usual practice.

For recommendations in the category of good practice statements, we followed published principles by the GRADE working group on how to identify such recommendations and use appropriate wording choices. Accordingly, a formal GRADE rating was not pursued for those statements [12].

Panel members were divided into 5 subgroups: (1) interventions, (2) optimization of antibiotic administration, (3) microbiology and laboratory diagnostics, (4) measurement and analysis, and (5) antibiotic stewardship in special populations. Each author was asked to review the literature, evaluate the evidence, and determine the initial strength of the recommendations along with an evidence summary supporting each recommendation in his/her assigned subgroup. The evidence was graded based on the effectiveness of the antibiotic stewardship intervention, not the underlying data that provided the groundwork for the intervention. The panel reviewed all recommendations, along with their strength and the quality of the evidence. Discrepancies were discussed and resolved, and all panel members are in agreement with the final recommendations.

**Consensus Development Based on Evidence**

The panel met face to face on 3 occasions and conducted numerous teleconferences to complete the work of the guideline. The purpose of the meetings and teleconferences was to develop and discuss the clinical questions to be addressed, assign topics for review and writing of the initial draft, and develop recommendations. The whole panel reviewed all sections. The guideline was reviewed and approved by the IDSA Standards and Practice Guidelines Committee (SPGC), the IDSA Board of Directors, the SHEA Guidelines Committee, and the SHEA Board of Directors, and was endorsed by ACEP, ASHP, ASM, PIDS, SAEM, SIDP, and SIS.

**Guidelines and Conflicts of Interest**

The expert panel complied with the IDSA policy on conflicts of interest, which requires disclosure of any financial or other interest that may be construed as constituting an actual, potential, or apparent conflict. Panel members were provided IDSA’s conflicts of interest disclosure statement and were asked to identify ties to companies developing products that may be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. Decisions were made on a case-by-case basis as to whether an individual’s role should be limited as a result of a conflict. Potential conflicts of interests are listed in the Notes section at the end of the guideline.

**Revision Dates**

At annual intervals, the panel chair, the SPGC liaison advisor, and the chair of the SPGC will determine the need for revisions to the guideline based on an examination of current literature. If necessary, the entire panel will reconvene to discuss potential changes. When appropriate, the panel will recommend revision of the guideline to the IDSA SPGC and SHEA guidelines committees.

**RECOMMENDATIONS FOR IMPLEMENTING AN ANTIBIOTIC STEWARDSHIP PROGRAM**

**Interventions**

I. Does the Use of Preauthorization and/or Prospective Audit and Feedback Interventions by ASPs Improve Antibiotic Utilization and Patient Outcomes?

**Recommendation**

1. We recommend preauthorization and/or prospective audit and feedback over no such interventions (strong recommendation, moderate-quality evidence).

Comment: Preauthorization and/or prospective audit and feedback improve antibiotic use and are a core component of any stewardship program. Programs should decide whether to include one strategy or a combination of both strategies
Evidence Summary

Preauthorization is a strategy to improve antibiotic use by requiring clinicians to get approval for certain antibiotics before they are prescribed. Prospective audit and feedback (PAF) is an intervention that engages the provider after an antibiotic is prescribed. Each type is associated with unique advantages and disadvantages (Table 1).

Preauthorization has been associated with a significant reduction in the use of the restricted agents and of associated costs [13–16]. Outcome studies with preauthorization have shown decreased antibiotic use and decreased antibiotic resistance, particularly among gram-negative pathogens [13–15, 17]. Preauthorization studies have demonstrated no adverse effects for patients [13, 14]. White et al [13] reported that initiation of a preauthorization requirement for selected antibiotics at a county teaching hospital was associated with a 32% decrease in total parenteral antibiotic expenditures (P < .01) and increased percentages of susceptible gram-negative isolates—all without changes in hospital length of stay and survival. For example, *Pseudomonas aeruginosa* susceptibility to imipenem increased for isolates recovered in the ICU (percentage of susceptible isolates before vs after preauthorization: 65% vs 83%; P ≤ .01) and other inpatient settings (83% vs 95%; P ≤ .01). Overall 30-day survival rates were unchanged in patients with gram-negative bacteremia (79% vs 75%; P = .49) [13]. In addition, restrictive policies such as preauthorization have been shown to be more effective than persuasive strategies in reducing CDI, according to a meta-analysis evaluating antibiotic stewardship and CDI [18].

There are several factors to consider when implementing a preauthorization intervention. The skills of the person providing approval are important. Antibiotic approval by an antibiotic stewardship team consisting of a clinical pharmacist and an infectious diseases attending physician was more effective than off-hour approval by infectious diseases fellows in recommendation appropriateness (87% vs 47%; P < .001), cure rate (64% vs 42%; P = .007), and treatment failures (15% vs 28%; P = .03) [19]. Inaccuracy in communication of the clinical scenario by the requesting prescriber to the antibiotic stewardship team increases the likelihood of inappropriate recommendations [20]. Direct chart review optimizes preauthorization. It is also important to consider the alternative treatments that clinicians may choose when antibiotics are restricted and monitor changes in usage patterns. Rahal et al [21] implemented a preauthorization requirement for cephalosporins. This was associated with a reduction in the incidence of cefazidime-resistant *Klebsiella*, but imipenem use increased and a 69% increase in the incidence of imipenem-resistant *P. aeruginosa* was seen. Preauthorization requires real-time availability of the person providing approval. Institutions that use preauthorization often allow administration of the restricted antibiotic overnight until approval can be obtained the next day. To provide 24-hour availability and to facilitate communication without impeding provider workflow, Buising et al [14] developed a computerized approval system based on defined indications for restricted agents, demonstrating reduced antibiotic consumption and increased *Pseudomonas* susceptibility rates over a 2-year period.

PAF interventions also have been shown to improve antibiotic use, reduce antibiotic resistance, and reduce CDI rates [22–27], without a negative impact on patient outcomes [26, 28–30]. For instance, PAF conducted by a clinical pharmacist and infectious diseases physician at a community hospital led to a 22% reduction in the use of parenteral broad-spectrum antibiotics as well as a reduction in rates of CDI and nosocomial infections due to antibiotic-resistant Enterobacteriaceae over a 7-year period of time [22]. PAF has also been effective in the ICU [24, 25]. For example, a PAF intervention in multiple ICUs at a large academic institution demonstrated decreased meropenem resistance and decreased CDIs (P = .04) without adversely affecting mortality [25]. PAF has been effective in children’s hospitals by significantly reducing antibiotic use and dosing errors while limiting the development of antibiotic resistance [26, 27]. PAF can also be a strategy to improve

<table>
<thead>
<tr>
<th>Table 1. Comparison of Preauthorization and Prospective Audit and Feedback Strategies for Antibiotic Stewardship</th>
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<tbody>
<tr>
<td><strong>Preauthorization</strong></td>
</tr>
<tr>
<td>Advantages</td>
</tr>
<tr>
<td>* Reduces initiation of unnecessary/inappropriate antibiotics</td>
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<tr>
<td>* Optimizes empiric choices and influences downstream use</td>
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<tr>
<td>* Prompts review of clinical data/prior cultures at the time of initiation of therapy</td>
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<tr>
<td>* Decreases antibiotic costs, including those due to high-cost agents</td>
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<tr>
<td>* Provides mechanism for rapid response to antibiotic shortages</td>
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<tr>
<td>* Direct control over antibiotic use</td>
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<tr>
<td>Disadvantages</td>
</tr>
<tr>
<td>* Impacts use of restricted agents only</td>
</tr>
<tr>
<td>* Addresses empiric use to a much greater degree than downstream use</td>
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<tr>
<td>* Loss of prescriber autonomy</td>
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<tr>
<td>* May delay therapy</td>
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<tr>
<td>* Effectiveness depends on skill of approver</td>
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<tr>
<td>* Real-time resource intensive</td>
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<tr>
<td>* Potential for manipulation of system (eg, presenting request in a biased manner to gain approval)</td>
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<tr>
<td>* May simply shift to other antibiotic agents and select for different antibiotic-resistance patterns</td>
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<tr>
<td>Prospective Audit and Feedback</td>
</tr>
<tr>
<td>Advantages</td>
</tr>
<tr>
<td>* Can increase visibility of antimicrobial stewardship program and build collegial relationships</td>
</tr>
<tr>
<td>* More clinical data available for recommendations, enhancing uptake by prescribers</td>
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<tr>
<td>* Greater flexibility in timing of recommendations</td>
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<tr>
<td>* Can be done on less than daily basis if resources are limited</td>
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<tr>
<td>* Provides educational benefit to clinicians</td>
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<tr>
<td>* Prescriber autonomy maintained</td>
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<tr>
<td>* Can address de-escalation of antibiotics and duration of therapy</td>
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<tr>
<td>Disadvantages</td>
</tr>
<tr>
<td>* Compliance voluntary</td>
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<tr>
<td>* Typically labor-intensive</td>
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<tr>
<td>* Success depends on delivery method of feedback to prescribers</td>
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<tr>
<td>* Prescribers may be reluctant to change therapy if patient is doing well</td>
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<tr>
<td>* Identification of interventions may require information technology support and/or purchase of computerized surveillance systems</td>
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<tr>
<td>* May take longer to achieve reductions in targeted antibiotic use</td>
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antibiotic use in hematology-oncology patients. In one study, the addition of PAF led to a significant decrease in the use of restricted antibiotics during the intervention period from 574.4 to 533.8 study-antibiotic days per 1000 patient-days (incidence rate ratio, 0.93; 95% confidence interval [CI], 0.88–0.97; \( P = .002 \)), although neutropenic patients and those undergoing hematopoietic stem cell transplant were excluded [31].

The effectiveness of PAF may depend on the infrastructure in place at an institution. A multicenter study of a PAF program added to existing ASPs found overall that 27.3% of antibiotic courses were determined to be unjustified, and clinicians accepted recommendations to change or stop the antibiotics in 66.7% of these. In the 2 sites with established ASPs and dedicated personnel, the addition of PAF led to significant reductions in antibiotic usage; however, among the 3 centers without established resources, no impact was identified [31].

PAF can be very labor intensive, and identification of appropriate patients for intervention can be challenging and require computerized surveillance systems; however, where daily review or preauthorization is not feasible, limited PAF can still have an impact [32]. A pharmacist-driven PAF intervention conducted 3 days a week at a 253-bed community hospital demonstrated a 64% decline in DOTs per 1000 patient-days after implementation, a 37% reduction in total antibiotic expenditures, and a decrease in use of carbapenems, vancomycin, and levofloxacin [33].

The benefit of preauthorization compared with PAF has had limited study. Restrictive measures such as preauthorization were compared with persuasive measures such as PAF in a meta-analysis of 52 interrupted time series in a Cochrane review [34]. Persuasive interventions included PAF, dissemination of educational resources, reminders, and educational outreach. Although equivalent to persuasive measures at 12 or 24 months, restrictive interventions had statistically greater effect size on prescribing outcomes at 1 month (+32%; 95% CI, 2%–61%; \( P = .03 \)) and on colonization or infection with \textit{C. difficile} or antibiotic-resistant bacteria at 6 months (+53%; 95% CI, 31%–75%; \( P = .001 \)). The authors concluded that restrictive interventions are preferred when the need is urgent [34]. Another study [35] at an academic institution demonstrated that when a preauthorization strategy was switched to a PAF strategy, overall antibiotic use increased (preauthorization vs PAF: \(-9.75 \text{ vs } +9.65 \) DOTs per 1000 patient-days per month; \( P < .001 \)), as did hospital length of stay (\(-1.57 \text{ vs } +1.94 \) days per 1000 patient-days; \( P = .016 \)).

Whether one chooses preauthorization, PAF, or a combination of those strategies, implementation should serve as the foundation of a comprehensive ASP. Effective implementation requires the support of hospital administration, allocation of necessary resources for a persistent effort by dedicated, well-trained personnel, and ongoing communication with clinicians.

II. Is Didactic Education a Useful Antibiotic Stewardship Intervention for Reducing Inappropriate Antibiotic Use?

Recommendation

2. We suggest against relying solely on didactic educational materials for stewardship (weak recommendation, low-quality evidence).

Comment: Passive educational activities, such as lectures or informational pamphlets, should be used to complement other stewardship activities. Academic medical centers and teaching hospitals should integrate education on fundamental antibiotic stewardship principles into their preclinical and clinical curricula.

Evidence Summary

Education is a common tool for ASPs. Strategies include educational meetings with didactic lectures and distribution of educational pamphlets and materials. No comparative studies are available to determine which educational strategy is most effective.

Dissemination of educational materials in the context of a focused stewardship goal can be successful. For example, in a Cochrane review published in 2013 [34], dissemination of educational materials via printed forms or meetings was associated with improved antibiotic use in 5 of 6 studies; the median effect size based on the type of study ranged from 10.6% to 42.5%. Education alone, however, can result in nonsustainable improvements in antibiotic prescribing. Landgren et al [36] performed a cross-over study with an educational marketing campaign that targeted perioperative prophylaxis. Prescribing improved during the intervention period but was not sustained over the next 12 months [36]. Educational strategies are likely most effective when combined with other stewardship strategies such as PAF [34].

Educational strategies should include medical, pharmacy, physician assistant, nurse practitioner, and nursing students and trainees. In a survey of fourth-year medical students at 3 schools in the United States [37], 90% of respondents confirmed that they would like more education on appropriate antibiotic use. In addition, they had low mean knowledge scores on this topic, suggesting the need for instruction in fundamental antibiotic stewardship principles. The Accreditation Council for Graduate Medical Education announced its commitment to antibiotic stewardship in 2015 and will provide resources and materials to postgraduate training hospitals [38].

III. Should ASPs Develop and Implement Facility-Specific Clinical Practice Guidelines for Common Infectious Diseases Syndromes to Improve Antibiotic Utilization and Patient Outcomes?

Recommendation

3. We suggest ASPs develop facility-specific clinical practice guidelines coupled with a dissemination and implementation strategy (weak recommendation, low-quality evidence).

Comment: Facility-specific clinical practice guidelines and algorithms can be an effective way to standardize prescribing
practices based on local epidemiology. ASPs should develop those guidelines, when feasible, for common infectious diseases syndromes. In addition, ASPs should be involved in writing clinical pathways, guidelines, and order sets that address antibiotic use and are developed within other departments at their facility.

**Evidence Summary**

Implementation of facility-specific clinical practice guidelines can lead to substantial changes in antibiotic use for infections commonly treated in hospitals. Most published studies of clinical practice guidelines have involved pneumonia, including community-acquired pneumonia (CAP) in adults [39–41] and children [42], and healthcare-associated pneumonia [43–46]. One study involved cellulitis and cutaneous abscesses [47]. Several of these studies described a process of interdisciplinary guideline development along with a multifaceted dissemination and implementation strategy to increase awareness and uptake of the guideline [40, 43, 45, 47]. Such strategies included guideline dissemination in electronic or hard-copy formats, provider education, engagement of peer champion advocates, audit and feedback of prescribing practices to providers, checklists, and incorporation of recommendations into electronic order sets.

Specific improvements in antibiotic use associated with implementation of facility-specific guidelines have included statistically significant increases in likelihood of appropriate initial therapy [40, 46], use of narrower-spectrum antibiotic regimens [41, 42, 47], earlier switch from IV to oral therapy [39], and shorter duration of treatment [39, 41, 45–47]—all without adverse effects on other clinical outcomes. For those studies powered to detect differences in clinical outcomes, reductions in mortality [40], length of hospital stay [39–41, 43, 44], adverse events [39, 48], recurrence or readmission [46], and treatment costs [40, 44] have been demonstrated.

The sustainability of the effects of guideline implementation has not been well established. In one study, changes in prescribing and outcomes were sustained 3 years after guideline implementation [43]; however, in another study, removal of measures to promote guideline adherence after 1 year was associated with a reduction in adherence [49]. Therefore, interventions to maintain guideline adherence over time may be necessary, and intended outcomes should be monitored.

**IV. Should ASPs Implement Interventions to Improve Antibiotic Use and Clinical Outcomes That Target Patients With Specific Infectious Diseases Syndromes?**

**Recommendation**

4. We suggest ASPs implement interventions to improve antibiotic use and clinical outcomes that target patients with specific infectious diseases syndromes (weak recommendation, low-quality evidence).

Comment: ASP interventions for patients with specific infectious diseases syndromes can be an effective way to improve prescribing because the message can be focused, clinical guidelines and algorithms reinforced, and sustainability improved. ASPs should regularly evaluate areas for which targeted interventions are needed and adapt their activities accordingly. This approach is most useful if the ASP has a reliable way to identify patients appropriate for review.

**Evidence Summary**

In addition to hospital-wide activities, such as preauthorization or development of clinical guidelines, a strategy for targeted efforts to improve antibiotic use and clinical outcomes for a specific infectious diseases issue has been shown to be effective. Studies have involved skin and soft tissue infections (SSTIs), asymptomatic bacteriuria (ASB), or CAP.

For example, to reduce the use of broad-spectrum therapy and shorten the duration of treatment for adults with uncomplicated SSTIs, an intervention was developed that included dissemination of a treatment algorithm, electronic order sets, recruitment of physician champions, and quarterly feedback to providers of compliance with the guideline. This study of 169 adults demonstrated a 3-day reduction in the length of therapy, 30% reduction in broad-spectrum antibiotic prescribing, and 0.3% reduction in clinical failure [47].

Interventions to reduce inappropriate treatment of ASB at geriatric or long-term care institutions have resulted in significant decreases in antibiotic use [50, 51]. For example, Zabarsky et al. [50] developed an intervention that discouraged both nurses from collecting urine cultures from asymptomatic patients and primary care providers from treating ASB. After the intervention, urine cultures decreased from 2.6 to 0.9 per 1000 patient-days (P < .0001), ASB overall rate of treatment declined from 1.7 to 0.6 per 1000 patient-days (P = .0017), and total days of antibiotic therapy were reduced from 167.7 to 117.4 per 1000 patient-days (P < .001). The improvements were sustained for 30 months of follow-up.

ASP interventions for CAP have increased the proportion of patients receiving appropriate therapy (54.9% to 93.4% in one hospital and 64.6% to 91.3% in a second hospital) [52]. In a pediatric population, a CAP intervention resulted in an increase in the proportion of patients receiving empiric ampicillin from 13% to 63% and a decrease in the proportion of patients receiving empiric ceftriaxone from 72% to 21%, without an increased risk of treatment failure [42]. Other studies have demonstrated optimization of antibiotic use, such as reduced time to oral antibiotic conversion by 1–2 days [39, 53], decreased duration of therapy from a median of 10 to 7 days [54] with 148 days of antibiotic therapy avoided in the 6-month study period, and improved appropriate narrowing of antibiotic therapy from 19% to 67%. There was no difference between the baseline and intervention periods in the proportions of patients who were readmitted within 30 days (14.5% vs 7.7%; P = .22) or who developed CDI (4.8% vs 1.5%; P = .28). In a study involving 5
hospitals, implementation of a guideline that included criteria for oral conversion and hospital discharge reduced length of stay from 7.3 to 5.7 days \((P < .001)\); 30-day readmission proportions did not differ \((1.9\% \text{ vs } 2.4\%; P = 6)\) [53].

An alternative approach is assessing patients with blood cultures growing specific pathogens. Patients with bacteria or yeast in their blood can usually be identified through communication with the microbiology laboratory or through alerts from computerized surveillance systems. For example, Antworth et al [55] described the impact of a candidemia-care bundle in which patients were identified by electronic medical records and clinical microbiology reports. Implementation of this bundle was associated with improved care related to both drug therapy (eg, appropriate antifungal therapy selection rates for bundle vs historic control: 100\% vs 86.5\%; \(P < .05\)) and nondrug therapy (eg, ophthalmologic examination rates: 97.6\% vs 75.7\%; \(P = .01\)). Similarly, Borde et al [56] observed improvements in both drug therapy (appropriate initial anti-infective therapy: 85\% vs 4\%; \(P < .001\)) and nondrug therapy (follow-up cultures: 65\% vs 33\%; \(P < .001\))—as well as decreased mortality (10\% vs 44\%; \(P < .001\)) after implementing an ASP bundle targeting *Staphylococcus aureus* bacteremia. In a study targeting gram-negative bacteremia, Pogue et al [57] combined active alerting of positive blood cultures with ASP intervention. In the subgroup of patients not on appropriate antibiotic therapy at the time of the initial positive blood culture, the intervention was associated with reduced mortality \((\text{odds ratio } \text{[OR]} 0.24; 95\% \text{ CI, .08–.76})\) and length of stay \((\text{OR} 0.76; 95\% \text{ CI, .66–.86})\). In all patients, the intervention group had shorter time to appropriate therapy \((8 \text{ vs } 14 \text{ hours; } P = .01)\) and length of stay \((7 \text{ vs } 8 \text{ days; } P < .001)\).

V. Should ASPs Implement Interventions Designed to Reduce the Use of Antibiotics Associated With a High Risk of CDI?

**Recommendation**

5. We recommend antibiotic stewardship interventions designed to reduce the use of antibiotics associated with a high risk of CDI compared with no such intervention \((\text{strong recommendation, moderate-quality evidence})\).

Comment: The goal of reducing CDI is a high priority for all ASPs and should be taken into consideration when crafting stewardship interventions.

**Evidence Summary**

ASP have been shown to reduce hospital-onset CDI. The primary ASP interventions were restriction of high-risk antibiotics such as clindamycin [58–61] and/or broad-spectrum antibiotics, especially cephalosporins [59–64] and fluoroquinolones [59–63, 65]. Climo et al [58] were among the first to report that restriction of clindamycin was associated with decreased clindamycin use, decreased CDI \((P < .001)\), increased clindamycin susceptibility \((P < .001)\), and overall cost savings attributable to fewer cases of CDI [58]. More recent studies have been conducted in a variety of hospital settings. Some have been prompted by outbreaks [59, 65], whereas others were performed in endemic situations [22, 63].

Implementation of ASPs has been associated with statistically significant sudden or linear trends decreases in nosocomial CDI rates [22, 58–61, 63–65], which have been sustained for up to 7 years [22]. A meta-analysis [18] highlights the effectiveness of stewardship for CDI prevention and outlines ASP intervention strategies. Other studies support that antibiotic restriction can further reduce CDI rates when added to previous infection control measures [58, 59]. In fact, Valiquette et al [59] reported that simply strengthening basic infection control measures did not reduce the CDI rate. CDI rates, however, declined \((P < .007)\) with antibiotic stewardship interventions to reduce the use of second- and third-generation cephalosporins, clindamycin, macrolides, and fluoroquinolones through dissemination of local treatment guidelines, PAF, and reduction in duration of therapy.


**Recommendation**

6. We suggest the use of strategies (eg, antibiotic time-outs, stop orders) to encourage prescribers to perform routine review of antibiotic regimens to improve antibiotic prescribing \((\text{weak recommendation, low-quality evidence})\).

Comment: Published data on prescriber-led antibiotic review are limited, but successful programs appear to require a methodology that includes persuasive or enforced prompting. Without such a mechanism, these interventions are likely to have minimal impact.

**Evidence Summary**

Strategies to prompt prescribers to assess antibiotic therapy without formal ASP intervention have undergone only limited evaluation. Lee et al [66] developed a structured electronic checklist for antibiotic time-out audit to be performed twice weekly by a senior resident on the medical care team (referred to as “self-stewardship”). Unit pharmacists reminded residents to complete the checklist and compliance was 80\%. Initially, the time-outs resulted in changes in antibiotic therapy in 15\% of cases; however, the magnitude of change diminished over the 18-month study period. CDI rates decreased by 19\% and annual antibiotic costs decreased by 46\% \((\text{from } 149 743 \text{ to } 80 319)\), but overall antibiotic use did not [66]. Checklists to guide process of care in a medical ICU have been studied [67, 68]. In one study [67], physicians received face-to-face prompting if they overlooked the antibiotic review on the checklist. Prompting improved compliance with the checklist and was associated with a reduced duration of antibiotic therapy and a lower risk-adjusted mortality than no prompting in patients receiving...
empiric antibiotics (OR, 0.41; 95% CI, .18–.92; P = .03) [67]. Even with prompting, prescribers may have difficulty performing self-stewardship. For example, in a study by Lesprit et al [69], clinicians were prompted to review IV therapy at 72 hours. There was no significant change in the frequency of antibiotic regimen modification compared with the control group; however, requests for infectious diseases input increased.

Antibiotic stop orders are another approach to requiring physicians to review their antibiotic use. This has been best studied for 3-day stop orders for vancomycin [70, 71]. Guglielmo et al [70] reported that the stop order was associated with less continuation of vancomycin in the absence of documented gram-positive infection (33/133 [25%] vs 15/142 [11%]; P = .002) and less use of vancomycin in febrile neutropenia (37/133 [28%] vs 22/142 [15%]; P < .013). Hospital-wide vancomycin use decreased as well (160 g vs 100–120 g per 1000 patient-days; P not stated) [70]. A safety mechanism should be paired with stop orders to avoid unintended interruptions and to prevent alienating prescribers against antibiotic stewardship interventions.

Collectively, these findings suggest that antibiotic review by the prescriber can have an important stewardship impact if done with appropriate reminders or prompting, but available data do not confirm feasibility or sustainability.

VII. Should Computerized Clinical Decision Support Systems Integrated Into the Electronic Health Record at the Time of Prescribing be Incorporated as Part of ASPs to Improve Antibiotic Prescribing?

Recommendation

7. We suggest incorporation of computerized clinical decision support at the time of prescribing into ASPs (weak recommendation, moderate-quality evidence).

Comment: Computerized clinical decision support for prescribers should only be implemented if information technology resources are readily available. However, computerized surveillance systems that synthesize data from the electronic health record and other data sources can streamline the work of ASPs by identifying opportunities for interventions.

Evidence Summary

Computerized decision support systems are designed to improve antibiotic use by providing treatment recommendations to clinicians at the time of prescribing [72–77].

Implementation of computerized decision support systems for prescribers has been associated with reduced use of broad-spectrum antibiotics [73, 74], improved antibiotic dosing [75], reduced antibiotic resistance [74], more appropriate antibiotic selection [73, 77], fewer prescribing errors [72, 75, 78], reduced adverse events [72, 76], reduced antibiotic costs [72, 73, 75, 76], reduced length of stay [72], and reduced mortality [76]. Computerized surveillance systems for ASPs may improve efficiency by facilitating more PAF interventions and reducing the time for such interventions [79–81]. Use of those systems by ASPs has been associated with reduced use of broad-spectrum antibiotics [81] and reduced antibiotic costs [79].

Among the potential disadvantages of computer decision support and surveillance systems are the time and financial resources required for implementation and maintenance, and the potential for a high proportion of nonactionable alerts that may lead to “alert fatigue” [80, 81].

VIII. Should ASPs Implement Strategies That Promote Cycling or Mixing in Antibiotic Selection to Reduce Antibiotic Resistance?

Recommendation

8. We suggest against the use of antibiotic cycling as a stewardship strategy (weak recommendation, low-quality evidence).

Comment: Available data do not support the use of antibiotic cycling as an ASP strategy, and further research is unlikely to change that conclusion. Because clinical data are sparse for antibiotic mixing, we cannot give any recommendation about its utility.

Evidence Summary

Antibiotic cycling involves withdrawal of an antibiotic or antibiotic class from general use (within a ward or an institution) for a designated period of time and substitution with antibiotics from a different class having a comparable spectrum of activity but for which bacteria may have different resistance mechanisms. Antibiotic cycling is difficult to achieve, labor intensive, and impractical for most inpatient facilities.

Many studies have been performed, but they fail to provide compelling evidence of the benefit of antibiotic cycling, partly because of methodologic shortcomings. Common weaknesses include single-center setting (usually in ICUs), before-and-after time-series analysis, lack of adherence to prescribing protocols, multiple simultaneous interventions (including infection prevention and guideline implementation), and lack of long-term follow-up. Brown and Nathwani [82] performed a systematic review of antibiotic cycling in 2005 and concluded that available study results did not permit conclusions regarding the efficacy of cycling.

In contrast to cycling that is performed at the level of the medical facility or patient care ward, a strategy known as antibiotic mixing is performed at the level of the individual patient, in which consecutive patients with the same diagnosis receive an antibiotic from a different class in rotation. Mathematical modeling suggests that antibiotic mixing is a more promising strategy for limiting emergence of resistance than cycling, but few clinical studies validate these models [83, 84]. Comprehensive reviews published in 2010 [85, 86] concluded that more work is needed to demonstrate the usefulness of antibiotic mixing.
Optimization
IX. In Hospitalized Patients IV Intravenous Antibiotics, Does a Dedicated PK Monitoring and Adjustment Program Lead to Improved Clinical Outcomes and Reduced Costs?

Recommendations

9. We recommend that hospitals implement PK monitoring and adjustment programs for aminoglycosides (strong recommendation, moderate-quality evidence).

10. We suggest that hospitals implement PK monitoring and adjustment programs for vancomycin (weak recommendation, low-quality evidence).

   Comment: PK monitoring and adjustment programs can reduce costs and decrease adverse effects. The ASP should encourage implementation and provide support for training and assessment of competencies. The conduct of those programs should be integrated into routine pharmacy activities.

Evidence Summary

In randomized studies, individualized PK monitoring and adjustment of aminoglycoside dosing compared with standard dosing is associated with increased likelihood of obtaining serum concentrations within therapeutic range [87, 88] and reduced institutional costs [87, 89]. Reductions in nephrotoxicity, hospital length of stay, and mortality [87, 90–92] have been observed in some studies. Leehey et al [88] randomized patients receiving aminoglycosides to dosing directed by one of 3 groups: (1) physicians with PK monitoring input from a pharmacist; (2) physician–pharmacist PK monitoring team; or (3) physicians with no external input (control group). The PK monitoring groups achieved higher peak and marginally lower trough concentrations; however, there was no statistically significant difference in the likelihood of nephrotoxicity among groups 1, 2, and 3 (27%, 16%, and 16%, respectively; P = .31). Clinical failure was less common in the PK-monitored groups across all patients (1%, 0%, and 11%, respectively; P = .004), but not among patients with microbiologically proven infection. Bartal et al [90] compared the outcomes of usual care vs an intensive PK monitoring program among patients receiving initial high-dose extended-interval gentamicin dosing. Nephrotoxicity was lower in the PK monitoring group (5% vs 21%; P = .03), with similar proportions of patients experiencing cure of infection or death at 28 days between the groups.

Only one randomized controlled study [93] has been performed assessing the impact of a PK monitoring and adjustment program for vancomycin; no difference in efficacy in the concentration-monitoring arm was demonstrated, but there was a lower incidence of nephrotoxicity (adjusted OR, 0.04; 95% CI, .006–.30) at a cost per case of nephrotoxicity avoided of $435. Observational studies [93–96] of vancomycin dose individualization showed similar effects, with costs stable or lower.

Broader interventions directed at antibiotic dosing, usually involving integration of dosing support into computerized physician order-entry systems, have shown improved adherence to dosing guidelines as well as fewer adverse effects, but no difference in effectiveness (eg, clinical cure, hospital mortality, or length of stay) [97–99]. No studies have examined the relationship between PK monitoring and adjustment programs and institutional antibiotic resistance prevalence.

X. In Hospitalized Patients, Should ASPs Advocate for Alternative Dosing Strategies Based on PK/Pharmacodynamic Principles to Improve Outcomes and Decrease Costs for Broad-Spectrum β-Lactams and Vancomycin?

Recommendation

11. In hospitalized patients, we suggest ASPs advocate for the use of alternative dosing strategies vs standard dosing for broad-spectrum β-lactams to decrease costs (weak recommendation, low-quality evidence).

   Comment: Although data for improved outcomes for broad-spectrum β-lactam dosing with this approach are still limited, these interventions are associated with antibiotic cost savings. ASPs should consider implementation but must take into account logistical issues such as nursing and pharmacy education and need for dedicated IV access. Considering the limited evidence, we cannot give any recommendation about the utility of alternative dosing strategies for vancomycin.

Evidence Summary

Dosing strategies based on PK/pharmacodynamic (PK/PD) principles for aminoglycosides, such as once-daily dosing, have been shown to be effective in reducing nephrotoxicity and, in some studies, improve clinical outcomes [100, 101]. The effectiveness of alternative dosing schemes for β-lactam antibiotics and vancomycin based on PK/PD principles is unclear.

For β-lactam antibiotics, one meta-analysis showed decreased mortality (risk ratio, 0.59; 95% CI, 0.41–0.83) among patients receiving continuous infusions of carbapenems or piperacillin–tazobactam vs standard infusions. This meta-analysis included 3 randomized controlled trials (RCTs) that comprised only 25% of the patient outcomes analyzed [102]. In contrast, another meta-analysis that included 14 RCTs did not support improved outcomes using prolonged infusions of broad-spectrum β-lactam antibiotics (either extended or continuous infusion) [103]. A Cochrane review [104] and a recent randomized trial [105] in critically ill patients of continuous infusions of β-lactam antibiotics compared with standard intermittent dosing also did not demonstrate benefits in outcome.

For vancomycin, continuous infusion has not been shown to improve clinical outcomes in adults but has been associated with decreased nephrotoxicity in a meta-analysis [106]. Similarly, continuous-infusion vancomycin has been associated with few adverse effects and no nephrotoxicity in children [107].

Alternative dosing strategies for β-lactam antibiotics [108] and vancomycin [109] were associated with significantly lower costs than intermittent infusions in randomized studies. Savings
were attributable to lower acquisition costs of β-lactam antibiotics but not overall hospital expenses [108], and lower costs of vancomycin acquisition and monitoring [109].

XI. Should ASPs Implement Interventions to Increase Use of Oral Antibiotics as a Strategy to Improve Outcomes or Decrease Costs?

Recommendation

12. We recommend ASPs implement programs to increase both appropriate use of oral antibiotics for initial therapy and the timely transition of patients from IV to oral antibiotics (strong recommendation, moderate-quality evidence).

Comment: Programs to increase the appropriate use of oral antibiotics can reduce costs and length of hospital stay. IV-to-oral conversion of the same antibiotic is less complicated than other strategies and is applicable to many healthcare settings. The conduct of those programs should be integrated into routine pharmacy activities. ASPs should implement strategies to assess patients who can safely complete therapy with an oral regimen to reduce the need for IV catheters and to avoid outpatient parenteral therapy.

Evidence Summary

The findings of many studies [110–116] have shown that programs aimed to increase the use of oral antibiotics are associated with reduced drug costs and length of hospital stay without compromising efficacy or safety. For example, Omidvari et al [115] reported that patients with CAP randomized to receive an abbreviated course of IV cephalosporin followed by oral cephalosporin had a lower total cost of care ($5002 vs $2953; P < .05) and shorter hospital stay (10 vs 7 days; P = .01) than those treated with conventional IV cephalosporin therapy. There were no differences in clinical course, cure rate, survival, or resolution of chest radiographs [115]. Laing et al [116] reported that the incidence of line complications was lower in patients who were switched to oral therapy than in those who remained on IV therapy (17/81 vs 26/81), but this difference was not significant (P = .077).

Unlike automatic conversion from IV to oral formulations of the same antibiotic, switching from IV antibiotics without an equivalent oral formulation needs more advanced assistance. Mertz et al [114] reported that early switching on medical wards was associated with a shorter duration of IV antibiotic treatment (reduction in median days, 19%; 95% CI, 9%–29%; P = .001), a trend toward a decreased overall duration of antibiotic treatment, and economic savings—all without significant changes in mortality or readmissions; however, only 151 of 246 (61.1%) of potential cases were switched. This might have been partly attributable to the lack of precise recommendations for switching when an oral equivalent was not available (eg, piperacillin-tazobactam or meropenem) as switching occurred less often in such patients. In contrast, Seviç et al [112] reported an increased percentage of eligible patients being converted from IV to oral antibiotics (52/97 [54%] vs 66/80 [83%]; difference, 29%; 95% CI, 16%–42%; P < .001) after implementation of guidelines for switching therapy. They directed providers to seek infectious diseases consultation for patients on IV formulations without an oral equivalent. ASPs can have an important role with more complicated IV-to-oral transitions.

Another example of the potential benefit of IV-to-oral transition is reduction in the need for outpatient parenteral antibiotic therapy (OPAT). For example, Conant et al [117] reported outcomes in 56 patients who received oral (n = 50) or no additional antibiotics (n = 6) after mandatory infectious diseases approval of OPAT. Denial of OPAT was associated with true clinical failure in only 1 of 56 patients and a per-patient cost savings of $3847.

XII. In Patients With a Reported History of β-Lactam Allergy, Should ASPs Facilitate Initiatives to Implement Allergy Assessments With the Goal of Improved Use of First-Line Antibiotics?

Recommendation

13. In patients with a history of β-lactam allergy, we suggest that ASPs promote allergy assessments and PCN skin testing when appropriate (weak recommendation, low-quality evidence).

Comment: Allergy assessments and PCN skin testing can enhance use of first-line agents, but it is largely unstudied as a primary ASP intervention; however, ASPs should promote such assessments with providers. In facilities with appropriate resources for skin testing, the ASPs should actively work to develop testing and treatment strategies with allergists.

Evidence Summary

PCN is the most common drug “allergy” noted at hospital admission, and is reported in 10%–15% of patients and 15%–24% of those requiring antibiotic therapy [118, 119]. Compared with nonallergic patients, patients labeled as having a PCN allergy are exposed to more alternative antibiotics; have increased prevalence of C. difficile, methicillin-resistant S. aureus, and vancomycin-resistant enterococcal infections; and have longer hospital stays [118].

Properly performed skin testing using major and minor PCN determinant reagents has a negative predictive value of 97%–99% and a positive predictive value of 50%. Studies demonstrate that PCN and other β-lactam antibiotics can be safely given to patients with a putative PCN allergy who have had an allergy assessment and negative PCN skin testing [119, 120]. Rimawi et al [121] reported that all but one of 146 patients with a history of PCN allergy who had a negative skin test tolerated β-lactam therapy, resulting in a negative predictive value of >99%. They also found that the use of skin testing to guide antibiotic therapy yielded an annual savings of $82,000 at a university teaching hospital.

Using structured drug allergy assessments has been associated with improved antibiotic stewardship as demonstrated by antibiotic selection, reduced alternative antibiotic use, decreased length of hospital stay and costs, and increased guideline
adherence [119, 120]. For example, Park et al [122] reported that collaboration between trained pharmacists and allergists was associated with increased β-lactam prescriptions in patients with a history of PCN allergy. ASPs should encourage mechanisms that ensure allergy assessments are performed.

XIII. Should ASPs Implement Interventions to Reduce Antibiotic Therapy to the Shortest Effective Duration?

Recommendation

14. We recommend that ASPs implement guidelines and strategies to reduce antibiotic therapy to the shortest effective duration (strong recommendation, moderate-quality evidence).

Comment: Recommending a duration of therapy based on patient-specific factors is an important activity for ASPs. Suitable approaches include developing written guidelines with specific suggestions for duration, including duration of therapy recommendations as part of the preauthorization or prospective audit and feedback process, or specifying duration at the time of antibiotic ordering (eg, through an electronic order entry system).

Evidence Summary

Findings from 2 pre–post investigations suggest that antibiotic stewardship interventions aimed at reducing the duration of antibiotic therapy lead to similar clinical outcomes compared with the preintervention period. Specifically, education and PAF for adult inpatients with CAP led to a median decrease in antibiotic use from 10 to 7 days (P < .001), with no significant differences in length of stay or 30-day readmission rates [54]. A second study [47] found reduced antibiotic utilization and duration of therapy (from 13 to 10 days; P < .001) after implementation of a guideline for inpatients with SSTIs. There are limited studies specifically evaluating the impact of ASP interventions to reduce duration of antibiotic therapy on clinical outcomes; however, evidence from systematic reviews [123–126] and RCTs [127–136] demonstrated that prescription of shorter courses of antibiotic therapy is associated with outcomes similar to those with longer courses in both adults and children with a variety of infection types (Table 2) and few adverse events.

Microbiology and Laboratory Diagnostics

XIV. Should ASPs Work With the Microbiology Laboratory to Develop Stratified Antibiograms, Compared With Nonstratified Antibiograms?

Recommendation

15. We suggest development of stratified antibiograms over solely relying on nonstratified antibiograms to assist ASPs in developing guidelines for empiric therapy (weak recommendation, low-quality evidence).

Comment: Although there is limited evidence at this time that stratified antibiograms (eg, by location or age) lead to improved empiric antibiotic therapy, stratification can expose important differences in susceptibility, which can help ASPs develop optimized treatment recommendations and guidelines.

Evidence Summary

Institutional antibiograms are helpful to ASPs for the development of guidelines for empiric therapy. The Clinical and Laboratory Standards Institute [137] provides guidelines for antibiogram construction and reporting, both for routine cumulative antibiograms and for enhanced antibiograms, which may be stratified by various parameters including patient location or population if at least 30 isolates are available for each organism. A single institutional, or hospital-wide, antibiogram may mask important susceptibility differences across units within the institution. For example, certain antibiotic-resistant organisms are often significantly more common in ICU than in non-ICU settings. At one medical center, the percentages of bacterial isolates resistant to antibiotics were significantly higher in medical and surgical ICUs than were those predicted by the hospital-wide antibiogram, whereas the percentage of isolates susceptible to antibiotics was higher in non-ICU units, compared with the hospital overall [138]. Similarly, antibiograms can be stratified by population age group (eg, pediatric) [139], by infection site (eg, blood or respiratory vs all sources) [140, 141], by patient comorbidities (eg, cystic fibrosis) [142], or by acquisition in the community vs healthcare setting [143].

One institution [144] constructed a pediatric-specific antibiogram for Escherichia coli and compared it with antibiograms generated from combined data from both adult and pediatric isolates. There were significant antibiotic susceptibility differences between E. coli isolates obtained from pediatric patients vs the hospital-wide antibiogram data [144]. Provision of pediatric-specific data optimized prescribing choice when compared with no antibiogram and also with the hospital-wide antibiogram. Another institution [139] also found age-specific differences with overestimation of resistance in E. coli and S. aureus for children and underestimation for the elderly.

XV. Should ASPs Work With the Microbiology Laboratory to Perform Selective or Cascade Reporting of Antibiotic Susceptibility Test Results?

Recommendation

16. We suggest selective and cascade reporting of antibiotics over reporting of all tested antibiotics (weak recommendation, low-quality evidence).

Comment: Although data are limited that demonstrate direct impact of those strategies on prescribing, some form of selective or cascaded reporting is reasonable. After implementation, ASPs should review prescribing to ensure there are no unintended consequences.

Evidence Summary

Selective reporting is the practice of reporting susceptibility results for a limited number of antibiotics instead of all tested
antibiotics. For example, a laboratory that practices selective reporting would routinely release linezolid and daptomycin results only when enterococci are nonsusceptible to ampicillin and vancomycin. In a randomized study for urinary tract infections, Coupel et al [145] used a case-vignette format and randomly assigned residents to an intervention group, which received antibiotic susceptibility results for 2–4 antibiotics, or to a control group, which received full-length results for all 25 antibiotics tested. The increase in appropriateness of antibiotic prescription with the use of selective reporting ranged from 7% to 41%, depending upon the clinical scenario. Similar results have been seen in some prospective surveys [146, 147].

Cascade reporting is one type of selective reporting in which susceptibility results of secondary antibiotics (either more costly or broader spectrum) are only reported if an organism is resistant to the primary antibiotic within the particular antibiotic class (eg, if the organism is cefazolin susceptible, ceftriaxone would not be reported). There are no published guidelines for cascade antibiotic reporting. The Clinical and Laboratory Standards Institute [148] provides guidance for testing and reporting susceptibilities for certain organisms, but does not cover all organism-antibiotic combinations. ASPs should work with the microbiology laboratory to assess the impact these strategies may have on development of the antibiogram (eg, susceptibility data for suppressed results may not be available for inclusion).

XVI. Should ASPs Advocate for Use of Rapid Viral Testing for Respiratory Pathogens to Reduce the Use of Inappropriate Antibiotics? Recommendation

17. We suggest the use of rapid viral testing for respiratory pathogens to reduce the use of inappropriate antibiotics (weak recommendation, low-quality evidence).

Comment: Although rapid viral testing has the potential to reduce inappropriate use of antibiotics, results have been inconsistent. Few studies have been performed to assess whether active ASP intervention would improve those results.

Evidence Summary

Studies of the value of ASP interventions based on rapid testing for respiratory viruses are lacking. However, some data are available on decreased inappropriate antibiotic use with rapid viral testing. Those studies have been performed primarily in pediatric populations such as children presenting to physicians’ offices [149] or emergency departments [150–152], or children requiring hospitalization [153]. One study focused specifically on immunocompromised children [154] and 2 focused on adults [155, 156].

Findings from some trials showed that rapid diagnostic testing for respiratory viruses by rapid antigen, rapid immunoassay, or direct fluorescent antigen was associated with decreased ancillary test orders (eg, chest radiograph, urinalysis) [150, 157], decreased...
antibiotic use [149, 150, 153, 156, 157], and increased antiviral use [149, 150, 157]. For example, Bonner et al [150] reported that physician awareness of positive influenza results by a rapid immunoassay reduced the number of laboratory tests ordered (P = .01), the number of radiographs ordered (P < .001), and the associated charges (P < .001). The authors also noted decreased antibiotic use (P < .001), increased antiviral use (P = .02), and shortened time to discharge (P < .001). There was no impact on the above outcomes for patients with negative rapid test results.

Kadmon et al [154] recently reported that polymerase chain reaction (PCR) test results prompted initiation of specific antiviral therapy and avoidance of unnecessary antibiotics in 17 of 50 episodes (34%). Other studies [152, 155], however, have failed to detect statistically significant benefits in antibiotic use, hospital stays, or hospital admissions when reporting PCR or direct fluorescent antigen results. The lack of an appreciable benefit was attributable in part to the time to reporting of PCR results, which ranged from 12 to 24 hours in one study [152] to a mean of 30 hours in another study [155].

**XVII. Should ASPs Advocate for Rapid Diagnostic Testing on Blood Specimens to Optimize Antibiotic Therapy and Improve Clinical Outcomes?**

**Recommendation**

18. We suggest rapid diagnostic testing in addition to conventional culture and routine reporting on blood specimens if combined with active ASP support and interpretation (weak recommendation, moderate-quality evidence).

Comment: Availability of rapid diagnostic tests is expected to increase; thus, ASPs must develop processes and interventions to assist clinicians in interpreting and responding appropriately to results.

**Evidence Summary**

The use of rapid molecular assays and mass spectrometry to identify bacterial species and susceptibility in blood cultures has been associated with statistically significant improvements in time to initiation of appropriate antibiotic therapy [158–162], rates of recurrent infection [159], mortality [159, 163], length of stay [159, 161], and hospital costs [160, 161]. For example, Forrest et al [163] described the use of peptide nucleic acid fluorescence in situ hybridization (PNA-FISH) for enterococci. Compared with pre–PNA-FISH, rapid testing coupled with antibiotic stewardship team support was associated with more rapid identification of *Enterococcus faecalis* (1.1 vs 4.1 days) and *Enterococcus faecium* (1.1 vs 3.4 days), faster time to effective therapy (1.3 vs 3.1 days), and decreased 30-day mortality for *E. faecium* (26% vs 45%) (all P < .05) [163]. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry can rapidly identify bacteria, including rare species not ordinarily associated with clinical infection or pathogens that are difficult to grow or to identify to the species level [164]. In the study by Huang et al [159], the stewardship team received immediate notification of blood culture Gram stain, MALDI-TOF identification, and susceptibility results, and then gave recommendations. MALDI-TOF was associated with more rapid identification of organisms (55.9 vs 84.0 hours; P < .001). Identification of organisms with MALDI-TOF in combination with real-time ASP review and intervention was associated with faster time to initiation of both effective (20.4 vs 30.1 hours; P = .021) and optimal antibiotic therapy (47.3 vs 90.3 hours; P < .001). A recent RCT [162] compared standard blood culture processing (that included MALDI-TOF for organism identification) with rapid multiplex PCR (rmPCR) with templated comments, and rmPCR with templated comments and real-time ASP audit and feedback (rmPCR/AS). Both interventions were associated with greater use of narrow-spectrum β-lactams (rmPCR 71 hours and rmPCR/AS 85 hours vs control 42 hours; P = .04) and faster time to appropriate escalation (rmPCR 6 hours and rmPCR/AS 5 hours vs control 24 hours; P = .04). The intervention with ASP involvement was also associated with more rapid appropriate de-escalation (21 hours vs control 34 hours and rmPCR 38 hours; P < .0001). These interventions were not, however, associated with improved mortality, length of stay, or cost, possibly because of the use of other rapid tests and ASP support at the institution.

These studies underscore the importance of combining use of rapid testing with 2 strategies to maximize the benefits and likelihood of a favorable impact on outcomes. First, ASP support [159–163] or rapid notification of results [158, 162] was a consistent feature of the studies that found statistically significant associations between rapid testing and outcomes. In contrast, studies lacking these features often did not find evidence of associations between rapid testing and improved antibiotic use [165], time to initiation of appropriate antibiotic therapy [166], or length of stay benefit [165]—despite shortening the time to pathogen identification. Second, rapid testing should be performed continuously (ie, 24/7) or at least in frequent batches [167, 168]. The optimal implementation of rapid testing requires increased laboratory resources and additional costs.

**XVIII. In Adults in ICUS With Suspected Infection, Should ASPs Advocate PCT Testing as an Intervention to Decrease Antibiotic Use?**

**Recommendation**

19. In adults in ICUs with suspected infection, we suggest the use of serial PCT measurements as an ASP intervention to decrease antibiotic use (weak recommendation, moderate-quality evidence).

Comment: Although randomized trials, primarily in Europe, have shown reduction in antibiotic use through implementation of PCT algorithms in the ICU, similar data are lacking for other regions including the United States where the patterns of antibiotic prescribing and approach to stewardship
may differ. If implemented, each ASP must develop processes and guidelines to assist clinicians in interpreting and responding appropriately to results, and must determine if this intervention is the best use of its time and resources.

Evidence Summary
PCT has been assessed for its role in (1) shortening the duration of antibiotic therapy for bacterial infection based on serial measurements of PCT levels, and (2) avoidance of initiation of antibiotic therapy when the PCT level is low. Evidence from several prospective RCTs supports the use of PCT in decisions concerning discontinuation of antibiotic therapy in critically ill patients in ICUs [169–172]. In general, trials assessing PCT-guided discontinuation of antibiotic therapy report significantly more antibiotic-free days (2–4 days) in the PCT arm, without a negative effect on mortality. A meta-analysis focusing exclusively on critically ill ICU patients with severe sepsis or septic shock (including 7 studies and 1075 patients) showed a significant difference in 28-day mortality or hospital mortality and a median reduction of approximately 2 days in the length of antibiotic therapy with PCT guidance [173]. In a European multicenter study, Bouadma et al [172] examined de-escalation of therapy in 621 septic patients and demonstrated 2.7 more antibiotic-free days in the PCT group (P < .001), although days of antibiotic exposure per 1000 inpatient-days were high for each group (653 PCT vs 812 control) [172]. Available evidence does not support the use of PCT to avoid initiation of antibiotics in the critically ill ICU population when the PCT result is negative [174, 175].

XIX. In Patients With Hematologic Malignancy, Should ASPs Advocate for Incorporation of Nonculture-Based Fungal Markers in Interventions to Optimize Antifungal Use?

Recommendation
20. In patients with hematologic malignancy at risk of contracting IFD, we suggest incorporating nonculture-based fungal markers in ASP interventions to optimize antifungal use (weak recommendation, low-quality evidence).

Comment: ASPs with an existing intervention to optimize antifungal use in patients with hematologic malignancy can consider algorithms incorporating nonculture-based fungal markers. Those interventions must be done in close collaboration with the primary teams (eg, hematology-oncology). Antibiotic steward must develop expertise in antifungal therapy and fungal diagnostics for the programs to be successful. The value of those markers for interventions in other populations has not been demonstrated.

Evidence Summary
Some studies have demonstrated that the use of nonculture-based fungal markers can safely reduce antifungal treatments for patients with hematologic malignancy at high risk for IFD. Although not specifically studied as part of an ASP intervention, incorporation into existing ASPs for antifungal stewardship in that population may be useful. A variety of fungal tests such as galactomannan (GM), (1,3)-β-D-glucan (BDG), or single- or multipathogen fungal PCR have been studied. For example, Cordonnier et al [176] compared a preemptive approach (antifungal treatment initiation using both clinical and GM evidence of IFD) with an empiric strategy (antifungal treatment for any high-risk patient with suggestive clinical signs of IFD). The preemptive approach was associated with decreased antifungal treatment (39.2% vs 61.3%; P < .001) and no detrimental effect on mortality.

Few studies assessed utilization of BDG or PCR to target therapy. An RCT [177] of Aspergillus and Candida PCR compared survival between allogeneic stem cell transplant recipients who received empiric antifungal treatment with those who received empiric plus PCR-based antifungal treatment. The authors demonstrated improved 30-day survival in the group in which treatment decisions were in part based upon PCR, but survival did not differ by day 100.

There are limited data assessing the value of fungal markers in other patient populations. Pediatric data are limited, but studies [178] have shown that GM assay is a useful adjunctive tool when monitored twice weekly in hospitalized children with hematologic malignancies and fever.

Measurement
XX. Which Overall Measures Best Reflect the Impact of ASPs and Their Interventions?

Recommendation
21. We suggest monitoring antibiotic use as measured by DOTs in preference to DDD (weak recommendation, low-quality evidence).

Comment: Every ASP must measure antibiotic use, stratified by antibiotic. DOTs are preferred, but DDDs remain an alternative for sites that cannot obtain patient-level antibiotic use data. ASPs should consider measurement of appropriate antibiotic use within their own institutions by examining compliance with local or national guidelines, particularly when assessing results of a targeted intervention, and share that data with clinicians to help inform their practice. Although rates of CDI or antibiotic resistance may not reflect ASP impact (because those outcomes are affected by patient population, infection control, and other factors), those outcomes may also be used for measurement of targeted interventions.

Evidence Summary
DOTs and DDDs are standardized methods for measurement of antibiotic use. Both are useful for facility-level monitoring and interfacility comparisons. DOTs have some important advantages. DOTs are not impacted by dose adjustments and can be used in both adult and pediatric populations, whereas DDDs have more limited use in pediatrics due to weight-based dosing. In addition, the Antimicrobial Use and Resistance Module in
the CDC’s National Healthcare Safety Network requires reporting of antibiotic use by DOTs [179]. DOTs, however, require patient-level antibiotic use data, which currently may not be feasible at every facility [180–182]. Either method can be used to examine overall use or specific use by unit, provider, or service in the hospital. In addition to measurement of antibiotic use, appropriateness of prescribing can be assessed by determining compliance with facility-specific antibiotic treatment guidelines. This is particularly useful when assessing the success of a targeted intervention.

Measurement of ASP impact on patient outcomes is important but is more challenging than measurement of antibiotic use or guideline compliance. For example, using CDI rates to measure the effectiveness of stewardship interventions has significant limitations. Although implementation of ASPs has been associated with reduced CDI rates in quasi-experimental studies [18], the quantitative relationships between changes in antibiotic use and CDI incidence are largely unknown. Because CDI rates are affected by other practices besides antibiotic use, such as compliance with infection control measures, they may be a relatively insensitive metric for judging the effectiveness of ASPs. Moreover, traditional statistical techniques have significant limitations when applied to nonindependent events such as CDI. Despite this, when implementing ASP interventions directed at reduction of antibiotics considered to be high risk for promoting CDI (eg, cephalosporins, clindamycin, fluoroquinolones), including rates of healthcare-facility-onset CDI as a secondary outcome measure is recommended in that population.

Antibiotic resistance is an even more complex metric than CDI because the development and spread of resistance is impacted by many factors. Implementation of stewardship interventions has been associated with reduced resistance in both gram-positive and gram-negative bacteria [34]; however, observed effects on resistance are unpredictable because of confounding variables and many pathogen and host factors. Still, measurement of resistance may be useful for selected bacterial pathogens and in focused patient populations receiving a targeted ASP intervention.

ASPs have the potential to decrease length of stay, primarily as a consequence of timely switching from IV to oral antibiotics or by stopping unnecessary IV antibiotics; however, the impact depends on the preexisting contribution of prolonged administration of parenteral antibiotics to excess length of stay. Days of hospitalization avoided is a better measure of the effectiveness of ASP. Parenteral therapy and days of central venous access avoided are other metrics that can be useful.

XXI. What is the Best Measure of Expenditures on Antibiotics to Assess the Impact of ASPs and Interventions?

Recommendation

22. We recommend measuring antibiotic costs based on prescriptions or administrations instead of purchasing data (good practice recommendation).

Evidence Summary

ASPs result in cost savings for facilities [183]. It is important to monitor program costs in addition to measuring antibiotic use as one way to justify continued administrative support for ASP activities. Antibiotic costs should be measured based on prescriptions or administrations instead of purchasing data [184] and normalized to account for patient census (eg, antibiotic cost per patient-day) [184]. Program costs (eg, salary for stewardship personnel) [19, 185] and adjustment for inflation or standardizing costs across years [185] should be considered. Analyses that measure the effects of an intervention over time should compare actual costs after the initiation of the intervention vs projected costs in the absence of the intervention, as direct cost reductions tend to plateau [185, 186]. More robust analyses include expenditures beyond drug acquisition such as those for drug administration, therapeutic drug monitoring, and toxicities [187]. If resources are available, programs should analyze broader effects on budgets, such as total hospitalization costs [58, 160, 188].

XXII. What Measures Best Reflect the Impact of Interventions to Improve Antibiotic Use and Clinical Outcomes in Patients With Specific Infectious Diseases Syndromes?

Recommendation

23. Measures that consider the goals and size of the syndrome-specific intervention should be used (good practice recommendation).

Evidence Summary

The choice of metrics for syndrome-specific interventions (see Section IV) to improve therapy can measure process or outcome (Table 3) [39, 50–57, 189–191]. For example, interventions designed to increase compliance with a guideline should evaluate the proportion of patients in each period who are compliant. Evidence of unintended negative effects such as hospital readmission or increase in rates of hospital-acquired CDI should also be monitored. The major limitation to these metrics is the availability of reliable data.

Special Populations

XXIII. Should ASPs Develop Facility-Specific Clinical Guidelines for Management of F&N in Hematology-Oncology Patients to Reduce Unnecessary Antibiotic Use and Improve Outcomes?

Recommendation

24. We suggest ASPs develop facility-specific guidelines for F&N management in hematology-oncology patients over no such approach (weak recommendation, low-quality evidence).

Comment: Clinical guidelines with an implementation and dissemination strategy can be successfully used in the care of cancer patients with F&N and are strongly encouraged.
Comment: In facilities with large immunocompromised patient populations, ASP interventions targeting antifungal therapy can show benefit. Those interventions must be done in close collaboration with the primary teams (eg, hematology-oncology, solid organ transplant providers). Antibiotic stewards must develop expertise in antifungal therapy and fungal diagnostics for the programs to be successful.

Evidence Summary

Programs that have successfully implemented antifungal stewardship interventions have used a multipronged approach that included PAF, education, and development of clinical guidelines [195–198]. Published studies have not focused exclusively on immunocompromised patients, but those patients accounted for the largest group in most reports. Patients in the ICU made up the second-largest group. One study [196] reviewed 636 antifungal prescriptions for 6 years after implementing an antifungal ASP, of which 72% were from the adult and pediatric hematology services. That study utilized their ASP to provide feedback to the primary teams regarding fungal diagnosis, serologic and radiographic investigations, drug therapeutic monitoring, and/or starting, stopping, or modifying antifungal therapy. The primary teams had a high compliance rate (88%) with the ASP recommendations. Process of care measures for the management of candidemia and aspergillosis (eg, optimal voriconazole monitoring, use of recommended first-line therapy) improved. Patient outcomes were favorable in 47 of 63 (75%) patients with aspergillosis and 52 of 60 (87%) with candidemia, and did not change significantly during the observation period—although the study was underpowered to demonstrate improvement. The total cost of antifungals was considered to be stable and actually decreased in the year just after the formal study ended.

In a second study [197], the stewardship team focused on high-cost antifungals at a tertiary hospital in 173 patients over a 12-month period. The following antifungal agents were successfully stopped or switched: liposomal amphotericin B (51/125 [41%]), caspofungin (8/11 [73%]), micafungin (33/51 [65%]), and combination therapy (5/10 [50%]). In contrast, voriconazole was stopped or switched in only 16 of 89 (18%) patients. The total annual cost for these 4 antifungal agents fell from £1.656 million during intervention, resulting in a crude savings of £179 000.

XXIV. In Residents of Nursing Homes and Skilled Nursing Facilities, do Antibiotic Stewardship Strategies Decrease Unnecessary Use of Antibiotics and Improve Clinical Outcomes?

Recommendation

25. We suggest implementation of ASP interventions to improve the appropriate prescribing of antifungal treatment in immunocompromised patients (weak recommendation, low-quality evidence).

Evidence Summary

Implementing clinical pathways for management of F&N can reduce unnecessary antibiotic use without adverse outcomes in hematology-oncology units, although data are limited. Nucci et al [192] reported that adoption of 1997 IDSA guidelines in patients with hematologic malignancies or who were undergoing hematopoietic stem cell transplant was associated with reductions in empiric glycopeptide use (pre- vs postguidelines: 33% vs 7% of F&N episodes; \(P < .0001\)) and total glycopeptide use (73% vs 43% of F&N episodes; \(P = .0008\)). Success rates for empiric regimen, time to defervescence, duration of antibiotic therapy, and death rates were similar before and after guideline adoption. No deaths were attributed to infections due to gram-positive organisms [192].

Studies have shown that adherence to treatment guidelines resulted in improvement in important clinical outcomes. For example, Pakakasama et al [193] demonstrated that implementation of clinical guidelines in pediatric cancer patients resulted in statistically significant reductions in septic shock (intervention vs control: 3.5% vs 10.9%; \(P = .011\)), ICU admissions (2.9% vs 9.4%; \(P = .016\)), and death (0% vs 6.5%; \(P = .001\)). In another study [194], adherence to an ASP protocol for initial antibiotic therapy based on IDSA guidelines was associated with lower mortality (hazard ratio, 0.36; 95% CI, .14–.92) in 169 adult patients with 307 episodes of F&N (79% with hematologic malignancy).

XXV. In Immunocompromised Patients Receiving Antifungal Therapy, do Interventions by ASPs Improve Utilization and Outcomes?

Recommendation

26. In nursing homes and skilled nursing facilities, we suggest implementation of antibiotic stewardship strategies to decrease unnecessary use of antibiotics (good practice recommendation).

Comment: Implementing ASPs at nursing homes and

### Table 3. Possible Metrics for Evaluation of Interventions to Improve Antibiotic Use and Clinical Outcomes in Patients With Specific Infectious Diseases Syndromes

<table>
<thead>
<tr>
<th>Process Measures</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess days of therapy (ie, unnecessary days of therapy avoided based on accepted targets and benchmarks)*</td>
<td>Hospital length of stay 30-day mortality</td>
</tr>
<tr>
<td>Duration of therapy</td>
<td>Unplanned hospital readmission within 30 d</td>
</tr>
<tr>
<td>Proportion of patients compliant with facility-based guideline or treatment algorithm*</td>
<td>Proportion of patients diagnosed with hospital-acquired Clostridium difficile infection or other adverse event(s) related to antibiotic treatment*</td>
</tr>
<tr>
<td>Proportion of patients with revision of antibiotics based on microbiology data</td>
<td>Proportion of patients with clinical failure (eg, need to broaden therapy, recurrence of infection)</td>
</tr>
<tr>
<td>Proportion of patients converted to oral therapy</td>
<td></td>
</tr>
</tbody>
</table>

Sources: [190, 50–57, 189–191]

* These metrics are applicable for antibiotic stewardship program interventions to reduce antibiotic treatment of asymptomatic bacteriuria, which, in most cases, should not be treated; therefore, the other metrics do not apply.
skilled nursing facilities is important and must involve point-of-care providers to be successful. The traditional physician–pharmacist team may not be available on-site, and facilities might need to investigate other approaches to review and optimize antibiotic use, such as obtaining infectious diseases expertise through telemedicine consultation.

**Evidence Summary**
Nursing homes are significant reservoirs for multidrug-resistant organisms [199]. Developing approaches to improve antibiotic use is important; however, few studies have shown an impact on clinical outcomes.

Jump et al [200] reported a decrease in systemic antibiotic use by 30.1% (P < .001) and fewer positive C. difficile tests (P = .04) after initiating an infectious diseases consultation service at a single Veterans Affairs long-term care facility. The intervention included 24/7 consultation availability by telephone, with weekly on-site case review by an infectious diseases physician and a nurse practitioner. This model, however, may not be possible in many US nursing homes given resource restraints such as lack of finances, availability of an infectious diseases physician, and interest.

Schwartz et al [201] conducted an intervention that included physician education, guideline implementation, and presentation of local baseline antibiotic use data in a public long-term care facility with 20 salaried internists. Antibiotic starts decreased by 25.9%, and antibiotic DOTs decreased by 29.7%; those decreases were sustained for a 2-year follow-up period. This level of physician staffing, however, is not typical of most facilities.

Stewardship interventions inclusive of the nursing staff have been successful in reducing antibiotic use, but the effect on clinical outcome is not usually reported. Fleet et al [202] evaluated the impact of the Resident Antimicrobial Management Plan at 30 nursing homes in England. The nursing staff received written educational materials and used this tool to record compliance with good practice points at treatment initiation and 48–72 hours later. Antibiotic consumption over 12 weeks decreased by 4.9% (95% CI, 1.0%–8.6%; P = .02) in the intervention group and increased by 5.1% (95% CI, 2%–10.2%; P = .04) in the control group. Loeb et al [189] studied a multifaceted educational intervention for urinary tract infections that included a diagnostic and treatment algorithm at 24 nursing homes in Ontario, Canada and Idaho. Antibiotic use for suspected urinary tract infection was lower at intervention than at usual-care nursing homes (1.17 vs 1.59 courses per 1000 resident-days; weighted mean difference, −0.49; 95% CI, −0.93 to −0.06). Zimmerman et al [203] assessed a quality improvement program at 12 nursing homes in North Carolina. This multifaceted program consisted of guideline education for providers, sensitization to antibiotic prescribing matters for nursing staff and family members, and prescribing feedback for providers and nursing staff. Between baseline and follow-up at 9 months, prescription rates dropped more at intervention homes (13.16 vs 9.51 per 1000 resident-days) than at comparison homes (12.70 vs 11.80 per 1000 resident-days; pooled difference in differences, −2.75; P = .05).

**XXVI. In NICUs, do Antibiotic Stewardship Interventions Reduce Inappropriate Antibiotic Use and/or Resistance?**

**Recommendation**

27. We suggest implementation of antibiotic stewardship interventions to reduce inappropriate antibiotic use and/or resistance in the NICU (good practice recommendation).

**Evidence Summary**
Limited evidence is available to determine the most effective ASP strategies in the NICU, but general principles should apply [204]. Antibiotic policy and guidelines have been shown to be effective in the NICU [205]. After implementing a vancomycin guideline, Chiu et al [206] saw a 35% reduction in the initiation of vancomycin and a 65% overall decrease in exposure to vancomycin compared with the preimplementation period. Zingg et al [205] evaluated antibiotic use after initiating a policy to shorten antibiotic therapy for sepsis and coagulase-negative staphylococcal infection, and to stop preemptive treatment if blood cultures were negative. They found an overall 2.8% yearly reduction in antibiotic use (P < .001) without increasing mortality. Antibiotic restriction interventions can be successful in the NICU. For example, Murki et al [207] reported that restricting all cephalosporin classes was associated with a 22% decreased incidence of extended-spectrum β-lactamase–producing, gram-negative infections compared with the previous year (P = .03). The proportion of ampicillin use increased from 12.8% to 25.7% (P < .001) after the intervention, and the proportion of cephalosporin use declined from 15.8% to 3.0% (P < .001).

**XXVII. Should Antimicrobial Stewardship Programs Implement Interventions to Reduce Antibiotic Therapy in Terminally Ill Patients?**

**Recommendation**

28. In terminally ill patients, we suggest ASPs provide support to clinical care providers in decisions related to antibiotic treatment (good practice recommendation).

**Evidence Summary**
End of life is defined as the final days or weeks of life in patients under hospice care where the primary goals are managing symptoms, improving comfort, and optimizing quality of life—not prolonging survival. In contrast, palliative care is more general and can be pursued along with curative therapies.

Antibiotic use, frequently with multiple antibiotics, is common in patients with terminal cancer. Therapy is often continued after transition to comfort care and discontinued less than 1 day prior to death [208]. Patients with advanced dementia also have high exposure to antibiotics, especially in the weeks prior
to death [209]. Therefore, older adults with advanced dementia or who are in long-term care facilities [209] and patients receiving end-of-life treatment in the ICU [210] may become reservoirs for resistant bacteria. For example, end-of-life antibiotic treatment in the ICU was independently associated with acquisition of resistant bacteria in a logistic regression analysis [210].

For patients under hospice care, the impact of antibiotic therapy on symptom alleviation should be considered in the context of specific infections [208, 211]. For example, treating urinary tract infection may improve dysuria and treating thrush may improve dysphagia [211, 212], but the impact of antibiotics on the symptoms of respiratory tract infection is less clear [213–216]. Givens et al [213] reported that, compared with no antibiotic therapy, antibiotic treatment of suspected pneumonia in patients with advanced dementia via any route of administration was associated with improved survival but less comfort (P < .001 for all comparisons) as measured by the Symptom Management at End of Life Dementia scale. In contrast, antibiotic treatment of pneumonia in nursing home residents with dementia was associated with fewer symptoms in 2 Dutch studies. Van der Steen et al [214] reported that the level of discomfort was generally higher in patients for whom antibiotic therapy was withheld in nonsurvivors compared with surviving patients treated with antibiotics; however, those nonsurvivor patients had more discomfort before pneumonia developed. Subsequently, Van der Steen et al [215] reported fewer symptoms if pneumonia was treated with antibiotics rather than just fluids in patients with dementia even if death was imminent; the majority of patients received oral therapy. If prolonging survival is not a primary goal, withholding antibiotic agents should be considered. If treatment is desired, antibiotic agents should be administered orally whenever possible.

Patients and their surrogates should be engaged in the decision to use antibiotic agents at end of life. Stiel et al [217] reported that families of terminally ill cancer patients are often consulted about stopping antibiotics, but the decision to start therapy is usually made by clinicians without much discussion. Similarly, Givens et al [218] reported that most infectious episodes in nursing home residents with advanced dementia did not involve healthcare proxies in decision making.

Given significant treatment burdens, potential for adverse effects such as CDI, and public health risks, antibiotic therapy should be viewed as aggressive care in the end-of-life setting.

CONCLUSIONS

This guideline discusses a broad range of possible ASP interventions. We have emphasized the need for each site to assess its clinical needs and available resources and individualize its ASP with that assessment in mind.

A powerful way to support antibiotic stewardship is to improve the scientific basis for ASP interventions. As outlined in Section XIII, ASPs can successfully intervene to reduce the duration of therapy for many infections because well-constructed, randomized controlled clinical trials have demonstrated that clinical outcomes are equivalent. Rigorous published evidence is often needed to convince clinicians to alter well-established, albeit suboptimal, practice. For example, ASPs can cite high-quality data to reduce unnecessary antibiotic treatment of uncomplicated diverticulitis [219], or ASB (eg, in women 60 years or younger, diabetic patients, or the elderly) [220]. Additional clinical trials that incorporate consideration of antibiotic stewardship in their design are critically needed.

Another significant gap is the dearth of implementation research in this area [28]. Although the National Action Plan for Combating Antibiotic-Resistant Bacteria [6] will require the institution of ASPs across healthcare facilities, little effort and limited research funding have been allocated to study how best to achieve large-scale implementation. Qualitative assessments that can examine the impact of factors such as organizational culture, prescriber attitudes, and the self-efficacy of the antibiotic steward (ie, the extent to which he/she believes his/her goals can be reached) are lacking and are important to establish the context in which ASP implementation occurs [221, 222]. There is inadequate information on the best model for an ASP. For example, should stewards use the “bundle” approach that has been applied to ventilator-associated pneumonia [223] and central line–associated bloodstream infection with great success [224]? Although ASPs have studied application of a combination of interventions, they are not comparable to existing bundles because they require interpretation, expertise, and persuasion [225]. A new or adapted model for ASP is likely needed and best developed through application of rigorous implementation science.

Despite the recognition that much more research is needed, this guideline identifies core interventions for all ASPs as well as other interventions that can be implemented based on facility-specific assessments of need and resources. Every healthcare facility is able to perform stewardship, and institution of an ASP is attainable and of great importance to public health.

Notes

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Potential conflicts of interest. The following list is a reflection of what has been reported to IDSA. To provide thorough transparency, IDSA requires full disclosure of all relationships, regardless of relevancy to the guideline topic. Evaluation of such relationships as potential conflicts of interest is determined by a review process that includes assessment by the Standards and Practice Guidelines Committee (SPGC) chair, the SPGC liaison to the
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GUÍA PARA LA IMPLEMENTACIÓN DE UN PROGRAMA DE OPTIMIZACIÓN DE ANTIMICROBIANOS (PROA) A NIVEL HOSPITALARIO

COMITÉ DE ANTIMICROBIANOS PROA Y RESISTENCIA

ASOCIACIÓN PANAMERICANA DE INFECTOLOGÍA (API)

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| Dr. Gabriel Levy Hara | Glosario | 8 |
| Dr. Gabriel Levy Hara | Introducción | 10 |
| Dr. Gabriel Levy Hara | Aspectos organizativos para la implementación de un PROA | 11 |
| Dr. Gabriel Levy Hara | Definición e impacto del PROA | 14 |
| Dr. Gabriel Levy Hara | Estrategias de uso apropiado de antibióticos | 17 |
| Dr. Gabriel Levy Hara | Cuáles son los miembros que deben conformar el equipo del PROA | 18 |
| Dr. Gabriel Levy Hara | Objetivos e indicadores del PROA | 25 |
| Dr. Gabriel Levy Hara | Métricas para un PROA | 29 |
| Dr. Gabriel Levy Hara | Ventajas y desventajas de las métricas | 30 |
| Dr. Gabriel Levy Hara | Intervenciones educativas del PROA | 32 |
| Dr. Gabriel Levy Hara | El rol del laboratorio de microbiología en el PROA | 36 |
| Dr. Gabriel Levy Hara | Conceptos a incorporar en las Guías de Antimicrobianos del PROA | 50 |
| Dr. Gabriel Levy Hara | Principales barreras para el desarrollo de los PROA | 59 |
| Dra. MSc. MBA. PhD. Rodolfo Quirós | Conclusiones y recomendaciones | 62 |
| Dra. MSc. MBA. PhD. Rodolfo Quirós | Programa de optimización de antimicrobianos paso a paso | 63 |
| Dra. MSc. MBA. PhD. Rodolfo Quirós | Anexo 1: Pie de notas en el antiograma | 68 |
| Dra. MSc. MBA. PhD. Rodolfo Quirós | Anexo 2: Cómo utilizar de manera práctica la información obtenida de las pruebas de susceptibilidad dentro de un PROA | 72 |
| Dra. MSc. MBA. PhD. Rodolfo Quirós | Anexo 3: Ejemplo de manejo de Infección del Tracto Urinario (ITU) complicada en urgencias | 82 |
| Dra. MSc. MBA. PhD. Rodolfo Quirós | Lecturas recomendadas | 84 |
| Dr. MSc. MBA. PhD. Rodolfo Quirós | Medicina Interna - Infectología | 11 |
| Dr. MSc. MBA. PhD. Rodolfo Quirós | Gerente General Clínica Angel Foianini | 14 |
| Dr. MSc. MBA. PhD. Rodolfo Quirós | Santa Cruz de la Sierra - Bolivia | 17 |
| Dra. MSc. FIDSA. María Virginia Villegas | Cuáles son los miembros que deben conformar el equipo del PROA | 18 |
| Dra. MSc. FIDSA. María Virginia Villegas | Objetivos e indicadores del PROA | 25 |
| Dra. MSc. FIDSA. María Virginia Villegas | Métricas para un PROA | 29 |
| Dra. MSc. FIDSA. María Virginia Villegas | Ventajas y desventajas de las métricas | 30 |
| Dra. MSc. FIDSA. María Virginia Villegas | Intervenciones educativas del PROA | 32 |
| Dra. MSc. FIDSA. María Virginia Villegas | El rol del laboratorio de microbiología en el PROA | 36 |
| Dra. MSc. FIDSA. María Virginia Villegas | Conceptos a incorporar en las Guías de Antimicrobianos del PROA | 50 |
| Dra. MSc. FIDSA. María Virginia Villegas | Principales barreras para el desarrollo de los PROA | 59 |
| Dra. MSc. FIDSA. María Virginia Villegas | Conclusiones y recomendaciones | 62 |
| Dra. MSc. FIDSA. María Virginia Villegas | Programa de optimización de antimicrobianos paso a paso | 63 |
| Dra. MSc. FIDSA. María Virginia Villegas | Anexo 1: Pie de notas en el antiograma | 68 |
| Dra. MSc. FIDSA. María Virginia Villegas | Anexo 2: Cómo utilizar de manera práctica la información obtenida de las pruebas de susceptibilidad dentro de un PROA | 72 |
| Dra. MSc. FIDSA. María Virginia Villegas | Anexo 3: Ejemplo de manejo de Infección del Tracto Urinario (ITU) complicada en urgencias | 82 |
| Dra. MSc. FIDSA. María Virginia Villegas | Lecturas recomendadas | 84 |
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| Dra. MSc. FIDSA. María Virginia Villegas | Cali - Colombia | 18 |
| Dra. Msc. Jeannette Zurita | El rol del laboratorio de microbiología en el PROA | 36 |
| Dra. Msc. Jeannette Zurita | Conceptos a incorporar en las Guías de Antimicrobianos del PROA | 50 |
| Dra. Msc. Jeannette Zurita | Principales barreras para el desarrollo de los PROA | 59 |
| Dra. Msc. Jeannette Zurita | Lecturas recomendadas | 84 |
| Dra. Msc. Jeannette Zurita | Medicina Interna - Infectología | 11 |
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| Dra. Msc. Jeannette Zurita | Quito - Ecuador | 18 |
| Dra. Msc. Jeannette Zurita | Glosario | 8 |
| Dra. Msc. Jeannette Zurita | Introducción | 10 |
| Dra. Msc. Jeannette Zurita | Aspectos organizativos para la implementación de un PROA | 11 |
| Dra. Msc. Jeannette Zurita | Definición e impacto del PROA | 14 |
| Dra. Msc. Jeannette Zurita | Estrategias de uso apropiado de antibióticos | 17 |
| Dra. Msc. Jeannette Zurita | Cuáles son los miembros que deben conformar el equipo del PROA | 18 |
| Dra. Msc. Jeannette Zurita | Objetivos e indicadores del PROA | 25 |
| Dra. Msc. Jeannette Zurita | Métricas para un PROA | 29 |
| Dra. Msc. Jeannette Zurita | Ventajas y desventajas de las métricas | 30 |
| Dra. Msc. Jeannette Zurita | Intervenciones educativas del PROA | 32 |
| Dra. Msc. Jeannette Zurita | El rol del laboratorio de microbiología en el PROA | 36 |
| Dra. Msc. Jeannette Zurita | Conceptos a incorporar en las Guías de Antimicrobianos del PROA | 50 |
| Dra. Msc. Jeannette Zurita | Principales barreras para el desarrollo de los PROA | 59 |
| Dra. Msc. Jeannette Zurita | Conclusiones y recomendaciones | 62 |
| Dra. Msc. Jeannette Zurita | Programa de optimización de antimicrobianos paso a paso | 63 |
| Dra. Msc. Jeannette Zurita | Anexo 1: Pie de notas en el antiograma | 68 |
| Dra. Msc. Jeannette Zurita | Anexo 2: Cómo utilizar de manera práctica la información obtenida de las pruebas de susceptibilidad dentro de un PROA | 72 |
| Dra. Msc. Jeannette Zurita | Lecturas recomendadas | 84 |
**Antimicrobial Stewardship:** Traducido al español como ‘Programas de Optimización de uso de Antimicrobianos’ (PROA), es el conjunto de acciones enfocadas al uso seguro de antimicrobianos, incorporando conceptos como indicación correcta, dosis correcta, ruta de administración y duración correcta.

**Betalactamasas de espectro extendido (BLEEs):** Son enzimas capaces de conferir resistencia a las penicilinas, a todas las cefalosporinas y al aztreonam, pero no a los carbapenémicos ni a las cefamicinas y son inhibidas por el ácido clavulánico.

**Costo biológico (Fitness Cost):** Es el desgaste energético y/o metabólico que se genera en un microorganismo con la expresión de un mecanismo de resistencia. Su impacto se refleja en una disminución en la virulencia y en la tasa de multiplicación bacteriana.

**Desescalar:** Es la reducción del espectro antimicrobiano que se realiza como parte de la antibiótico terapia dirigida, una vez que se tienen los resultados de los cultivos. Este término incluye varios conceptos como terapia secuencial, si se pasa la misma molécula de su administración IV a su presentación oral, o el cambio a una molécula de otra familia de antimicrobianos con menor espectro, pero con sensibilidad confirmada por el antibiograma.

**Epidemiólogo hospitalario:** Es el profesional encargado de estudiar la distribución, la frecuencia, los factores predisponentes, las predicciones y el control de enfermedades a nivel hospitalario.

**Farmacéutico hospitalario:** Es el profesional que se ocupa de servir a la institución a través de la selección, preparación, adquisición, control, dispensación e información de los medicamentos y otras actividades orientadas a conseguir una utilización apropiada, segura y costo-efectiva de medicamentos y productos sanitarios.

**Fenotipo de resistencia antimicrobiana:** Es la expresión de un mecanismo molecular de resistencia antibiótica que se refleja en un antibiograma con un patrón determinado. Por ejemplo: BLEEs, metilasas, VanA, etc.

**Genotipo de resistencia antimicrobiana:** Es el gen o conjunto de genes que codifican un mecanismo de resistencia antimicrobiana particular. Por ejemplo, CTX-M codifica una BLEE, mecA codifica la PBP2a, MCR-1 codifica una fosfoetanolamina transferasa, etc.

**Grupos Relacionados por el Diagnóstico (GRD):** Constituyen un sistema de clasificación de pacientes que permite relacionar los distintos tipos de pacientes tratados en un hospital, con el coste que representa su asistencia.

**Maldi-Tof:** Es una técnica de identificación bacteriana a través de ionización utilizada en espectrometría de masas. Se denomina MALDI por sus siglas en inglés que se derivan de Matrix-Assisted Laser Desorption/Ionization (desorción/ionización láser asistida por matriz, en español) y TOF por el detector de iones que se acopla al MALDI y cuyo nombre procede también de sus siglas que en inglés hacen referencia a Time-Of-Flight.

**Médico hospitalario:** Es el profesional dedicado al cuidado comprehensivo de los pacientes hospitalizados. En otros países es conocido como médico tratante.

**Multirresistencia:** Es la resistencia a tres o más familias de antimicrobianos.

**Appraisal of Guidelines Research and Evaluation (AGREE):** Es una herramienta genérica diseñada principalmente para ayudar a productores y usuarios de guías de práctica clínica, en la evaluación de la calidad metodológica de estas.
El dramático aumento del uso de antibióticos en los hospitales es uno de los factores asociados al incremento de la resistencia bacteriana. Al mismo tiempo, la disponibilidad de nuevos antibióticos es cada día más limitada, dejando a los clínicos con muy pocas o con ninguna opción terapéutica.

Se ha reportado que entre el 30 al 50% del uso de antibióticos a nivel hospitalario es innecesario e inapropiado. El uso inadecuado de antibióticos conlleva a la selección de bacterias multirresistentes (MDR), las cuales se asocian a mayores días de hospitalización, mortalidad y costos.

La Sociedad Americana de Enfermedades Infecciosas (IDSA, por sus siglas en inglés) publicó unas guías en las que cataloga como necesario y urgente que todos los hospitales desarrollen un programa institucional de Antimicrobial Stewardship, que en español se podría traducir como Programas de Optimización de Antimicrobianos (PROA). Un PROA debe considerar varias intervenciones para reducir el uso inapropiado de antibióticos; para ello implementa la optimización en la selección del antibiótico, la dosis, ruta y duración de la terapia para maximizar la curación clínica o aun la prevención de la infección, así como para limitar las consecuencias indeseables de la terapia antibiótica, como son la emergencia de resistencia, efectos adversos y la selección de patógenos MDR.

**ASPECTOS ORGANIZATIVOS PARA LA IMPLEMENTACIÓN DE UN PROGRAMA PARA LA OPTIMIZACIÓN DEL USO DE ANTIMICROBIANOS A NIVEL INSTITUCIONAL**

**Nivel básico**
Conformación y nombramiento del equipo de antibióticos dependiente de la Comisión de Infecciones y Política Antibiótica, integrado al menos por especialistas en estas áreas: enfermedades infecciosas, farmacia hospitalaria y microbiología, con elección de sus miembros en función del liderazgo científico y profesional en el uso de antimicrobianos y las resistencias. Considerar la inclusión de especialistas en medicina intensiva, cirugía, pediatría y medicina preventiva.

Establecimiento de las funciones del equipo de antibióticos, que incluyen: el diseño del PROA adaptado al centro, institucionalización del programa, difusión a todos los profesionales implicados del centro, y seguimiento del mismo.

**Nivel intermedio**
Normalización de las actividades del equipo de antibióticos, actas de reuniones, presentación de informes y evaluación periódica de objetivos.

**Nivel avanzado**
Diseño de mapa de competencias para los distintos miembros necesarios en el equipo de antibióticos y acreditación de las actividades profesionales de los integrantes del equipo de antibióticos en sus actividades específicas. Acreditación en Calidad del PROA.
Institucionalización

Nivel básico
Aprobación del PROA por la Comisión de Infecciones y Política Antibiótica del centro, con apoyo explícito de la Dirección del hospital.

Nivel intermedio
Inclusión del PROA entre los objetivos estratégicos del hospital.

Nivel avanzado
Inclusión de incentivos ligados a objetivos del PROA para los distintos servicios asistenciales y los miembros del equipo de antibióticos.

Reursos técnicos y humanos

Nivel básico
Análisis detallado de las necesidades de recursos talento humano en función de las actividades y objetivos planteados.

Disponibilidad de profesionales para dedicar el tiempo de trabajo imprescindible según el análisis realizado para las actividades básicas del PROA. En caso de que exista necesidad de incrementar recursos humanos, establecer acuerdos con la Dirección del centro respecto a la redistribución de tareas de los profesionales de los servicios implicados y/o al aumento del número de profesionales.

Disponibilidad de un lugar para mantener las reuniones del equipo de antibióticos, contar con recursos informáticos y medios para la formación, así como posibilitar el acceso a bibliografía actualizada.

Accesibilidad a datos hospitalarios básicos necesarios para la medición de indicadores (estancias e ingresos totales y por servicios).

Para el área de microbiología, es necesario tener los insumos necesarios para la realización de informes periódicos de resistencias. En farmacia, se requieren los medios necesarios para el cálculo fiable de consumos de antimicrobianos y para la implantación de la prescripción electrónica generalizada.

Nivel intermedio
En cuanto al talento humano, se requiere disponer de profesionales para dedicar el tiempo de trabajo imprescindible, en función del análisis realizado para las actividades avanzadas del PROA.

Accesibilidad a datos hospitalarios para la medición de indicadores avanzados (estancia y mortalidad por GRD = grupos relacionados por el diagnóstico).

En microbiología se requieren los medios necesarios para la realización de informes periódicos de resistencias, incluyendo un aislamiento por paciente y diferenciado por tipos de servicios.

En farmacia se debe contar con el sistema de prescripción electrónica asistida con disponibilidad de alertas informáticas para alergias medicamentosas, duración de los tratamientos, riesgos de interacciones farmacológicas y fomento de la terapia secuencial.

Nivel avanzado
En cuanto a los recursos humanos, se requiere la disponibilidad de profesionales para dedicar el tiempo de trabajo imprescindible en función del análisis realizado para las actividades excelentes del PROA.

En microbiología, se debe contar con los medios necesarios para la realización de informes periódicos de incidencia de patógenos resistentes de interés según mecanismos de resistencia específicos y clonalidad.

En farmacia, se deben implementar sistemas de prescripción asistidos con consejo de ajuste de dosis según la función renal y/o hepática del paciente, el peso y los parámetros farmacocinéticos y farmacodinámicos.
DEFINICIÓN E IMPACTO DEL PROA

Los términos usados para referirse a un programa de optimización de antimi-crobianos PROA pueden variar considerablemente, encontrándose en la literatura las siguientes denominaciones: política de antibióticos, programas de control de antibióticos, manejo de antimi-crobianos y otros términos intercambiables. Cualquiera que sea el término, normalmente se refiere a un programa general que tiene el objetivo de cambiar y dirigir el uso de antimi-crobianos en las instituciones de salud. Para ello se han utilizado varias estrategias individuales, como se exponen en la Tabla 1.

En su concepto fundamental, el PROA se enfoca, entre otros, en el uso apropiado de antibióticos para ofrecer los mejores resultados clínicos, menores riesgos de efectos adversos, promover el costo-efectividad de la terapia, y reducir o estabilizar los niveles de resistencia bacteriana. La reducción de la selección de bacterias resistentes durante o al final del tratamiento, está asociada con resultados clínicos adversos y mayores costos, por lo que se ha convertido recientemen-te en una meta de gran importancia para cualquier PROA.

Cualquier antibiótico, utilizado apropiado o inapropiadamente, afectará la ecología bacteriana al ejercer presión selectiva y, por lo tanto, seleccionará resistencia en mayor o menor grado. Por ello, el uso de antibióticos se considera un factor determinante en la salud pública y difiere entonces de otros medicamentos.

En el caso de pacientes con infecciones severas, el PROA tiene mayor importancia ya que el clínico desconoce el agente etiológico y tendrá que escoger en forma empírica la mejor opción terapéutica. Una de las metas del programa será, entonces, impactar en la elección empírica en un antibiótico, que de lo contrario, existe una mayor morbi-mortalidad.

El desenlace de mayor sobrevida ha sido reportado en innumerables estudios. Para ello se requiere iniciar el tratamiento en el momento preciso, administrar las dosis apropiadas consistentes con los parámetros farmacocinéticos y farmacodinámicos (PK/PD), y realizar cambios en el tratamiento de acuerdo con la respuesta clínica y los resultados microbiológicos.

Otro predictor importante de la probabilidad de terapia inapropiada es la prevalencia local de resistencia. Los clínicos deberán conocer la epidemiología institucional por servicios, los patrones microbiológicos y la prevalencia de resistencia de acuerdo con el microorganismo, para poder alcanzar una mayor probabilidad de terapia apropiada.

Una vez los resultados microbiológicos y la información clínica están disponibles, el tratamiento deberá ser ajustado, generalmente reduciendo el espectro antimi-crobiano. Por ejemplo, de un antibiótico con espectro anti-*Pseudomonas* a otro que no tenga este espectro cuando el patógeno es una *Enterobacteriaceae*, o retirar la cobertura de Gram negativos cuando se documenta la presencia de Gram positivos como único agente etiológico.

La terapia de desescalaramiento, así como la certeza de la heterogeneidad del uso de los antibióticos, permitirán un balance entre el impacto del daño colateral (y de salud pública) y el beneficio para el paciente en forma individual. La creación de guías para su uso será un aporte valioso para los médicos y la institución, pero especialmente para el paciente.

Los beneficios significativos demostrados de los PROA son los siguientes:

- Reducción en un 20 a 50% en el uso de antimi-crobianos
- Reducción significativa en los costos, variable de acuerdo con el país y programa.
- Minimizar los efectos adversos a las drogas.
- Reducción de infecciones por *Clostridium difficile*. 

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GUÍA PARA LA IMPLEMENTACIÓN DE UN PROGRAMA DE OPTIMIZACIÓN DE ANTIMICROBIANOS (PROA) A NIVEL HOSPITALARIO
• Reducción de las infecciones asociadas al cuidado de la salud, debido al acortamiento de la internación.
• Minimizar las interacciones medicamentosas.
• Disminución de la resistencia antimicrobiana.

En el Anexo 3 se expone un ejemplo de flujograma para la toma de decisiones en el manejo de la infección del tracto urinario complicada, en la cual se incluyen conceptos como factores de riesgo para desarrollar una infección por organismos MDR, estratificación por severidad y desescalamiento.

<table>
<thead>
<tr>
<th>Estrategia</th>
<th>Procedimiento</th>
<th>Personal</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td><strong>Formularios/ Restricción</strong></td>
<td>Restringir la entrega de antimicrobianos seleccionados sólo para indicaciones aprobadas.</td>
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<tr>
<td><strong>Revisión y retroalimentación</strong></td>
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<td><strong>Asistencia computarizada</strong></td>
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<td>Comité de antimicrobianos para crear lineamientos en sistemas computarizados. Personal para aprobación o revisión (médicos, farmacéuticos) Programadores de sistemas.</td>
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**TABLA 1. Estrategias para el Uso Apropiado de Antibióticos**

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Una encuesta internacional que se desarrolló en los cinco continentes y fue publicada recientemente, mostró que –además de las estrategias globales señaladas en la Tabla 1– existen varias intervenciones que han sido adoptadas, la mayoría de ellas con éxito, por una alta proporción de los PROA a nivel global.

Las más utilizadas son la adaptación de guías de tratamiento y profilaxis quirúrgica a cada institución, el asesoramiento telefónico por infectólogo o microbiólogo y/o visita conjunta a los pacientes entre los dos especialistas señaladas en la Tabla 1.

¿CUÁLES SON LOS MIEMBROS QUE DEBEN CONFORMAR EL EQUIPO DE PROA?

Establecer un equipo multidisciplinario para el desarrollo de un PROA es esencial en la promoción de una atención segura a los pacientes. El liderazgo de un médico especialista en enfermedades infecciosas y un farmacéutico hospitalario con estudios en enfermedades infecciosas son elementos clave que, sumados a los representantes de los procesos asistenciales, al control de infecciones, a la seguridad del paciente y de la sección de calidad institucional, permitirán el adecuado desarrollo del PROA. En países con recursos económicos limitados, se deberán realizar ajustes en el diseño del programa debido a la ausencia de alguno de los actores principales para la ejecución del mismo. Sin embargo, estos ajustes no deberán afectar la formulación de estrategias, el establecimiento de metas y el compromiso multidisciplinario de las partes en la institución.

En las unidades de terapia intensiva es común tener especialistas en cuidados intensivos, cirujanos o farmacéuticos expertos en atención crítica, capaces de realizar las actividades operativas diarias de un PROA. En cualquier caso, esta presencia no debe reemplazar la responsabilidad y experiencia adicional de un equipo multidisciplinario dedicado a supervisar el uso de antimicrobianos en la institución, sino que –en forma sinérgica– debe trabajar día a día en conjunto, por ejemplo, mediante la visita a los pacientes o recorridos clínicos por parte de los involucrados en el PROA.

A continuación, se describen algunas de las funciones principales de cada uno de los miembros del equipo del PROA.

Especialista en enfermedades infecciosas
El médico especialista en enfermedades infecciosas es esencial para el PROA. Él deberá, dentro de sus funciones, establecer el liderazgo del diseño, implementación y evaluación del programa. El liderazgo del especialista en enfermedades infecciosas permite aumentar la aceptación y el cumplimiento del programa por otras especialidades clínicas, además de disminuir la percepción de que el PROA es principalmente un plan de ahorro de costos. Su trabajo deberá incluir actividades de coordinación y colaboración con el farmacéutico, microbiólogo clínico, epidemiólogos hospitalarios y la administración del hospital. Además deberá participar activamente durante las interconsultas, fomentar el desarrollo de jornadas educativas en el uso adecuado de antimicrobianos y motivar estrategias de investigación dentro de la institución. Es importante contar con un médico infectólogo con disponibilidad en la institución para proporcionar una guía clínica de apoyo operativo en el programa. Además, el especialista en enfermedades infecciosas tiene la función de establecer un consenso general respecto al contenido de las guías y directrices institucionales entre diferentes departamentos clínicos y especialidades.

Microbiólogos clínicos
El rol imprescindible del microbiólogo clínico será detallado en la siguiente sección. A modo de síntesis, este especialista proveerá al programa de elementos fundamentales como:

a) Un informe diario al médico prescriptor respecto de aislamientos bacterianos y antibiogramas, incluyendo los resultados preliminares, tanto de exámenes directos como de cultivos.
b) Aportará información actualizada –idealmente semestral– acerca de la resistencia en diferentes unidades del hospital. Esto permitirá actualizar las guías terapéuticas, definir los antimicrobianos cuya utilización deberá ser más estrictamente vigilada y los servicios asistenciales que requieren de un control más estricto.

c) De implementarse, el informe de antibiograma selectivo permitirá identificar la sensibilidad a determinados fármacos (más antiguos, de menor costo y/o con menor presión selectiva de resistencia). De este modo, el médico prescriptor no se verá “tentado a” utilizar drogas más costosas o de espectro más amplio sin necesidad.

**Farmacéutico hospitalario**

Se requiere la presencia de farmacéuticos hospitalarios. Idealmente, ellos debieran contar con un entrenamiento en el uso apropiado de antimicrobianos para establecer y mantener el PROA. Estos podrán realizar la mayoría de las actividades del día a día del programa, incluyendo la educación institucional en el uso adecuado de antimicrobianos según se definió en la guía de PROA. También podrían contribuir en el desarrollo de protocolos de terapia empírica dirigida desde la perspectiva de farmacodinamia y farmacocinética de los antimicrobianos, y retroalimentación a los equipos clínicos de atención. Otras actividades diarias importantes son la revisión previa y posterior a la prescripción, la revisión de casos complejos junto con el equipo del PROA, la asistencia a las reuniones educativas y las visitas en sala.

Sin embargo, necesitarán apoyo de un médico especialista en enfermedades infecciosas frente a decisiones clínicas en la interpretación de los reportes de laboratorio, hallazgos radiográficos, historial médico y exploración física de los pacientes. Los farmacéuticos generales podrán identificar casos de especial interés y comunicarlo al equipo del PROA.

Si el recurso del especialista en enfermedades infecciosas es limitado, el farmacéutico clínico podrá realizar actividades que permitan reducir costos, tales como recomendar la conversión de agentes intravenosos a orales, dosificación adecuada, duración del tratamiento, notificación al médico tratante respecto a múltiples antimicrobianos de espectro superpuesto en un mismo paciente. También podrían identificar las prescripciones de antimicrobianos para microorganismos que presenten una falsa susceptibilidad (*in vitro*) o resistencias naturales, así como la suspensión de tratamientos prolongados o la restricción del uso de ciertos antimicrobianos.

Otro papel que podría desempeñar es liderar procesos de auditorías como parte integral de los círculos de calidad, lo cual contribuye como herramienta educativa o como base para intervenciones que busquen mejorar las políticas de prescripción de antimicrobianos.

Adicionalmente, la presencia de un farmacéutico en los servicios de emergencias ofrece un valor agregado en la atención de los pacientes contribuyendo a las prácticas adecuadas de prescripción en tiempo real, la verificación de las prácticas de distribución y dispensación de medicamentos, como también la identificación de posibles interacciones medicamentosas durante la atención urgente.

**Epidemiólogo hospitalario**

El epidemiólogo hospitalario es un miembro importante del equipo multidisciplinario del PROA a nivel institucional. Como parte de sus funciones, deberá participar en la adaptación y/o el desarrollo de las guías que permitan estandarizar el manejo de los pacientes con profilaxis médica o quirúrgica así como también el tratamiento de las infecciones frecuentes, reduciendo la variabilidad observada. Para ello se deberán seguir las pautas establecidas por la institución para la adaptación de guías clínicas en cuanto a su fuente, el nivel de evidencia, la periodicidad de su revisión y la medición del nivel de adherencia a las mismas.
Además, el epidemiólogo hospitalario deberá tener bajo su responsabilidad el desarrollo de las métricas que permitan monitorear el cumplimiento de los objetivos del PROA. Para ello deberá interactuar con el área de Tecnología de la Información (Departamento de Sistemas) para identificar las fuentes de información necesarias para la elaboración de los indicadores. Una vez desarrollados, deberá asegurar la calidad de estos indicadores a través de estrategias de validación en conjunto con el área de Calidad de la institución. Como toda actividad vinculada a la mejora asistencial, deberá adherir a los procesos de mejora continua (Planificar, Ejecutar, Controlar, Ajustar).

Por último, el epidemiólogo hospitalario tendrá la responsabilidad de colaborar en el desarrollo de trabajos de investigación a partir de la información generada por el PROA. Esto permite consolidar las estrategias implementadas y contribuir al conocimiento médico general.

Durante la implementación del PROA, el comité de control de infecciones deberá fortalecer un conjunto de estrategias para la prevención y el control de la transmisión de microorganismos multirresistentes con el objetivo de lograr el impacto esperado. Dentro de estas estrategias están la vigilancia epidemiológica diaria de pacientes infectados, el cumplimiento de barreras de contacto y la higiene de manos. El equipo de control de infecciones debe generar escenarios que fortalezcan los canales de comunicación entre el laboratorio de microbiología y los médicos de la institución, para dar un especial énfasis en la importancia de ajustar los tratamientos antibióticos a los cultivos microbiológicos y alentar estrategias como desescalar, cuando se haya iniciado empíricamente una terapia antimicrobiana de amplio espectro. Los epidemiólogos hospitalarios pueden contribuir al programa con su experiencia en la vigilancia y el diseño de estudios que pueden ser útiles en el análisis de los hallazgos identificados durante la ejecución del PROA.

Otros profesionales de la salud que podrían ser convocados al PROA son:

**Médicos hospitalarios**

Incluir a médicos hospitalarios como apoyo en el desarrollo del PROA, permite que, en la primera línea de atención a los pacientes, exista una persona con total disponibilidad para explicar y aplicar los principios y prácticas del programa. Idealmente, debiera involucrarse en el PROA al menos un médico representante de las Unidades de Internación consideradas como clave (Emergencias, Terapia Intensiva, Medicina Interna, Cirugías, y otras, según las características particulares de la institución), de tal modo que se faciliten las interacciones entre el equipo. Un médico hospitalario puede participar en diferentes niveles dentro del PROA, desde la atención directa del paciente hasta la socialización de las guías de uso apropiado de los antimicrobianos con todas las especialidades, explicando los principios de una adecuada terapia empírica, el concepto de desescalar y la duración adecuada del tratamiento antibiótico a nivel individual. Su rol es determinante para alcanzar una adecuada implementación de las guías del programa, reducir la estancia hospitalaria e impactar en la disminución de los recursos y costos asociados a la atención. Los médicos hospitalarios deberán trabajar en forma coordinada con el infectólogo y consultar si existe discrepancia en el manejo de los antibióticos definidos en la guía institucional de uso apropiado de antimicrobianos. Su papel más importante es ayudar en la adherencia a estas guías y, por lo tanto, su entrenamiento y consenso deberá estar a cargo del infectólogo asignado al PROA.

**Rol de la enfermera en los Programas de Optimización de Antimicrobianos**

La participación de enfermeras líderes para el PROA en escenarios de atención crítica ha revelado que su labor permite el desarrollo de programas de educación que fortalezcan los conocimientos y prá-
ticas en el uso adecuado de los antimicrobianos, vigilando la duración de la administración de antimicrobianos por vía intravenosa. Su valor en estos programas radica en la mayor cantidad de tiempo que pasan junto al paciente y la capacidad de articular, en el escenario de atención, los conceptos de los riesgos del tratamiento con antimicrobianos intravenosos, así como los beneficios resultantes de la terapia secuencial. También juegan un papel definitivo en el fortalecimiento de estrategias de cuidados de la herida y prevención de la flebitis, campañas y seguimiento a la higiene de manos y barreras de contacto.

Generalmente, las enfermeras líderes de un PROA cumplen un rol destacado en la transformación de las prácticas inadecuadas dentro de un servicio hospitalario, y tienen además un gran potencial de influencia, incluso con más eficacia que las estrategias aisladas de educación ya que interactúan con médicos de diferentes especialidades.

**Rol del ambiente físico**

Si bien no forma parte activa de la vigilancia y evaluación de la pertinencia de los tratamientos antibióticos, la limpieza y desinfección del ambiente físico son fundamentales para evitar la transmisión cruzada de microorganismos. Las malas prácticas en limpieza y desinfección hospitalaria impiden que las tasas de resistencia antimicrobiana y de infecciones asociadas a la atención sanitaria disminuyan en el tiempo. Adicionalmente, la presencia de brotes por bacterias multirresistentes impacta en el consumo de antibióticos de amplio espectro que afectan a otras áreas de la institución.

**Rol del área administrativa**

Es poco probable que pueda aplicarse con éxito un PROA sin el aval de la gerencia o administración de la institución. El compromiso para la puesta en práctica de un PROA debe venir desde los niveles superiores de la administración del hospital y verse reflejado en la disponibilidad de invertir recursos para el adecuado desarrollo del programa. Si el apoyo administrativo es deficiente, la capacidad para cumplir con las recomendaciones de uso de antimicrobianos se verá afectada. La gerencia hospitalaria debe garantizar la disponibilidad de personal calificado y asegurar un espacio y un equipo adecuados de trabajo. También deberá analizar, conjuntamente con el equipo del PROA, los datos y recomendaciones durante las reuniones que definen las políticas hospitalarias.

La gerencia deberá poner a disposición del equipo de PROA tecnologías de la información en función de la gestión en el consumo de antimicrobianos, a través de la vinculación de los registros médicos de los pacientes con farmacia, laboratorio de microbiología y servicios clínicos. Finalmente facilitará la generación de estrategias para mejorar la prescripción de antimicrobianos, educación médica, auditoría y monitorización del cumplimiento de protocolos.

**OBJETIVOS E INDICADORES DE LOS PROA**

**Nivel básico**

El PROA debe especificar que sus objetivos genéricos son, en este orden: a) mejorar los resultados clínicos de los pacientes con infecciones; b) minimizar los efectos adversos asociados a la utilización de antimicrobianos (incluyendo aquí la aparición y diseminación de resistencias); y, c) garantizar la utilización de tratamientos costo-eficaces.

El PROA debe definir indicadores medibles tanto de proceso como de resultado, en función de los objetivos fijados, que permitan evaluar el grado de consecución de esas metas.

En una fase inicial, el PROA debe establecer como prioridad el conocimiento de la situación basal de los indicadores y su análisis para el establecimiento y priorización de los objetivos específicos, así como la elección de estándares externos en el consumo (por ejemplo, da-
tos de la red europea de vigilancia de consumo de antibióticos), resistencias (por ejemplo, datos de la red europea para la vigilancia de la resistencia antimicrobiana, considerando que estos datos son sólo de bacteriemias), calidad de prescripción y resultados clínicos.

La periodicidad (mensual, trimestral, semestral, etc.) con que deben recogerse los indicadores dependerá del propio indicador, del tamaño del centro o unidad y de las intervenciones implantadas.

En la medida de lo posible, los distintos indicadores de consumo de antimicrobianos y de resistencias se referirán a los mismos períodos de tiempo y unidades o servicios.

El indicador básico recomendado para medir el consumo de antimicrobianos es el número de dosis diarias definidas (DDD) por cada 100 estancias, medido en función del antimicrobiano dispensado. Este indicador debe ofrecerse para el consumo global de antimicrobianos y para el consumo de antimicrobianos por áreas (médicas, quirúrgicas y de medicina intensiva), y por subgrupos o subfamilias de antimicrobianos según su utilización clínica, e incluyendo además el consumo de antimicrobianos específicos en función de su mayor consumo o relevancia en cada situación.

Se debe elaborar informes periódicos acumulados de resistencia a antimicrobianos en función de los puntos de corte recomendados por CLSI o EUCAST, incluyendo un aislado por paciente, y clasificando los mismos en «extra hospitalarios» y «hospitalarios» (véase texto), y organizando de manera individual los de las Unidades de Cuidados Intensivos (UCI).

La selección de los microorganismos y mecanismos de resistencia, y los antibióticos para estos informes se realizarán de acuerdo con el equipo de control de infecciones.

El PROA definirá al menos un indicador de resultado clínico pronóstico de la antibioticoterapia medible en el centro.

Los indicadores deben remitirse regularmente a la Dirección del centro y al Comité de Infecciones y Política Antibiótica, o similar, con la realización de un informe reflexivo sobre los mismos. Esta información debe extenderse a todos los servicios del hospital.

**Nivel intermedio**

Una vez conocido el nivel de situación de partida, el PROA debe incluir objetivos específicos dentro de los genéricos, priorizados en función del análisis de la situación local.

De manera adicional al indicador del consumo de antimicrobianos en DDD/100 estancias se añade el de DDD/100 ingresos.

Los indicadores de consumo se deben medir también por grupos de antimicrobianos en función de indicaciones clínicas (anti-Pseudomonas, fármacos frente a Gram positivos resistentes, etc.).

Además de lo referido respecto a los informes de resistencia, se incluirá en estos la interpretación de fenotipos asociados a mecanismos de resistencia.

Se realizarán evaluaciones de calidad de prescripción de antimicrobianos mediante estudios transversales que permitan identificar áreas de intervención o el impacto de las mismas, al menos en unidades o situaciones específicas seleccionadas, basándose en la reflexión de datos de consumo, resistencia o datos clínicos.

Como referencia de calidad de prescripción, se utilizará el protocolo o guía del centro y, en su defecto, una guía clínica externa evaluada y adaptada a la situación epidemiológica local. Para la metodología, véase el texto.

Como indicadores de resultado, se incluirá al menos un indicador relacionado con efectos adversos y uno relacionado con el pronóstico de las infecciones tratadas con antibióticos.
**Nivel avanzado**

Se realizará un análisis periódico sobre el nivel de cumplimiento de los objetivos en función de los indicadores medidos. También se diseñarán planes de mejora y, en relación a estos, se plantearán nuevos objetivos.

La medición de DDD se realizará en función de los antimicrobianos administrados.

Adicionalmente, se medirán la dosis diaria prescrita (DDP) y los días de tratamiento (DDT), para unidades o antimicrobianos específicos.

A más de lo referido anteriormente respecto a los informes de resistencia, se redactarán informes en base a puntos de corte epidemiológicos (ECOFFs = epidemiological cut-off values, por sus siglas en inglés).

Se llevarán a cabo evaluaciones de calidad de prescripción de antimicrobianos, mediante estudios longitudinales que permitan la identificación de áreas de intervención o el impacto de las mismas, al menos en unidades o situaciones específicas seleccionadas según la reflexión de datos de consumo, resistencia o datos clínicos.

Como indicadores de resultado pronóstico, se incluirá al menos uno relacionado con efectos adversos y al menos dos relacionados con el pronóstico.

Los indicadores que se recomiendan en el PROA se encuentran en la Tabla 2 y las ventajas y desventajas de estas métricas se encuentran en la Tabla 3.

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**TABLA 2. Métricas para un programa de optimización de uso de antimicrobianos**

<table>
<thead>
<tr>
<th>Tipo de indicador</th>
<th>Indicador</th>
<th>Construcción del indicador</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consumo de antimicrobianos</strong></td>
<td>Dosis Diaria Definida (DDD)</td>
<td>Dosis Diarias Definidas (DDD) / 1000 días-paciente = gramos de un agente consumido en un período x 1000/DDD x Total de días-paciente del período.</td>
</tr>
<tr>
<td></td>
<td>Días de Tratamiento (DDT)</td>
<td>Días de Tratamiento (DDT) / 1000 días-paciente = días de tratamiento con un agente durante un periodo x 1000/Total de días-paciente del periodo.</td>
</tr>
<tr>
<td><strong>Gastos en antimicrobianos</strong></td>
<td>Gastos en antimicrobianos por paciente</td>
<td>Gasto total de antimicrobianos consumidos en un período / Total de días-paciente en ese periodo.</td>
</tr>
<tr>
<td></td>
<td>Gastos por DDD consumida</td>
<td>Gasto total de antimicrobianos consumidos en un periodo / DDD consumidas en ese periodo.</td>
</tr>
<tr>
<td><strong>Uso apropiado de antimicrobianos</strong></td>
<td>DDD inapropiadas</td>
<td>DDD inapropiadas / DDD consumidas.</td>
</tr>
<tr>
<td></td>
<td>Adherencia a guías clínicas</td>
<td>Indicaciones para una patología ajustadas a una guía clínica x 100 / Total de indicaciones para esa patología.</td>
</tr>
<tr>
<td></td>
<td>Desescalamiento</td>
<td>Desescalamentos realizados de tratamientos empíricos iniciales x 100 / Total de tratamientos empíricos indicados.</td>
</tr>
<tr>
<td></td>
<td>Rotación a vía oral</td>
<td>Tratamientos efectivamente rotados a vía oral x 100 / Totalidad de tratamientos que pueden ser rotados a vía oral.</td>
</tr>
<tr>
<td></td>
<td>Duración de tratamiento</td>
<td>Total de días de tratamiento para una patología dada / Total de casos tratados.</td>
</tr>
<tr>
<td></td>
<td>Profilaxis quirúrgica dentro de los 60 minutos</td>
<td>Profilaxis quirúrgicas administradas dentro de los 60 minutos prequirúrgicos x 100 / Total de cirugías requiriendo profilaxis.</td>
</tr>
<tr>
<td></td>
<td>Profilaxis quirúrgica suspendida dentro de las 24 horas post-operatorias</td>
<td>Profilaxis quirúrgicas suspendidas dentro de las 24 horas post-operatorias x 100 / Total de cirugías requiriendo profilaxis.</td>
</tr>
<tr>
<td><strong>Resultados</strong></td>
<td>Mortalidad hospitalaria</td>
<td>Egresos fallecidos por tipo de infección / Total de pacientes con esa infección.</td>
</tr>
<tr>
<td></td>
<td>Tiempo promedio de internación</td>
<td>Días de internación por tipo de infección / Total de pacientes con esa infección.</td>
</tr>
<tr>
<td></td>
<td>Readmisión hospitalaria a 30 días</td>
<td>Pacientes con infección readmitidos dentro de los 30 días post-alta / Total de pacientes egresados vivos con esa infección.</td>
</tr>
<tr>
<td></td>
<td>Infección por microorganismos resistentes a múltiples medicamentos (MDRO)</td>
<td>Número de infecciones no duplicadas por tipo MDRO en un período x 1000 / Total de días-paciente en ese periodo.</td>
</tr>
<tr>
<td></td>
<td>Infección por Clostridium difficile</td>
<td>Número de infecciones por Clostridium difficile de adquisición hospitalaria en un período x 1000 / Total de días-paciente en ese periodo.</td>
</tr>
</tbody>
</table>
### Estrategias asistidas por computador

Un PROA abarca muchas de las estrategias diseñadas para optimizar el uso de antibióticos en un entorno determinado, es decir, para evitar la falta de tratamiento de la infección y reducir al mínimo el uso excesivo de antibióticos que podrían contribuir a la selección de patógenos resistentes. Los métodos para la administración varían, pero, por lo general, puede ser clasificada como ‘persuasiva’ (provisión de la educación y la retroalimentación sobre el uso de los antibióticos) o ‘restrictiva’ (requiere la aprobación para el uso particular de un antibiótico).

Las computadoras se han vuelto cada vez más comunes en las instituciones médicas y pueden ser utilizadas para facilitar la aplicación de programas integrales de uso racional de antibióticos. La administración de antimicrobianos que incorpore programas de computador puede ser tan simple como vinculación de pautas antimicrobianas de la institución a la prescripción electrónica, o puede ser más sofisticada, como un sistema en el que se pueda incluir información de apoyo a la decisión tomada, que proporcione recomendaciones individualizadas a través de la alimentación al programa de diversos factores específicos del paciente.

Se han creado programas de computación que emiten una alerta cuando se prescribe una combinación de antibióticos que lleven a la superposición de espectros de actividad antimicrobiana. También hay programas que vinculan la información de los pacientes en los computadores, haciendo recomendaciones para el mejor régimen antimicrobiano, complementando con interacción de medicamentos y ajustando las dosis de acuerdo a la función renal o hepática o los antecedentes alérgicos del paciente. Estos programas han demostrado la disminución en reacciones alérgicas a los antibióticos, disminución en las dosis excesivas de los mismos y la disminución en la terapia inapropiada de acuerdo con la susceptibilidad antimicrobiana del microorganismo aislado en el paciente. También se han reportado reducciones significativas en los costos hospitalarios totales y la duración de la estancia hospitalaria.
Se debe resaltar que una vez que se establece el sistema, sigue siendo necesaria una vigilancia estrecha.

INTERVENCIONES EDUCATIVAS EN EL PROA

Nivel básico
Se debe establecer un programa formativo continuo en el uso de antibióticos, que sea evaluable y esté dirigido al menos a los prescriptores más relevantes, incluyendo especialistas en formación.

También es necesario priorizar las actividades encaminadas a la resolución de casos prácticos y la toma de decisiones.

Nivel intermedio
Se requiere evaluar las necesidades formativas de los prescriptores. Para ello, se debe llevar un registro de consultas sobre antibioterapia por los consultores y miembros del equipo de antibióticos. También es necesario realizar un análisis de los indicadores para el diseño de estrategias formativas.

Es importante lograr la acreditación del programa o programas formativos con obtención de créditos de formación. De igual manera, se deberían incluir actividades formativas en los objetivos individuales de las unidades y los especialistas del centro.

Se recomienda, asimismo, incorporar el programa de antibioterapia al plan de formación específica y obligatoria de especialistas en formación, mediante un acuerdo con el Comité de Docencia, o similar.

Nivel avanzado
Integrar herramientas de e-learning (educación virtual a distancia mediante canales electrónicos, utilizando aplicaciones digitales) para el fortalecimiento continuo del equipo.

Intervenciones restrictivas

Nivel básico
Es necesario desarrollar una guía fármaco-terapéutica que indique el procedimiento normalizado para la inclusión/exclusión de fármacos específicos para antimicrobianos. Este documento también debe incluir el informe del equipo de PROA.

Cualquier medida restrictiva para la indicación de fármacos debe haber sido explicada a los prescriptores, debe adaptarse a los protocolos del centro, tener la menor carga burocrática posible y ser razonablemente flexible. En ningún caso, las medidas restrictivas serán las únicas, ni serán priorizadas sobre las medidas de ayuda a la prescripción.

Para los antimicrobianos nuevos que tienen un costo muy alto o una alta toxicidad, podrían considerarse medidas restrictivas temporales. Se desaconseja emitir órdenes de suspensión automáticas (salvo en profilaxis quirúrgica) y la rotación cíclica de antibióticos, salvo en circunstancias excepcionales.

Nivel intermedio
Es importante mantener una evaluación periódica de los antibióticos y de las indicaciones incluidas en la guía fármaco-terapéutica del hospital.

De igual forma, se debe llevar a cabo una evaluación periódica del impacto positivo y negativo de las medidas restrictivas para fármacos concretos.

Deben considerarse medidas restrictivas temporales para determinados fármacos en determinadas situaciones epidemiológicas, que puedan ser de ayuda para el control de dicha situación.

Nivel avanzado
En esta fase, se requiere la disponibilidad del equipo de PROA durante las 24 horas del día, todos los días del año.
Medidas no impositivas de ayuda a la prescripción

Nivel básico
Para facilitar la prescripción de antimicrobianos, es necesario elaborar guías o protocolos locales de profilaxis, tratamiento empírico y tratamiento dirigido, basados en la adaptación de guías externas a la situación epidemiológica y las costumbres locales. Estos instrumentos se deben desarrollar con el consenso de los distintos servicios implicados y deben ser aprobados por el Comité de Infecciones, o similar.

Estos protocolos se deben revisar periódicamente (al menos cada dos años). Se requiere, además, la disponibilidad de infectólogos o expertos en el manejo clínico de enfermedades infecciosas y antibióterapia para consultoría.

Es necesario posibilitar el acceso informatizado a datos analíticos, microbiológicos y radiológicos de los pacientes en tiempo real.

Para el análisis de las tendencias locales en resistencia antimicrobiana, elaborar un informe interpretado según las normas estándarizadas establecidas por comités internacionales (CLSI, EUCAST) y promover que el laboratorio se encuentre adscrito a programas de control de calidad externo. Se requiere que los antibióticos a vigilar, hayan sido previamente discutidos y acordados por el comité de PROA. Los reportes deben estar debidamente documentados y con comentarios cuando proceda. Los comentarios deben tener sustento bibliográfico.

Otra medida importante es establecer procedimientos que garanticen la administración segura de los antimicrobianos, como por ejemplo: administración inmediata de la primera dosis del antibiótico una vez prescrito, cumplimiento de la pauta y dosificación de administración, evaluación de posibles alergias, compatibilidad de infusiones, tiempo de estabilidad de los fármacos.

Para la Unidad de Cuidados Intensivos, existen aspectos específicos que se deben tomar en cuenta. Principalmente, se requiere priorizar el seguimiento de protocolos y guías clínicas, desarrollar campañas formativas, enfatizar en la importancia de la toma de muestras antes de iniciar o cambiar la antibióterapia, necesidad de desescalar o ajustar el tratamiento con datos microbiológicos, y normalizar la consulta a enfermedades infecciosas.

Nivel intermedio
Evaluación permanente (mediante AGREE) de la calidad de las guías externas y la adaptación sistematizada de las mismas al entorno epidemiológico local para la elaboración de los protocolos locales.

Desarrollar un programa de auditorías con objetivos prefijados en unidades prescriptoras o en situaciones priorizadas o, de manera rotatoria, con evaluación de la prescripción y realización de recomendaciones no impositivas en tiempo real, previo acuerdo con los prescriptores.

Mantener programas activos de apoyo al manejo de determinados problemas, como las bacteriemias, microorganismos de difícil tratamiento, etc.

Contar con sistemas de alerta ante la disparidad entre sensibilidad y antibiótico prescrito, y dosificaciones potencialmente inadecuadas.

Emplear técnicas rápidas para la identificación de microorganismos resistentes que permitan la optimización precoz de tratamientos, cuando sean costo-efectivas.

Nivel avanzado
Mantener una evaluación periódica de las guías locales en cuanto a su grado de acierto en los tratamientos empíricos y sus resultados clínicos.

Desarrollar auditorías de prescripción en todo el hospital.
EL ROL DEL LABORATORIO DE MICROBIOLOGÍA EN EL PROA

El laboratorio de microbiología juega un papel fundamental en el desarrollo del programa de optimización de antibióticos. La información generada por el laboratorio no sólo es la base para la definición de una terapia individual, sino que permite generar los datos relacionados con las tasas de resistencia y los principales microorganismos involucrados en las infecciones. Esta información es relevante en la terapia empírica y en la aplicación de medidas de control de infecciones.

El laboratorio de microbiología es el responsable de proveer resultados de calidad. Para ello, debe facilitar la entrega oportuna de los mismos e implementar nuevas técnicas de diagnóstico que permitan la identificación rápida del agente etiológico y sus mecanismos de resistencia, especialmente la detección de β-lactamasas a través de pruebas confirmatorias debido al gran impacto epidemiológico de la transmisión. Dentro de las enzimas de mayor importancia a nivel clínico y epidemiológico están las β-lactamasas de espectro extendido (BLEE) y las carbapenemases.

Las BLEE pueden ser inhibidas por ácido clavulánico, mientras que las carbapenemases requieren otros inhibidores de acuerdo con el tipo de enzima. Por ejemplo, están las sustancias como el ácido borónico utilizado para la detección de carbapenemases tipo serina (como KPC) y el EDTA, SMA o Ácido Dipicolínico que permite la identificación de carbapenemases tipo metaloenzimas (como las VIM y NDM). Recientemente, la CLSI adoptó como método de referencia el test colorimétrico Carba NP que permite la identificación de carbapenemases por cambios en un indicador de pH cuando es hidrolizado el carbapenémico indicador (Imipenem). Este test muestra sensibilidad y especificidad >90% y la versión Carba NP II puede utilizarse para diferenciar carbapenemases en lugar de los métodos con inhibidores.

En general, entre los métodos diagnósticos utilizados para la detección de β-lactamasas, están la prueba de sinergia y la prueba de doble disco combinado. Los resultados de estas pruebas deben reportarse al médico en forma de pie de nota en el antibiograma, explicando el mecanismo de resistencia. También se podrá suprimir el reporte de antibióticos de amplio espectro cuando la bacteria encontrada sea sensible a los de espectro reducido; esto permitirá al clínico tomar mejores decisiones para una terapia adecuada. Las figuras 1 y 2 presentan ejemplos de los fenotipos asociados a este tipo de enzimas. En el Anexo 1 se puede encontrar información más detallada sobre las reglas de supresión para el reporte de antibióticos.

Otra de las responsabilidades del laboratorio dentro del programa de control de antibióticos, es la inclusión de recomendaciones para la adecuada toma de muestras y el envío de las mismas al laboratorio, de manera que puedan asegurar la calidad del resultado.

Finalmente, es muy importante mantener una buena comunicación con los médicos, ya que se deben considerar los resultados positivos dentro de un contexto clínico para evitar el tratamiento de pacientes con simples colonizaciones. A continuación, se presentan dos ejemplos con sugerencias para el reporte adecuado e interpretación terapéutica del resultado.
Guía para la implementación de un programa de optimización de antimicrobianos (PROA) a nivel hospitalario

Figura 1. Fenotipo asociado a la presencia de β-lactamasa de espectro extendido (BLEE) en aislamientos de Enterobacteriaceae

**Microorganismo:** Klebsiella pneumoniae
Tipo de muestra: Absceso intra-abdominal

<table>
<thead>
<tr>
<th>ANTIBIÓTICO</th>
<th>CIM</th>
<th>INTERPRETACIÓN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicilina/sulbactam</td>
<td>≥32</td>
<td>R</td>
</tr>
<tr>
<td>Piperacilina/tazobactam</td>
<td>≤16</td>
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</tr>
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<td>Cefazolina</td>
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</tr>
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<td>Aztreonam</td>
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</tr>
<tr>
<td>Ertapenem</td>
<td>≤0.5</td>
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</tr>
<tr>
<td>Imipenem</td>
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<td>S</td>
</tr>
<tr>
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<tr>
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<td>≤1</td>
<td>S</td>
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<tr>
<td>Ciprofloxacino</td>
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<td>R</td>
</tr>
<tr>
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</tr>
<tr>
<td>TMP/SMX</td>
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</tbody>
</table>

Interpretación del fenotipo en Figura 1: Se observa resistencia a las aminopenicilinas, cefalosporinas de todas las generaciones y aztreonam. Los carbapenémicos son estables a la acción de estas enzimas y en el ejemplo particular se muestra sensibilidad a piperacilina/tazobactam que dependerá del tipo genético de BLEEs (CTX-M es más sensible que otras familias de BLEE) y el grado de expresión de la enzima. Otras familias de antibióticos permanecen estables a la hidrólisis como colistina, tigeciclina y fosfomicina. Es frecuente encontrar corresponsidad con fluoroquinolonas y aminoglucósidos. Se recomienda indicar que el resultado de fosfomicina es para uso con fosfomicina disódica (IV).

Figura 2. Fenotipo asociado a la presencia de β-lactamasa de espectro extendido (BLEE) en aislamientos de Enterobacteriaceae

**Microorganismo:** Escherichia coli
Tipo de muestra: Orina

<table>
<thead>
<tr>
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<th>CIM</th>
<th>INTERPRETACIÓN</th>
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</tr>
<tr>
<td>Nitrofurantoina</td>
<td>≤32</td>
<td>S</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>≥64</td>
<td>R</td>
</tr>
</tbody>
</table>
Interpretación del fenotipo en Figura 2: Se observa resistencia a las aminopenicilinas, cefalosporinas de todas las generaciones y aztreonam. Aunque piperacilina/tazobactam muestra un resultado sensible, su uso en productoras de BLEE estará condicionado a infecciones urinarias sin impacto de sepsis grave o shock séptico y causadas por *Escherichia coli*. No se recomienda utilizarlo en *Klebsiella* productora de BLEE en ningún tipo de infección. Los carbapenémicos son estables a la acción de estas enzimas. Se debe considerar la posibilidad de resistencia cruzada con las fluoroquinolonas y el uso de levofloxacino está supeditado a la sensibilidad deciprrofloxacino, ya que es un mejor indicador de la presencia de mutaciones que pueden llevar a falla terapéutica. Es importante indicar que la interpretación de fosfomicina en aislamientos de infecciones urinarias bajas no complicadas está orientada hacia el uso de fosfomicina-trometamol (oral). No se recomienda el tamizaje de tigeciclina en aislamientos de orina por su escasa eliminación. Recomendaciones para la interpretación terapéutica del fenotipo asociado a la presencia de BLEE se encuentran en la tabla 4.

<table>
<thead>
<tr>
<th>Interpretación del fenotipo</th>
<th>Pruebas confirmatorias asociadas</th>
<th>Tratamiento de elección</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-lactamasa de espectro extendido</strong></td>
<td>Test de BLEE con ácido clavulánico.</td>
<td><strong>Carbapenémicos</strong>: (especialmente: <strong>tertapenem</strong> en pacientes no críticos y meropenem en pacientes con infecciones graves); <strong>Fluoroquinolonas</strong>: (si son sensibles y cuando la concentración inhibitoria mínima [CIM] sea ≤0.25ug/mL). <strong>Cefepima</strong> suele tener mayor resistencia a la hidrolisis por BLEE, por lo que puede ser una alternativa en infecciones graves cuando la CIM es ≤2µg/mL. No se recomienda su uso en infecciones moderadas a severas y/o cuando la CIM sea ≥4µg/mL. <strong>Piperacilina/tazobactam</strong> puede ser utilizada para el tratamiento de infecciones urinarias y bacteriemias con foco en orina o tejidos blandos, si la CIM es ≤4ug/mL. No se recomienda su uso en infecciones graves y se recomienda tener en cuenta la CIM del patógeno involucrado. <strong>Tigeciclina</strong>: Puede emplearse en infecciones mixtas intra-abdominales o de tejidos blandos. En infecciones moderadas a severas se recomienda su uso como parte de la terapia combinada. <strong>Fosfomicina</strong>: La presentación oral puede utilizarse para el manejo de ITU baja no complicada por bacterias productoras de BLEE.</td>
</tr>
</tbody>
</table>
Figura 3. Fenotipo asociado a la presencia de carbapenemasas tipo Serina (KPC-like) en aislamientos de Enterobacteriaceae

Microorganismo: Enterobacter cloacae
Tipo de muestra: Líquido pleural

<table>
<thead>
<tr>
<th>ANTIBIÓTICOS</th>
<th>CIM</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacina</td>
<td>≤ 16</td>
<td>S</td>
</tr>
<tr>
<td>Cefotaxima</td>
<td>≥ 64</td>
<td>R</td>
</tr>
<tr>
<td>Cefazidima</td>
<td>≥ 32</td>
<td>R</td>
</tr>
<tr>
<td>Ceftriaxona</td>
<td>≥ 64</td>
<td>R</td>
</tr>
<tr>
<td>Cefepima</td>
<td>16</td>
<td>R</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>≥ 32</td>
<td>R</td>
</tr>
<tr>
<td>Piperacilina/tazobactam</td>
<td>≥ 128</td>
<td>R</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>2</td>
<td>R</td>
</tr>
<tr>
<td>Imipenem</td>
<td>4</td>
<td>R</td>
</tr>
<tr>
<td>Meropenem</td>
<td>8</td>
<td>R</td>
</tr>
<tr>
<td>Doripenem</td>
<td>4</td>
<td>R</td>
</tr>
<tr>
<td>Ciprofloxacino</td>
<td>2</td>
<td>I</td>
</tr>
<tr>
<td>Fosfomicina</td>
<td>≤ 32</td>
<td>S</td>
</tr>
<tr>
<td>Polimixina B</td>
<td>≤ 2</td>
<td>S</td>
</tr>
<tr>
<td>Tigeciclina</td>
<td>2</td>
<td>S</td>
</tr>
</tbody>
</table>

Interpretación del fenotipo en Figura 3: En este ejemplo típico de una KPC, se observa resistencia a betalactámicos con inhibidores, todas las cefalosporinas y carbapenémicos. Aztreonam es hidrolizado por la carbapenemasa y se observa resistente. Polimixina B, tigeciclina y fosfomicina permanecen estables a la acción de esta enzima teniendo en cuenta que pertenecen a familias diferentes de antimicrobianos. Es importante enfatizar que el perfil hidrolítico de las KPC es variable y pueden presentarse resultados inclusivo con sensibilidad a los carbapenémicos y cefepime; por lo cual su detección es crítica para frenar su diseminación y hacer un abordaje terapéutico adecuado.

Figura 4. Fenotipo asociado a la presencia de carbapenemasas tipo Metalo-Carbanemasa MBL (VIM, NDM, etc.) en aislamientos de Enterobacteriaceae

Microorganismo: Providencia rettgeri
Tipo de muestra: Herida quirúrgica

<table>
<thead>
<tr>
<th>ANTIBIÓTICOS</th>
<th>CIM</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacina</td>
<td>≤ 16</td>
<td>S</td>
</tr>
<tr>
<td>Cefotaxima</td>
<td>≥ 64</td>
<td>R</td>
</tr>
<tr>
<td>Cefazidima</td>
<td>≥ 32</td>
<td>R</td>
</tr>
<tr>
<td>Ceftriaxona</td>
<td>≥ 64</td>
<td>R</td>
</tr>
<tr>
<td>Cefepima</td>
<td>16</td>
<td>R</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>≤ 4</td>
<td>S</td>
</tr>
<tr>
<td>Piperacilina/tazobactam</td>
<td>≥ 128</td>
<td>R</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>2</td>
<td>R</td>
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<td>4</td>
<td>R</td>
</tr>
<tr>
<td>Meropenem</td>
<td>8</td>
<td>R</td>
</tr>
<tr>
<td>Doripenem</td>
<td>4</td>
<td>R</td>
</tr>
<tr>
<td>Ciprofloxacino</td>
<td>2</td>
<td>I</td>
</tr>
<tr>
<td>Fosfomicina</td>
<td>≤ 32</td>
<td>S</td>
</tr>
</tbody>
</table>

Interpretación del fenotipo en Figura 4: En este ejemplo, se observa resistencia a betalactámicos con inhibidores, todas las cefalosporinas y carbapenémicos. Aztreonam no es un sustrato de las MBL, por lo cual permanece estable y puede ser una opción terapéutica como parte de la terapia combinada. Fosfomicina y amikacina permanecen estables a la acción de esta enzima. Interpretación del fenotipo asociado a la presencia de una carbapenemasa se encuentra en la Tabla 5.
TABLA 5. Interpretación del fenotipo asociado a la presencia de una carbapenemasa

<table>
<thead>
<tr>
<th>Interpretación del fenotipo</th>
<th>Pruebas confirmatorias asociadas</th>
<th>Pie de nota</th>
<th>Tratamiento de elección</th>
</tr>
</thead>
<tbody>
<tr>
<td>Producción de Carbapenemasa</td>
<td>• Test de Hodge modificado</td>
<td>“Resultados consistentes con la producción de carbapenemasa. Se sugiere aislamiento de contacto e interconsulta por infectólogo”.</td>
<td>Se debe dar siempre terapia combinada y considerar de acuerdo con la CIM la asociación de carbapenémicos del grupo 2 (meropenem o doripenem) a dosis altas e infusión prolongada con polimixina B o colistina y/o aminoglucósido y/o aminoglicósido o el antibiótico que sea reportado como sensible. En infecciones por MBL, si es sensible, aztreonam podría ser parte de la terapia combinada con polimixina B. En algunas carbapenemadas, cefepime puede tener resultados sensibles o sensible dosis dependiente (SDD), sin embargo, no se recomienda su uso porque es afectado por el inoculo bacteriano y hay riesgo de falla terapéutica.</td>
</tr>
<tr>
<td></td>
<td>• DDC/SDD con ácido borónico y EDTA/SMA</td>
<td></td>
<td>Se debe dar siempre terapia combinada y considerar de acuerdo con la CIM la asociación de carbapenémicos del grupo 2 (meropenem o doripenem) a dosis altas e infusión prolongada con polimixina B o colistina y/o aminoglucósido o el antibiótico que sea reportado como sensible. En infecciones por MBL, si es sensible, aztreonam podría ser parte de la terapia combinada con polimixina B. En algunas carbapenemadas, cefepime puede tener resultados sensibles o sensible dosis dependiente (SDD), sin embargo, no se recomienda su uso porque es afectado por el inoculo bacteriano y hay riesgo de falla terapéutica.</td>
</tr>
<tr>
<td></td>
<td>• Carba NP</td>
<td></td>
<td>Se debe dar siempre terapia combinada y considerar de acuerdo con la CIM la asociación de carbapenémicos del grupo 2 (meropenem o doripenem) a dosis altas e infusión prolongada con polimixina B o colistina y/o aminoglucósido o el antibiótico que sea reportado como sensible. En infecciones por MBL, si es sensible, aztreonam podría ser parte de la terapia combinada con polimixina B. En algunas carbapenemadas, cefepime puede tener resultados sensibles o sensible dosis dependiente (SDD), sin embargo, no se recomienda su uso porque es afectado por el inoculo bacteriano y hay riesgo de falla terapéutica.</td>
</tr>
<tr>
<td></td>
<td>• Blue Carba</td>
<td></td>
<td>Se debe dar siempre terapia combinada y considerar de acuerdo con la CIM la asociación de carbapenémicos del grupo 2 (meropenem o doripenem) a dosis altas e infusión prolongada con polimixina B o colistina y/o aminoglucósido o el antibiótico que sea reportado como sensible. En infecciones por MBL, si es sensible, aztreonam podría ser parte de la terapia combinada con polimixina B. En algunas carbapenemadas, cefepime puede tener resultados sensibles o sensible dosis dependiente (SDD), sin embargo, no se recomienda su uso porque es afectado por el inoculo bacteriano y hay riesgo de falla terapéutica.</td>
</tr>
<tr>
<td></td>
<td>• Test de inactivación del carbapenémico</td>
<td></td>
<td>Se debe dar siempre terapia combinada y considerar de acuerdo con la CIM la asociación de carbapenémicos del grupo 2 (meropenem o doripenem) a dosis altas e infusión prolongada con polimixina B o colistina y/o aminoglucósido o el antibiótico que sea reportado como sensible. En infecciones por MBL, si es sensible, aztreonam podría ser parte de la terapia combinada con polimixina B. En algunas carbapenemadas, cefepime puede tener resultados sensibles o sensible dosis dependiente (SDD), sin embargo, no se recomienda su uso porque es afectado por el inoculo bacteriano y hay riesgo de falla terapéutica.</td>
</tr>
</tbody>
</table>

Recomendaciones para el tamizaje de polimixinas y circulación del gen mcr-1

Las polimixinas (colistina y polimixina B), son antibióticos catiónicos utilizados a nivel hospitalario para el manejo de infecciones por bacilos Gram negativos multi-resistentes, fundamentalmente productores de carbapenemases. Estas moléculas interactúan con el lípido A del lipopolisacárido (LPS) de membrana, generando su desestabilización y posterior muerte celular. Algunas especies presentan resistencia intrínseca a las polimixinas como son (Proteus, Providencia, Serratia, Morganella, Edwardsiella, Burkholderia). En especies diferentes la resistencia se desarrolla principalmente por mutaciones en el LPS que generan cambios en la carga eléctrica del mismo generando repulsión a las polimixinas. Recientemente se ha descrito la circulación de un gen conocido como mcr-1 por “Mobile Colistin-Resistance” que codifica para una fosfoetanolamina transferasa que modifica el lípido A del LPS generando resistencia a las polimixinas. Este gen, que inicialmente fue descrito en plásmidos circulantes en el sudeste Asiático y detectado fundamentalmente en aislados de E. coli de origen animal. Sin embargo también se ha reportado este hallazgo en aislados de humanos y fue recientemente encontrado en América Latina (Argentina, Ecuador y Colombia). Los reportes indican que la circulación de este gen ha circulado por el mundo por más 30 años, lo que muestra que no es un fenómeno realmente nuevo. Se desconoce la razón por la cual su diseminación en especies diferentes a E. coli no ha sido tan exitosa como para otros mecanismos de resistencia pero que merece ser vigilado. Los autores de este documento realizan las siguientes sugerencias para el tamizaje y vigilancia de este nuevo determinante de resistencia:

- Realizar el tamizaje de colistina por el método de microdilución en caldo. No se recomienda utilizar disco difusión o método de gradiente ya que se han reportado errores muy graves (falsos sensibles) con el uso de estos métodos.
- Reportar los resultados de colistina en infecciones por bacilos Gram negativos multi-resistentes. Principalmente productores de carbapenemases.
- Controlar los resultados de las pruebas de susceptibilidad para colistina mediante el uso de cepas de referencia ATCC. Promover que el laboratorio se encuentre adscrito a un programa de control externo de la calidad.
- Utilizar un punto de corte de sensibilidad a la colistina ≤ 2µg/ml para todos los Gram negativos (incluyendo no fermentadores de lactosa).
• Para la vigilancia de mcr-1 en *Enterobacteriaceae* se sugiere utilizar un punto de corte ≥ 4µg/ml para considerar la realización de pruebas moleculares (PCR) en un laboratorio de referencia.

• En hospitales que utilizan polimixina B, un resultado de sensibilidad a la colistina puede extrapolarse para este antibiótico, ya que no existen mecanismos de resistencia diferenciales entre las dos polimixinas.

• En *Enterobacteriaceae* resistentes a colistina (principalmente *Klebsiella* y *Enterobacter*) se sugiere implementar precauciones de contacto hasta que los resultados moleculares descarten la presencia de mcr-1. Si el microorganismo produce simultáneamente carbapenemasas, se sugiere continuar con las precauciones de contacto hasta el egreso del paciente.

• Aunque se ha descrito la presencia de mcr-1 en aislados de *Salmonella*, colistina no se encuentra indicado para el tamizaje primario, ni para el manejo inicial de los pacientes con infecciones por Salmonella. Se sugiere contactar a su laboratorio nacional de referencia para las indicaciones del caso.

Para entregar resultados oportunos y precisos es necesario establecer procedimientos de buenas prácticas para la evaluación microbiológica rápida.

En la última década ha aparecido una pléyora de pruebas diagnósticas sin precedentes que sirven tanto para la identificación de los microorganismos como para la detección de marcadores genéticos de resistencia. Por lo que las pruebas microbiológicas deben ser realizadas y supervisadas por una persona experimentada, calificada en microbiología o su equivalente. Como recomienda la Organización Panamericana de la Salud, el personal debe tener entrenamiento básico en microbiología y experiencia práctica relevante antes de ser autorizado para realizar ensayos microbiológicos. Aunque, en general, las técnicas rápidas proteómicas y moleculares, que ayudan en la toma de decisiones terapéuticas y epidemiológicas, no están al alcance de todos los laboratorios; en otros países fuera de América Latina, han demostrado mucha utilidad en los PROA. Estas son:

1. PNA-FISH
2. MALDI-TOF
3. Gene Xpert®
4. FilmArray®
5. PCR/ESI-MS
6. Secuenciación del genoma completo
7. PCR en tiempo real (RT-PCR)
8. PCR

Como la mayoría de estas tecnologías no se han implementado en la rutina de muchos de los laboratorios asistenciales y por el momento únicamente están disponibles en laboratorios de referencia, y teniendo en cuenta que se requiere un resultado rápido y a tiempo, las pruebas rápidas que se pueden utilizar este momento son:

   1. La coloración clásica de Gram
   2. Medios de cultivo cromogénicos
   3. Aglutinación en látex
   4. Antígenos en orina
   5. Blue Carba/Carba NP
   6. Pruebas de sinergia por difusión con disco

En sus reportes, el servicio de microbiología debe incluir comentarios a manera de pie de nota, que le ayuden al clínico a interpretar el significado de los aislamientos, la susceptibilidad y algunas advertencias de manejo.

Si el laboratorio incluye opiniones, comentarios e interpretaciones de los resultados de las pruebas realizadas en la identificación y sensibilidad, estos deben ser realizados por personal autorizado con
experiencia adecuada y conocimientos relevantes de la aplicación específica incluyendo; por ejemplo, requisitos regulatorios y tecnológicos y criterios de aceptación (OPS, CLSI, EUCAST, CLIA, CAP). Además estas recomendaciones deben ser discutidas al interior del Comité de Infecciones en el que participan los integrantes del PROA. Es importante prestar atención particularmente a servicios como UCI y Urgencias que pueden impactar en otras áreas del hospital; por ejemplo, en la generación de brotes. Para ello es necesaria una comunicación permanente entre el microbiólogo, los médicos y/o enfermeras de estos servicios.

Recomendaciones de buenas prácticas en microbiología

- Mantener un antibiograma acumulativo semestral y anual, que indique patrones de susceptibilidad para patógenos “clave” por servicios de la institución.
- Mejorar las prácticas para tests diagnósticos de infecciones por patógenos más prevalentes.
- Incorporar pruebas rápidas para apoyar el diagnóstico.
- Contar con personal entrenado para interpretar la coloración de Gram. Instaurar pruebas de acuerdo con su capacidad y patógenos prevalentes.
- Posibilitar la consulta al servicio de microbiología en elección, naturaleza y manejo de especímenes para diagnóstico (especialmente en casos en los que el diagnóstico diferencial es amplio).
- Informar directamente al clínico cuando se detectan bacteriemias, fungemias, infecciones meníngeas o infecciones causadas por microorganismos multirresistentes.

Para apoyar el PROA, se sugiere que los Laboratorios de Microbiología realicen las siguientes funciones de acuerdo con experiencias internacionales exitosas:

- Proveer un servicio de microbiología de emergencia que cubra un horario extendido, fuera de la jornada regular.
- Examinar diariamente y generar informes preliminares de los hemocultivos.
- Proporcionar a los médicos los datos de las pruebas de sensibilidad a los antibióticos a para orientar el tratamiento empírico y dirigido.
- Aplicar reglas de supresión e interpretación para antibióticos restringidos por el comité del PROA.
- Incluir comentarios a pie de nota en los reportes, para apoyar un uso racional de los antimicrobianos.
- Participar de las rondas diarias del microbiólogo clínico / infectólogo por las salas o viceversa (el infectólogo visita al laboratorio), para asesorar sobre pruebas diagnósticas e interpretación de las pruebas de susceptibilidad.

Uso del Software Whonet®

Whonet® es un programa para el manejo de bases de datos y la administración de los resultados del laboratorio de microbiología. Los principales objetivos del programa son:

- Optimizar el uso local de los datos del laboratorio.
- Promover la colaboración entre diferentes centros a través del intercambio de datos.

El programa fue diseñado para la administración de los resultados de rutina del laboratorio, pero también ha sido usado para alimentar estudios de investigación. El desarrollo del programa se ha enfocado en el análisis de datos, particularmente de los resultados de las pruebas de sensibilidad y resistencia a antibióticos.
Las herramientas analíticas de Whonet® pueden facilitar:
- La selección de agentes antibacterianos.
- La identificación de brotes intrahospitalarios.
- La detección de problemas de control de calidad. Analizar la distribución de las CIM de los antimicrobianos por especie (ver ejemplos en el manual).

Además de examinar la resistencia a antibióticos, permite identificar:
- Mecanismos de resistencia.
- La epidemiología de cepas resistentes.

Para descargar el aplicativo así como los manuales de instalación y uso, puede consultar la siguiente dirección: http://www.who.int/drugresistance/whonetsoftware/en/#

CONCEPTOS INDISPENSABLES PARA LAS GUÍAS ANTIMICROBIANAS DEL PROA

La dosis diaria definida (DDD), como se verá más adelante, se refiere a la medición de un antimicrobiano concreto, a través de una fórmula, para calcular el consumo de este antibiótico a nivel hospitalario. Esta medición se ha considerado útil para el estudio de las tendencias de consumo de los antibióticos en hospitales, con el objetivo de obtener una serie de indicadores estandarizados que se utilizan para efectuar comparaciones sobre el uso de antibióticos entre distintas instituciones y países.

El conocimiento de las tendencias de resistencia que proporciona regularmente el laboratorio permitirá planear el uso de ciertos antibióticos para disminuir la presión selectiva. Aunque se ha reportado que la disminución del uso de un antimicrobiano, en un contexto donde existe ya el mecanismo de resistencia específico para este antibiótico (ej.: el uso de ceftriaxona y la selección de BLEE), se asocia a una reducción en las tasas de resistencia al mismo; en muchas otras situaciones, el efecto es limitado debido a la co-resistencia o al bajo costo biológico del mecanismo implicado. Por ello es muy importante conocer qué mecanismos son prevalentes y cuáles podrían aparecer con el uso indiscriminado de ciertos antibióticos que tienen mayor presión selectiva, para hacer una planeación ponderada de los antibióticos en cada situación clínica. De la heterogeneidad del uso de ellos, por bacteria y patología, probablemente se logre un mejor control de la resistencia bacteriana.

El papel de la presión antibiótica selectiva y el desarrollo de la resistencia bacteriana.

La sola exposición bacteriana a los antibióticos no determina directamente la aparición de resistencia sino que causa la eliminación de bacterias sensibles, permitiendo la proliferación de organismos resistentes de una subpoblación preexistente. Por otro lado, se han visto mutaciones espontáneas que aparecen durante la replicación del ADN o a través de la adquisición horizontal de genes de otra bacteria. Las bacterias también pueden contener genes “pre-resistentes”, los cuales confieren bajo nivel de resistencia, pero le permiten a la bacteria sobrevivir a concentraciones subterapéuticas de antibióticos.

Dentro de una población bacteriana, algunas bacterias pueden sobrevivir (persistiendo) a las condiciones letales del antibiótico; se comportan como seres inactivos, incapaces de crecer en la presencia del antibiótico, pero reasumiendo su función metabólica cuando desaparece el antibiótico. Estas bacterias son fuente de acumulación de mutaciones o de la adquisición de elementos resistentes. Por ello se considera que la concentración del antibiótico en el medio donde la bacteria está presente es de crítica importancia en términos de selección de resistencia, ya que concentraciones sub-inhibitorias pueden seleccionar recombinaciones genéticas, aumentando la tasa de transferencia entre bacterias. Esta transferencia genética se da a través de elementos genéticos móviles.
En el ambiente clínico, la selección de un organismo resistente es un proceso complejo que no se explica únicamente por la presión directa que ejerce el antibiótico per se. Es importante considerar el fenómeno de co-resistencia, en el cual el uso de un antibiótico conlleva a la resistencia de otra clase totalmente diferente de antibiótico(s). Ejemplos claros de este fenómeno son los antibióticos anti-anaerobios, la colonización por *Enterococcus* resistente a glucopéptidos o el efecto de muchos antibióticos que permiten la infección por *Clostridium difficile*.

También debe tenerse en cuenta que el uso de antibióticos en animales y en el medio ambiente ha generado reservorios de genes resistentes que posteriormente se transmiten al humano.

**El costo biológico de la resistencia bacteriana**

Es también interesante considerar la noción de costo biológico o ‘fitness-cost’. Este concepto está enfocado en la posibilidad de que la resistencia bacteriana impone un costo para la replicación de viabilidad del microorganismo por la carga energética necesaria para mantener el mecanismo de resistencia. En estos casos, cuando el antibiótico es removido, desaparece su presión selectiva, por lo que la cepa resistente será reemplazada por una sensible. Sin embargo, si el costo biológico es mínimo, la bacteria resistente no será reemplazada por la sensible y este bajo costo biológico podría ser una explicación parcial de algunos estudios ecológicos en los que persiste la resistencia o reaparece.

Por otro lado, se ha reportado resistencia antimicrobiana mucho antes de la introducción de un antibiótico. Ejemplo de esto son los reportes de bacterias resistentes en la Antártica, donde la exposición de las bacterias a antibióticos es improbable. Por tanto, la resistencia antimicrobiana puede ser parte integral de la evolución bacteriana y su selección se ha vuelto exponencial con el uso de antibióticos.

**La importancia de la inducción vs. la selección de resistencia**

Algunos de los mecanismos de resistencia reportados en bacterias Gram negativas son: la producción de enzimas que inactivan un grupo importante de antibióticos (como β-lactámicos, quinolonas y aminoglicósidos, entre otros); la alteración del sitio de unión del antibiótico; la activación de las bombas de expulsión y la baja regulación o modificación de las porinas en la membrana externa. De todos los mecanismos descritos, la producción de β-lactamasas es el más prevalente en la actualidad y el de mayor impacto epidemiológico, clínico y terapéutico.

Para entender cómo opera la resistencia antibiótica es importante diferenciar entre inducción y selección de resistencia.

**Inducción** es la activación de un gen resistente resultando en la producción de β-lactamasas. Por ejemplo, cuando una bacteria como *Enterobacter cloacae* es expuesta a un inductor como imipenem, el gen AmpC, que codifica para la producción de esta enzima, se activa generando una alta producción de la β-lactamasa AmpC. Sin embargo, es un fenómeno temporal ya que no ha ocurrido una mutación. Por eso cuando el inductor es removido, la producción de la β-lactamasa inducida se suspende, y la cantidad de β-lactamasa en el espacio periplásmico cae a su nivel basal en más o menos seis u ocho horas. Además, como imipenem es muy estable a la presencia de AmpC, puede eliminar la bacteria, aunque ella produzca la enzima. De tal forma que la bacteria muere y no se selecciona. En contraste, selección es cuando un antibiótico elimina las bacterias con un fenotipo silvestre (‘wild type’) que tiene baja producción de β-lactamasas, pero no elimina a las mutantes hiperproductoras de esta β-lactamasa. Por otro lado, en una población de organismos, las mutaciones ocurren a una baja frecuencia (~1x10⁻⁷-1x10⁻⁸), pero pueden llevar a que las bacterias de fenotipo silvestre inicien la producción de grandes cantidades de β-lactamasa (sin la necesidad de un inductor) y su producción se vuelve constitutiva.
Muchos antibióticos β-lactámicos como las penicilinas y cefalosporinas (a diferencia de los carbapenémicos), eliminarán las cepas silvestres, que son bajas productoras de β-lactamasas, pero no lograrán ser estables frente a un número alto de la producción de estas enzimas. Por lo tanto, el antibiótico será hidrolizado y, después de pocas horas, las mutantes hiperproductoras serán las predominantes y continuarán su replicación. En este caso, la selección es permanente.

Por todo lo anterior, en pacientes infectados, el fenómeno final es la selección y no la inducción, ya que la bacteria sobrevive o muere de acuerdo al antibiótico escogido. Esta diferencia hace parte del concepto de presión selectiva.

DESESCALAR en la disminución de la presión selectiva
Luego de iniciar un tratamiento con un antibiótico empírico de amplio espectro, desescalar comprende cualquiera de los siguientes tres escenarios:
1. El compromiso de suspender el tratamiento antimicrobiano si no hay una infección bacteriana.
2. Limitar o estrechar el espectro de cobertura antimicrobiana según la respuesta clínica, los resultados de los cultivos y la susceptibilidad de los patógenos identificados. Clásicamente se refiere a pasar de un antibiótico que tiene espectro anti-Pseudomonas a otro antibiótico sin esta cobertura, cuando el cultivo reporta una Enterobacteriaceae.
3. El paso de terapia combinada a monoterapia.
4. El paso de intravenosa (IV) a oral: esto en general será posible a partir de las 72 horas de estabilidad clínica, incluyendo afebridad y asegurando la buena tolerancia digestiva del paciente.

En los estudios de práctica clínica, las tasas de desescalamento variarían del 10% al 70% en los ensayos específicamente diseñados, lo que sugiere que los conceptos médicos son en realidad una barrera principal. Desafortunadamente, existe la tendencia a continuar el tratamiento antibiótico empírico de amplio espectro, a pesar de tener la oportunidad de desescalar por antibiógrama, particularmente en los pacientes con infecciones severas que presentan mejoría con el tratamiento inicial. Aún más preocupante es la tendencia a continuar con el tratamiento antibiótico sin encontrar evidencia de infección.

En las guías publicadas en 2007 para el desarrollo de programas institucionales de uso de antimicrobianos IDSA-SHEA, se estableció, con grado de recomendación A, que desescalar con terapia antimicrobiana empírica con base en los resultados del cultivo, lleva a una disminución en la exposición de los antimicrobianos y, por lo tanto, es una estrategia para lograr la disminución de la resistencia y de los costos. De allí la importancia de laboratorios de microbiología que trabajen con calidad y eficiencia.

Debido a los pocos antibióticos para el tratamiento de P. aeruginosa existentes y casi ninguno en desarrollo, la utilización de un antibiótico anti-Pseudomonas para una Enterobacteriaceae es inadecuada desde el punto de vista de daño colateral o presión selectiva. Estudios recientes han mostrado que la microbiota juega un papel definitivo en la resistencia bacteriana y en la población que posteriormente podrá infectar a un paciente. Alterar la microbiota intestinal de un paciente con un tratamiento anti-Pseudomonas cuando la P. aeruginosa no es causante de infección en ese momento, va en contra de un pilar fundamental de todo PROA. Además se debe insistir sobre la responsabilidad que tiene la formulación inapropiada sobre la seguridad del paciente al incrementarle la posibilidad de tener una infección por P. aeruginosa MDR, poniendo a la institución también en riesgo de una transmisión cruzada por esta bacteria, cuyas opciones terapéuticas son cada vez más limitadas.

Estrategias para el uso adecuado de antibióticos en un PROA
1. Restricción del uso de ciertos antibióticos
Una de las estrategias para lograr el uso adecuado de antibióticos es...
la restricción de su uso. Generalmente, la restricción se basa en un formulario en el que algunos antibióticos son de libre formulación, mientras que otros requerirán la interconsulta por parte del médico infectólogo o médicos asignados en el PROA (pre-autorización). Este grupo deberá contar siempre con un infectólogo y con el respaldo de farmacia.

El objetivo de la política de restricción deberá impactar en el costo, por la limitación en el uso de antibióticos con precios más altos o por la reducción en la resistencia bacteriana (a través de la limitación de antibióticos con mayor posibilidad de seleccionar resistencia), o debido a ambos factores.

El impacto, en ambos objetivos, probablemente se deba al efecto educativo del especialista frente al médico que lo ordenó. Deberá ser una oportunidad para que el infectólogo o el grupo liderando el programa, puedan explicar al médico que ordenó el antibiótico acerca del uso apropiado de los antimicrobianos formulados y que están restringidos, su administración, duración, efectos secundarios y la interpretación de la microbiología institucional dentro del contexto de su uso.

En el contexto clínico, la diferencia de varios antibióticos aun de la misma clase, frente a la selección de resistencia (y, por ende, la razón de su restricción) deberá ser un argumento definitivo en la selección de unos antibióticos frente a otros. Por ejemplo, las diferencias entre quinolonas y su propensión para seleccionar P. aeruginosa –quinolina resistente–, así como también su impacto en la selección de ciertas cepas de Staphylococcus aureus resistente a meticilina (SAMR) o C. difficile, se han explicado por la diferencia entre su habilidad para erradicar el organismo frente a su propensión para promover resistencia. Tal vez puede contribuir el hecho de que ya existen determinantes genéticos de resistencia en algunas de estas bacterias para quinolonas, por lo cual, el uso de quinolonas no podrá erradicarlas y sobrevivirán. Otra explicación es su limitación para inhibir en forma permanente la replicación de bacterias como P. aeruginosa.

Esta misma situación se observa entre los carbapenémicos con espectro antipseudomona; a mayor consumo éstos, mayor incremento de la resistencia de P. aeruginosa a estos antibioticos. En contraste, múltiples estudios han confirmado un impacto positivo en la ecología hospitalaria cuando se restringe el uso de carbapenémicos anti-Pseudomonas u otros antibióticos con actividad anti-Pseudomonas, para el tratamiento de Enterobacteriaceae y se reemplaza por ertapenem (el cual no tiene actividad anti-Pseudomonas).

Finalmente, el uso de cefalosporinas o de cualquier β-lactámico que pueda ser hidrolizado por la producción plasmídica BLEE permitirá la supervivencia de esta población bacteriana y su predominio en el tracto gastrointestinal del paciente. El tipo de BLEE definirá entonces a qué β-lactámico podrá sobrevivir y seleccionarse.

En resumen, las ventajas y desventajas principales de las estrategias restrictivas son:
• Requieren personal entrenado y fácilmente localizable durante las 24 horas del día, 7 días a la semana.
• Optimiza rápidamente el uso de antimicrobianos, por lo que puede ser recomendable en situaciones especiales (ej., exceso de consumo de antimicrobianos de difícil control, brotes epidemiológicos).
• Genera mayor oposición por parte de los médicos.
• Riesgo de aumentar la resistencia a otras drogas esenciales por exceso de utilización (para evitar completar formularios o evadir restricciones).

2. Revisión conjunta y retroalimentación
Esta estrategia ofrece algunas ventajas con respecto a las más restrictivas: pueden llevarse adelante aún con pocos recursos humanos disponibles; se acompaña de una actitud formativa de recursos que a su vez puede ser multiplicada por los mismos prescriptores (por ejemplo, recorridas con médicos residentes de diferentes unidades
del hospital) y es considerablemente más aceptada por los médicos. Además, tras un año de implementación de un PROA, los resultados en términos de eficacia de adecuación del consumo de antimicrobianos son comparables entre las estrategias más persuasivas y aquellas más disuasivas o restrictivas.

En definitiva, el tipo de estrategias que se incorporarán en un PROA dependerá por completo de las características generales y específicas de cada institución. Por ejemplo, si un programa está recién siendo iniciado y el consumo de antimicrobianos es verdaderamente alto en, al menos, determinadas unidades de internación; es posible que sea necesario restringir por formulario el uso de ciertos antimicrobianos en algunas unidades. Simultáneamente, es imprescindible que se pongan en marcha las recorridas conjuntas que permitirán explicar el por qué de las restricciones, cuál o cuáles serían las opciones terapéuticas, y otras cuestiones referidas al uso racional de estas drogas.

3. Rotación de antibióticos
Mediante la rotación de antibióticos se pretende que el consumo total se mantenga por debajo de un determinado umbral a partir del cual se desarrollarían resistencias, lo cual permitiría un uso ecológico de los antibióticos. Desafortunadamente, en la práctica, la evidencia acumulada sugiere que la rotación tiene una eficacia limitada. Rotar uno o varios antibióticos en el tiempo ha tenido innumerables limitaciones, como son: su uso en una población que podría seleccionar un mecanismo de resistencia y amplificarse por la continuación del mismo antibiótico; toxicidad; no seguimiento de la rotación por desconocimiento o tipo de infección y mal diseño en los estudios que no pudieron demostrar su efectividad. Además, modelos matemáticos de la evolución de la resistencia bacteriana sugieren que rotar antimicrobianos es una estrategia pobre para prevenir la emergencia de la resistencia. La estrategia que en la actualidad se considera más prometedora consiste en la diversificación o el uso heterogéneo de antibióticos. El uso de diversas clases de antibióticos existentes, sin que se sobrecargue especialmente un grupo, podría limitar el desarrollo de resistencias de los diferentes antibióticos utilizados, aunque todavía falta evidencia en la eficacia de esta estrategia.

En el anexo 2 se describe cómo utilizar de manera práctica la información obtenida de los perfiles de sensibilidad en un PROA, y cómo esta información puede servir de base para el desarrollo de estrategias encaminadas al uso adecuado de antibióticos en una institución.

PRINCIPALES BARRERAS PARA EL DESARROLLO DE LOS PROA

La mayoría de los PROA a nivel mundial, en mayor o menor medida e incluso aquellos consolidados en países con mayores ingresos, ha enfrentado o sigue teniendo dificultades para su implementación y continuidad. El cuello de botella para la implementación de programas efectivos y sustentables, tanto en países desarrollados como en aquellos de menores ingresos, son con frecuencia sorprendentemente similares: falta de suficiente liderazgo, compromiso y financiamiento.

De hecho, muchas de estas barreras no están estrictamente relacionadas con la escasez de recursos humanos o materiales. Una de las deficiencias esenciales reside en elementos subjetivos: pobre percepción del problema y su impacto o desinterés por parte de los potenciales actores principales (administradores, jefes de unidades, prescriptores, etc.), esto sumado a la muy limitada educación y entrenamiento sobre el serio problema relacionado con el uso y abuso de los antimicrobianos. Las principales barreras encontradas y breves recomendaciones de cómo procurar superarlas se encuentran en la Tabla 6.
<table>
<thead>
<tr>
<th>COMPONENTE DEL PROGRAMA</th>
<th>BARRERAS</th>
<th>POSIBLES SOLUCIONES</th>
</tr>
</thead>
</table>
| Recursos humanos        | Baja disponibilidad de diferentes especialistas para crear y mantener un equipo PROA activo.  
Los especialistas disponibles están sobrecargados con otras tareas.  
Las actividades de optimización y control del uso de antimicrobianos no suelen ser remuneradas, pese a los beneficios que otorgan. | Alertar a las autoridades de la institución acerca de los beneficios del PROA.  
Entrenamiento de médicos, microbiólogos y farmacéuticos.  
Tender a que los PROA se conviertan en un estándar de cuidado y sean necesarios para las acreditaciones institucionales.  
Procurar la remuneración por estas actividades a sus integrantes clave y con mayor dedicación horaria. |
| Educación en uso racional de los antibióticos | Entrenamiento sub-óptimo en los aspectos microbiológicos, ecológicos y farmacológicos de la resistencia a los antimicrobianos.  
Los programas de educación médica continua hacia los electores son limitados.  
Muchos médicos reciben información principalmente proveniente de las compañías farmacéuticas.  
La selección de drogas puede estar influenciada por dicha propaganda, incluyendo incentivos. | Revisión del currículo relacionado con la resistencia a antimicrobianos y uso prudente de los mismos, en las carreras de Medicina, Farmacia, Química, Bioquímica y otras relacionadas, según corresponda a cada país de América Latina.  
Proveer de educación médica continua de alta calidad, certificada por instituciones de jerarquía.  
Adoptar combinación de iniciativas, como por ejemplo, cursos a distancia con encuentros presenciales.  
Realizar iniciativas educativas conjuntas entre sociedades científicas y gobiernos.  
Incluir la elaboración y distribución amplia y suficiente de material educativo y guías de tratamiento basadas en evidencias.  
Visitas a los pacientes a través de recorridas clínicas conjuntas con prescriptores, en particular en unidades críticas o de cuidados intensivos.  
Control y supervisión por parte de las autoridades respecto de las actividades promocionales de las compañías farmacéuticas. |
| Guías y recomendaciones terapéuticas | Existe una multitud de guías, frecuentemente desactualizadas e inapropiadas.  
Falta de recursos, tanto humanos como materiales, en los laboratorios de microbiología.  
Falta de reconocimiento, por parte de las autoridades de salud, de la importancia de los laboratorios de microbiología. | Seleccionar las guías más adecuadas y adaptables a cada institución. No “importar” recomendaciones que no se ajusten a la realidad epidemiológica y presupuestaria de cada institución.  
Revisar y consensuar las guías que se utilizarán junto con los efectores de las mismas.  
Evitar solamente distribuir las guías sin procurar una discusión y acuerdo previo.  
Dotar de insumos necesarios para el desenvolvimiento normal del laboratorio.  
Contratar personal competente en los laboratorios.  
Optimizar el funcionamiento del laboratorio: calidad del trabajo, comunicación con los médicos, celeridad para el procesamiento de resultados, entre otros.  
Participar en programas de control de calidad.  
Introducir pruebas rápidas que resulten relevantes. |
| Prácticas prescriptivas | “Libertad terapéutica” es muy valorada por muchos médicos.  
Falta de provisión estable de medicamentos. | Capacitación inicial seguida de educación médica continua, auditoria y retroalimentación.  
Evitar demasiadas restricciones y/o necesidad de autorizaciones en el PROA.  
Respetar la lista de drogas esenciales que deben incluirse en el formulario hospitalario.  
Alertar a las autoridades hospitalarias, responsables de las Farmacias y de los Departamentos de Compras acerca de la importancia de la provisión estable y consistente de drogas, y el manejo rápido y adecuado frente a la escasez de alguna de ellas. |
| Control de infecciones | Un eficiente control y prevención de infecciones es imprescindible para reducir el uso de los antimicrobianos. De todos modos, dado que su análisis no es un objetivo de las presentes recomendaciones, sugerimos a los lectores recurrir a la bibliografía de referencia en la materia. |                                                                                                                                                                                                |

**TABLA 6.** Principales barreras encontradas y breves recomendaciones de cómo procurar superarlas.
CONCLUSIONES Y RECOMENDACIONES

Múltiples organizaciones nacionales e internacionales han reportado el problema creciente de la resistencia bacteriana no sólo a nivel hospitalario sino de la comunidad y se han publicado recomendaciones para afrontar el problema. Aunque la resistencia es un fenómeno mundial, su mayor esfuerzo en la contención y el manejo deberá desarrollarse en cada institución.

La implementación de un programa de optimización de antimicrobianos (PROA) deberá ser una prioridad institucional, con el respaldo total del área administrativa y la participación de un grupo multidisciplinario. La mayoría de reportes económicos de estos programas demuestran que demandan un costo asequible y además generan ahorros para los hospitales. El sólo impacto en la reducción de la resistencia bacteriana y la disminución de costos asociados al uso de antibióticos, deberían ser suficientes para justificarlo. De acuerdo al tipo de hospital y la prevalencia de resistencia, el programa deberá escoger qué estrategia implementar. Esta decisión deberá tener en cuenta el tamaño del hospital, la densidad de uso de antibióticos, la capacidad de sistematizar la información y el personal disponible.

La educación pasiva y/o esporádica –por sí sola– es muy poco efectiva en la reducción y optimización del consumo de antimicrobianos, por lo que deben implementarse intervenciones multifacéticas, procurando una mayor interacción con los efectores/prescriptores y manteniéndolas de forma continua. El desarrollo de guías institucionales es un pilar fundamental en el uso apropiado de antibióticos y, por lo tanto, de cualquier PROA. Las guías deberán reflejar la epidemiología local, los conceptos de presión selectiva, los mecanismos de resistencia prevalentes y la desescalación. Desafortunadamente, por el desconocimiento de sus beneficios, los médicos aún no incorporan conceptos fundamentales para lograr una terapia apropiada ligada a una menor mortalidad y un uso adecuado de antibióticos que conlleve la disminución de la resistencia bacteriana. Dentro de estos conceptos, la estrategia de desescalar es imprescindible para disminuir el daño ecológico a nivel hospitalario y en la comunidad. El uso de antibióticos deberá entenderse no como una solución puntual para el paciente, sino como una responsabilidad de la salud pública. Cada tratamiento inadecuado está generando la posibilidad de magnificar la resistencia y empeorar el problema. El buen uso de los antibióticos es una responsabilidad de todos, como lo es la no transmisión de bacterias MDR entre pacientes. El comité de infecciones, como pilar fundamental de un PROA, deberá integrar ambas aproximaciones.

Finalmente, los PROA bien diseñados y con resultados de impacto medidos serán necesarios para ayudar a otros hospitales a seguir el camino.

PROGRAMA DE OPTIMIZACIÓN DE ANTIMICROBIANOS A NIVEL HOSPITALARIO: PASO A PASO

1. IMPLEMENTAR UN PROA

- Existe evidencia que un PROA mejora el uso de antibióticos, reduce la morbi-mortalidad, la resistencia bacteriana y los costos hospitalarios.
- Todo PROA debe involucrar equipos multidisciplinarios que cuenten con el respaldo de la administración del hospital y tengan entrenamiento en el mejoramiento de la calidad.
- Dos de los métodos más exitosos son la restricción en la prescripción de antimicrobianos y la estrategia de revisión prospectiva con intervención y retroalimentación.

Tenga en cuenta

Para completar este paso, el hospital requiere:
- Política de prescripción de antibióticos.
- Plan y estrategia de implementación del PROA.
- Equipo multidisciplinario (que incluya al menos un infectólogo, epidemiólogo hospitalario o microbiólogo clínico y un farmacéutico), con roles claros y entrenamiento para optimizar el uso de antibióticos acorde a las necesidades y recursos del hospital.
- El PROA debe estar incluido en el plan institucional de calidad y seguridad del paciente.
- Evaluación periódica de indicadores de proceso y resultado, que debe ser conocida por la administración del hospital.
2. FORMULARIOS Y SISTEMAS DE APROBACIÓN DE ANTIMICROBIANOS

Tenga en cuenta
- Los formularios pueden usarse para influenciar patrones de uso de antibióticos en hospitales. El comité deberá definir las reglas que restringen el acceso a determinados antibióticos.
- El uso de sistemas de aprobación de antibióticos se ha asociado con menores volúmenes de uso de medicamentos, reducción de costos, menores efectos adversos y menores días de estancia.

Para completar este paso, el hospital requiere:
- Generar lista de antibióticos restringidos y los criterios para su uso.
- Implementar un sistema de aprobación de antimicrobianos.
- Evaluar regularmente la adherencia a este proceso.
- Disponibilidad de consulta continua para guiar a los clínicos en la prescripción.

3. REVISIÓN DE ANTIMICROBIANOS Y RETROALIMENTACIÓN A LOS PRESCRIPTORES

Tenga en cuenta
- Estas intervenciones proveen retroalimentación directa en el momento de la prescripción y el diagnóstico por laboratorio, siendo una oportunidad para educar al personal clínico.

Para completar este paso, el hospital requiere:
- La revisión de antimicrobianos y la retroalimentación deben ser parte de la atención clínica.
- El equipo de PROA debe revisar y retroalimentar a nivel individual y en los sitios hospitalarios en donde encuentre uso masivo de antibióticos.

4. INTERVENCIONES EN EL PUNTO DE ATENCIÓN

Tenga en cuenta
- Estas intervenciones proveen retroalimentación directa en el momento de la prescripción y el diagnóstico por laboratorio, siendo una oportunidad para educar al personal clínico.

Para completar este paso, el hospital requiere:
- Incluir dentro del PROA, de acuerdo a los recursos y experticia local, alguna de estas intervenciones:
  - Revisión de las elecciones de manejo antibiótico para determinar si son adecuadas.
  - Establecer terapias dirigidas de acuerdo a los resultados del cultivo, antibiograma u otros test rápidos.
  - Optimización de dosis.
  - Cambio de administración parenteral a oral.
  - Monitoreo terapéutico del fármaco.
  - Órdenes de suspensión automática.

5. MEDIR EL DESEMPEÑO DE LOS PROA

Tenga en cuenta
- Es necesario el reporte y análisis de uso de antibióticos por sala y para todo el hospital, de forma que sea posible monitorear tendencias e identificar áreas donde se requiera intervenir.
- Deben evaluarse los indicadores de proceso y resultado. Se sugiere dar retroalimentación regular y sistematizada, para que pueda ser interpretada y usada por los clínicos.

Para completar este paso, el hospital requiere:
- Recolectar y revisar regularmente los datos de uso de antibióticos, empleando todos los recursos tecnológicos disponibles en el hospital.
- Monitorear indicadores de calidad para evaluar la práctica de prescripción.
- Interpretar los datos de uso de antibióticos junto con los datos de resistencia bacteriana y control de infecciones.
6. EDUCACIÓN Y COMPETENCIA DE QUIENES PRESCRIBEN

Tenga en cuenta
- Las técnicas de educación activa (educación individual, sesiones para crear consensos y talleres) son más efectivas para cambiar prescripciones que las técnicas pasivas. Estas deberían empezar desde el pregrado y consolidarse con el entrenamiento en el posgrado.

Para completar este paso, el hospital requiere:
- Educar al personal clínico en el PROA y la prescripción adecuada de antibióticos, tanto en pregrado como en posgrado.

7. EL PAPEL DEL SERVICIO DE MICROBIOLOGÍA CLÍNICA

Tenga en cuenta
- Para entregar resultados precisos y a tiempo, es necesario establecer procedimientos de buenas prácticas para la evaluación microbiológica rápida.
- En sus reportes, el servicio de microbiología debe incluir comentarios que le ayuden al clínico a interpretar el significado de los aislamientos, la susceptibilidad y algunas advertencias de manejo.
- Es importante prestar atención particularmente a servicios como UCI y Urgencias que pueden afectar a otras áreas del hospital.

Para completar este paso, el hospital requiere:
- Antibiograma acumulativo semestral y anual que indique patrones de susceptibilidad para patógenos clave, tanto a nivel general como por servicios.
- Mejores prácticas para test diagnósticos de infecciones por patógenos más prevalentes.
- Disponibilidad de consulta al servicio de microbiología en elección, naturaleza, manejo y diagnóstico de especímenes para detectar infección (especialmente en casos en los que el diagnóstico diferencial es amplio).
- Informe directo al clínico cuando se detectan bacteriemias, infecciones meníngeas u otras infecciones críticas.
- Proveer análisis regulares de resistencia bacteriana a grupos responsables de la generación de guías locales.

8. EL PAPEL DEL SERVICIO DE INFECTOLOGÍA

Tenga en cuenta
- Los infectólogos dan legitimidad a los PROA y juegan un papel determinante al contribuir a la toma de decisiones en los formularios, las políticas de restricción de antibióticos, la generación de guías basadas en la evidencia para el uso apropiado de antibióticos y colaborar con especialistas locales para que los objetivos del programa se entiendan y cumplan. El infectólogo deberá tener un entrenamiento en uso optimizado de antibióticos.

Para completar este paso, el hospital requiere:
- Incluir un infectólogo o microbiólogo clínico en el PROA.
- Tener acceso a un servicio de infectología (intrahospitalario o externo) para consultar casos y educar a quienes formulan y desarrollan políticas de prescripción.

9. PAPEL DEL SERVICIO DE FARMACIA

El rol primario es promover y coordinar las actividades del PROA en el hospital.

Tenga en cuenta

Para completar este paso, el hospital requiere:
- Incluir un farmacéutico en el equipo de PROA, que:
  • Revise de manera prospectiva o retrospectiva las órdenes de antibióticos, participando en la retroalimentación y educación del personal del hospital, cuando sea necesario.
  • Colabore en el desarrollo de la política de formulación antibiótica y guías de prescripción, así como en las actividades de seguimiento para el uso apropiado de antimicrobianos.
10. USO DE TECNOLOGÍAS COMPUTARIZADAS EN LOS PROA

**Para completar este paso, el hospital requiere:**

- Los sistemas electrónicos de apoyo a la decisión clínica son herramientas potenciales para los PROA.
- Estos sistemas se pueden implementar según los recursos disponibles, teniendo en cuenta factores organizacionales, sociales y culturales alrededor de la prescripción de antibióticos.
- Trabajar en la implementación de sistemas de soporte electrónico que permitan integrar la información de las prescripciones con la historia clínica del paciente y guiar las prescripciones de antibióticos.
- El equipo del PROA y el farmacéutico deben tener acceso a esta información y contribuir al mantenimiento de estos sistemas.


**ANEXO 1: PIE DE NOTAS EN EL ANTIBIOGRAMA**

La información que se obtiene en el antibiograma es una herramienta de gran importancia en el ámbito clínico y epidemiológico; además de ser una pieza fundamental en la implementación de un PROA.

La decisión de qué antibióticos informar o cuáles suprimir en el reporte del laboratorio debe ser por consenso con el comité de infecciones. Hay que tener en cuenta criterios como la epidemiología local, las indicaciones clínicas, las resistencias naturales, el uso aprobado, el uso de antibióticos de primera línea y las alternativas existentes.

La información del antibiograma pretende predecir la eficacia clínica. Sin embargo, hay que recordar que la eficacia es multifactorial; depende además de factores como el uso de una dosis adecuada que permita alcanzar parámetros farmacodinámicos y farmacocinéticos en el sitio de la infección, la presencia de biopolélicas, entre otros aspectos.

<table>
<thead>
<tr>
<th>Especie</th>
<th>Fenotipo</th>
<th>Comentario</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. saprophyticus</td>
<td>Aislamientos urinarios.</td>
<td>S. saprophyticus no requiere antibiograma de rutina, ya que se inhibe con las concentraciones alcanzadas en orina de todos los antibióticos excepto fosfomicina.</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>Aislamientos en hemocultivo de botellas tomadas por venopunción.</td>
<td>Correlacionar el resultado con la historia clínica del paciente y posibilidad de contaminación. En infecciones documentadas clínicamente utilizar vancomicina, linezolid o daptochin.</td>
</tr>
<tr>
<td>S. aureus</td>
<td>Sensibilidad a oxacilina.</td>
<td>Puede utilizarse cualquier betalactámico activo contra S. aureus (oxacilina, cefozolin, ampicilina/sulbactam, etc). No se recomienda el uso de vancomicina, excepto en pacientes de alta severidad.</td>
</tr>
<tr>
<td>S. aureus</td>
<td>Resultado sensible a clindamicina con intermedio o resistente a eritromicina.</td>
<td>Realizar el D-test por método automatizado o manual. Si éste es positivo incluir la siguiente nota: No se recomienda el uso de clindamicina por resistencia inducible. Considerar otras opciones. Si el D-test es negativo, reportar el resultado de clindamicina como sensible.</td>
</tr>
<tr>
<td>E. faecalis</td>
<td>Aislamientos sensibles a ampicilina.</td>
<td>Ampicilina alcanza suficientes concentraciones en orina, en pacientes con función renal normal, y es el tratamiento recomendado en las infecciones urinarias por E. faecalis. En infecciones sistémicas o complicadas considere adicionar gentamicina al tratamiento con ampicilina si el resultado de sinergia con gentamicina de alta carga es sensible.</td>
</tr>
<tr>
<td>E. faecium</td>
<td>Aislamientos sensibles a ampicilina y vancomicina.</td>
<td>Se sugiere evitar el uso de ampicilina en aislamientos de E. faecium en infecciones sistémicas. Vancomicina es el tratamiento de elección. Considere adición de gentamicina o alternativas en infecciones graves (ver nota E. faecalis).</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>Aislamientos vancomicina-resistentes.</td>
<td>Se sugiere aislamiento de contacto e interconsultar a infectología. Considere el uso de daptochin a dosis altas.</td>
</tr>
<tr>
<td>Streptococcus beta-hemolíticos</td>
<td>Todos los aislamientos.</td>
<td>No se requiere antibiograma para β-lactámicos que constituyen el tratamiento de elección. Informar al laboratorio si se requiere el resultado de clindamicina, eritromicina o vancomicina que deben ser probados in vitro.</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>Aislamientos respiratorios sensibles al screening con oxacilina de 1µg (Halo&lt;20mm).</td>
<td>Este aislamiento puede tratarse con cualquier β-lactamico empleado en el manejo de neumonía. Considerar opciones en pacientes alérgicos.</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>Aislamientos respiratorios no sensibles al screening con oxacilina de 1µg (Halo&gt;19mm).</td>
<td>Se requiere la CIM para la interpretación de los β-lactámicos. En neumonía grave, considerar dosis altas del β-lactamico, uso de terapia combinada o alternativas hasta que el dato de la CIM esté disponible.</td>
</tr>
</tbody>
</table>

**COCOS GRAM POSITIVOS DE IMPORTANCIA CLÍNICA Y EPIDEMIOLÓGICA**

<table>
<thead>
<tr>
<th>Especie</th>
<th>Fenotipo</th>
<th>Comentario</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. saprophyticus</td>
<td>Aislamientos urinarios.</td>
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</tr>
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<td>Correlacionar el resultado con la historia clínica del paciente y posibilidad de contaminación. En infecciones documentadas clínicamente utilizar vancomicina, linezolid o daptochin.</td>
</tr>
<tr>
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<td>Sensibilidad a oxacilina.</td>
<td>Puede utilizarse cualquier betalactámico activo contra S. aureus (oxacilina, cefozolin, ampicilina/sulbactam, etc). No se recomienda el uso de vancomicina, excepto en pacientes de alta severidad.</td>
</tr>
<tr>
<td>S. aureus</td>
<td>Resultado sensible a clindamicina con intermedio o resistente a eritromicina.</td>
<td>Realizar el D-test por método automatizado o manual. Si éste es positivo incluir la siguiente nota: No se recomienda el uso de clindamicina por resistencia inducible. Considerar otras opciones. Si el D-test es negativo, reportar el resultado de clindamicina como sensible.</td>
</tr>
<tr>
<td>E. faecalis</td>
<td>Aislamientos sensibles a ampicilina.</td>
<td>Ampicilina alcanza suficientes concentraciones en orina, en pacientes con función renal normal, y es el tratamiento recomendado en las infecciones urinarias por E. faecalis. En infecciones sistémicas o complicadas considere adicionar gentamicina al tratamiento con ampicilina si el resultado de sinergia con gentamicina de alta carga es sensible.</td>
</tr>
<tr>
<td>E. faecium</td>
<td>Aislamientos sensibles a ampicilina y vancomicina.</td>
<td>Se sugiere evitar el uso de ampicilina en aislamientos de E. faecium en infecciones sistémicas. Vancomicina es el tratamiento de elección. Considere adición de gentamicina o alternativas en infecciones graves (ver nota E. faecalis).</td>
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<td>Aislamientos respiratorios no sensibles al screening con oxacilina de 1µg (Halo&gt;19mm).</td>
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</tr>
</tbody>
</table>
Sugerencias:
- Considerando la variabilidad de los sistemas automatizados de microbiología para el tamizaje de vancomicina en *S. aureus*, se recomienda incorporar método de gradiente (E-test, MICE o similar) en todos los aislamientos de MRSA con origen en pulmón o sangre.
- Se recomienda el uso de método de gradiente (E-test, MICE o similar) para el tamizaje de daptomicina en *Enterococcus* spp aislados de bacteriemia y endocarditis bacteriana.

### BACILOS GRAM NEGATIVOS DE IMPORTANCIA CLÍNICA Y EPIDEMIOLÓGICA

<table>
<thead>
<tr>
<th>Especie</th>
<th>Fenotipo</th>
<th>Comentario</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Klebsiella E. coli</em></td>
<td>Producción de BLEEs</td>
<td>Microorganismo productor de BLEEs. No se recomienda el uso de cefalosporinas ni aztreonam. El uso de piperacilina/tazobactam estará supeditado a CIM, localización y severidad de la infección, y a criterio clínico. Considere carbapenémicos en infecciones graves. Para todas las especies: Microorganismo productor de AmpC. No se recomienda el uso de cefalasporinas de tercera generación ni aztreonam. Para <em>Enterobacter</em> y <em>Serratia</em>: Microorganismo productor de AmpC. No se recomienda el uso de cefalosporinas de tercera generación, piperacilina/-tazobactam y aztreonam ya que son las especies con mayor tasa de de-represión o hiper-expresión de la enzima AmpC que puede llevar a fallas terapéuticas. Se sugiere interconsulta con el infectólogo.</td>
</tr>
<tr>
<td><em>Enterobacter Serratia</em></td>
<td>Producción de AmpC</td>
<td>Los resultados son consistentes con la producción de cefalasporinas. Se sugiere aislamiento de contacto e interconsulta con el infectólogo.</td>
</tr>
<tr>
<td><em>Providencia Aeromonas</em></td>
<td>Resistencia a carbenémicos con test de carbapenemasas (Hodge, EDTA, Borónico, Carha NP, etc.) positivos.</td>
<td>Los resultados son consistentes con la producción de cefalasporinas. Se sugiere aislamiento de contacto e interconsulta con el infectólogo.</td>
</tr>
<tr>
<td><em>Citrobacter Eduarsiella</em></td>
<td>Resistencia a carbenémicos con test de carbapenemasas (Hodge, EDTA, Borónico, Carha NP, etc.) negativos.</td>
<td>Los resultados son consistentes con la producción de cefalasporinas. Se sugiere aislamiento de contacto e interconsulta con el infectólogo.</td>
</tr>
<tr>
<td><em>Haftea alvei</em></td>
<td></td>
<td>Los resultados son consistentes con la producción de cefalasporinas. Se sugiere aislamiento de contacto e interconsulta con el infectólogo.</td>
</tr>
<tr>
<td><em>Morganella</em></td>
<td></td>
<td>Los resultados son consistentes con la producción de cefalasporinas. Se sugiere aislamiento de contacto e interconsulta con el infectólogo.</td>
</tr>
</tbody>
</table>

Sugerencias:
- Para predecir la actividad de las cefalosporinas orales (cefalexina, cefradina, etc.), en el manejo de infecciones urinarias bajas no complicadas, se sugiere tamizar con cefazolina en lugar de cefalotina. Una CIM ≤ 16µg/ml o un halo de inhibición ≥ 15 mm para cefazolina, indica sensibilidad a las cefalosporinas orales sin que se requiera su prueba in vitro. Para los países que utilicen cefadroxilo, se sugiere continuar realizando el tamizaje con cefalotina para predecir la sensibilidad de este antibiótico.
- En *Pseudomonas aeruginosa* se recomienda el tamizaje de todos los antibióticos con actividad frente a este microorganismo. Estos son: piperacilina/tazobactam, cefepima, aztreonam, gentamicina, amikacina, tobramicina, imipenem, doripenem, meropenem, ciprofloxacina, colistina, polimixina B, fosfomicina, cefoperazona y ceftazidima. La institución puede considerar el tamizaje de cefotolozane/tazobactam cuando lo considere apropiado.
- En *Acinetobacter* spp, se sugiere reportar todos los antibióticos activos frente a este microorganismo. Estos son: ampicilina/sulbactam, cefoperazona/sulbactam, cefepima, meropenem, imipenem, doripenem, amikacina, ciprofloxacino, tigeciclina, colistina, polimixina B.
• Con la implementación de los puntos de corte CLSI 2010 para carbapenémicos, los aislamientos de *Proteus, Providencia y Morganella* pueden mostrar CIM más elevada para imipenem, llegando hasta resistente, sin que esto signifique producción de carbapenemasas. Para estos microorganismos revisar las cefalosporinas en conjunto con los carbapenémicos, principalmente ertapenem y meropenem. Sugerimos en este caso omitir el reporte de imipenem o escribir un pie de nota que indique que la resistencia al imipenem está mediada por un mecanismo diferente a la producción de carbapenemasas y no se requiere aislamiento de contacto.

ANEXO 2: Cómo utilizar de manera práctica la información obtenida en los perfiles de sensibilidad dentro de un programa de optimización de Antimicrobianos (PROA)

1. Suponga que su hospital tiene menos de 500 camas y el perfil de susceptibilidad para bacilos Gram negativos obtenido durante un semestre es similar al siguiente:

Porcentajes de resistencia de las cinco bacterias Gram-negativas más frecuentemente aisladas en salas de internación médico-quirúrgicas de un hospital, desde enero a junio de 2015.

<table>
<thead>
<tr>
<th>Microorganismo</th>
<th>Cefotaxima %</th>
<th>Ceftazidima %</th>
<th>Ceftriaxona %</th>
<th>Aztreonam %</th>
<th>Cefepima %</th>
<th>Piperacilina/tazobactam %</th>
<th>Ampicilina/sulbactam %</th>
<th>Ciprofloxacino %</th>
<th>Amikacina %</th>
<th>Tigeciclina %</th>
<th>Ertapenem %</th>
<th>Imipenem</th>
<th>Meropenem</th>
<th>Doripenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>7 (1/14)</td>
<td>10 (1/21)</td>
<td>0 (0/1)</td>
<td>0 (0/2)</td>
<td>0 (0/2)</td>
<td>0 (0/2)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>10 (1/23)</td>
<td>20 (2/10)</td>
<td>0 (0/1)</td>
<td>0 (0/2)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>5 (2/3)</td>
<td>0 (0/2)</td>
<td>0 (0/1)</td>
<td>0 (0/2)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. cloacae</td>
<td>5 (1/11)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P. mirabilis</td>
<td>3 (1/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
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<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td>0 (0/1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. A continuación, trate de analizar de manera global qué sugieren estos porcentajes en su institución.

3. Luego, observe cada bacteria de manera particular e intente plantear qué mecanismos de resistencia podrían explicar el perfil fenotípico observado.

4. Finalmente, incluya esta tabla junto con el análisis anterior (que preferiblemente debe ser hecho por el infectólogo o microbiólogo clínico) en el reporte final que el comité de enfermedades infecciosas entrega a la institución. Esto ayudará al programa de uso racional de antibióticos a tener una idea aproximada del perfil de resistencia de las bacterias más frecuentes en la institución y tomar decisiones sobre el manejo empírico de algunas de ellas.

En este caso, el análisis podría hacerse de la siguiente manera:

El perfil de resistencia observado en la tabla sugiere la presencia de Betalactamasas de Espectro Extendido (BLEEs) en *E. coli*. Para *K. pneumoniae* se sugiere una mayor presencia de BLEEs, sumado a la posible presencia de carbapenemasas; *P. aeruginosa* y *P. mirabilis* presentan un perfil bajo de multirresistencia. *E. cloacae* sugiere un perfil de de-represión de AmpC con cierre de porinas y/o carbapenemasas.

5. Esta misma descripción debe hacerse para las bacterias Gram positivas más frecuentes en su institución, para la contención de los mismos que impliquen cambio en las estrategias actuales de vigilancia y control de infecciones.
Porcentaje de resistencia de las cinco bacterias Gram-positivas más frecuentemente aisladas en salas médico-quirúrgicas de internación de un hospital, desde enero a junio de 2015.

<table>
<thead>
<tr>
<th>Microorganismo</th>
<th>n</th>
<th>Ampicilina%</th>
<th>Gentamicina Alta Carga%</th>
<th>Linezolid %</th>
<th>Oxacilina %</th>
<th>Vancomicina%</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>62</td>
<td>0 (0/62)</td>
<td></td>
<td>56 (35/62)</td>
<td>0 (0/62)</td>
<td></td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>46</td>
<td>0 (0/46)</td>
<td></td>
<td>78 (35/45)</td>
<td>0 (0/46)</td>
<td></td>
</tr>
<tr>
<td>S. hominis</td>
<td>36</td>
<td>0 (0/36)</td>
<td></td>
<td>69 (25/36)</td>
<td>0 (0/36)</td>
<td></td>
</tr>
<tr>
<td>E. faecalis</td>
<td>34</td>
<td>0 (0/34)</td>
<td></td>
<td>2 (2/34)</td>
<td>3 (1/34)</td>
<td></td>
</tr>
<tr>
<td>E. faecium</td>
<td>11</td>
<td>0 (0/11)</td>
<td></td>
<td>0 (0/11)</td>
<td>64 (7/11)</td>
<td></td>
</tr>
</tbody>
</table>

Supongamos que su hospital presenta el anterior perfil de susceptibilidad para Gram positivos. En este caso, el análisis podría hacerse de la siguiente manera:

El perfil de resistencia observado en la tabla muestra al 56% de S. aureus resistentes a oxacilina; mientras que E. faecalis presentó un (1) caso de resistencia a vancomicina y E. faecium, siete (7) casos.

6. También puede mostrarse en este reporte la distribución de la CIM de las poblaciones bacterianas más frecuentes frente a los antibióticos de interés, bien sea porque se desee priorizar su uso en la institución o se pretende describir cómo es su desempeño en el tiempo.

En este ejemplo podría mencionarse que: El 17% de los aislamientos presentaron una CIM a vancomicina de 2 µg/ml, mientras que el 67% de 1 µg/ml. No olvide sugerir que estos aislamientos requieren un seguimiento clínico de la respuesta a vancomicina por su asociación con falla terapéutica en neumonías y bacteriemias. También puede hacerse uso de la distribución de CIM cuando se desee saber cómo estas se ven afectadas por un cambio en los puntos de corte a nivel institucional o en poblaciones mayores.

Distribución de las Concentraciones Inhibitorias Mínimas (CIM) para la población de P. aeruginosa aisladas en salas de internación médico-quirúrgicas de un hospital, en el período de enero a junio de 2015.
En este caso, se puede decir que:

En el caso de *P. aeruginosa*, meropenem mostró “poblaciones no susceptibles” en promedio del 10%. El cambio en los puntos de corte propuestos por CLSI 2012 sumará un 20% más de resistencia frente meropenem.

7. Finalmente, es necesario incluir recomendaciones en el reporte que se haga a la institución, de manera que esta información no se quede simplemente en el papel sino que, por el contrario, contribuya al control de las infecciones y al uso racional de los antibióticos.

Algunas recomendaciones que podrían incluirse, teniendo en cuenta el ejemplo que hemos desarrollado en este apartado, son:

La presencia de BLEE y en mayor proporción de probables carbapenemasas, requiere continuar con la implementación de un PROA, en este hospital, asociado a un buen diagnóstico del laboratorio. Se debe realizar un test de Hodge modificado en *K. pneumoniae* y *E. coli* para descartar la presencia de carbapenemasas, especialmente en infecciones severas como bacteremia y neumonía, ya que la presencia de KPC se ha asociado a mortalidad hasta del 60% cuando se usa monoterapia; por lo cual es vital diferenciar entre KPC y BLEE.

La presencia de *E. cloacae* con de-represión refuerza la necesidad de un uso racional de cefalosporinas.

*P. aeruginosa* presenta un perfil bajo de multirresistencia para todos los antibióticos, incluyendo los carbapenémicos, en salas de hospitalización. A pesar de tener un menor número de cepas reportadas, doripenem presentó una resistencia muy baja. Por su parte, *S. aureus* presenta un perfil elevado de resistencia en salas (56%). La CIM para vancomicina está en su mayoría por encima de 1 µg/ml, por lo que requiere de vigilancia clínica cuando se use este antibiótico. Existe además el problema de *Enterococcus* vancomicina-resistente en salas, que requiere la implementación de campañas para la higiene de manos y barreras de contacto, así como revisar los protocolos de desinfección y limpieza. Son vitales las guías de uso adecuado de antibióticos basados en factores de riesgo para minimizar la presencia de estos mecanismos de resistencia.

Vamos ahora a hacer este mismo ejercicio, pero con un hospital de más de 500 camas y una epidemiología un poco diferente. Suponga que este es el perfil de susceptibilidad para Gram negativos en las Unidades de Cuidados Intensivos de esta institución:

<table>
<thead>
<tr>
<th>Microorganismo</th>
<th>n</th>
<th>Cefotaxime</th>
<th>Ceftriaxona</th>
<th>Cephalotina</th>
<th>Aztreonam</th>
<th>Ciprofloxacina</th>
<th>Tigeciclina</th>
<th>Ertapenem</th>
<th>Imipenem</th>
<th>Meropenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. baumannii</td>
<td>105</td>
<td>55/50</td>
<td>60/50</td>
<td>40/45</td>
<td>30/30</td>
<td>20/20</td>
<td>10/10</td>
<td>5/5</td>
<td>0/0</td>
<td>1/0</td>
</tr>
<tr>
<td>E. coli</td>
<td>94</td>
<td>60/50</td>
<td>70/50</td>
<td>50/50</td>
<td>40/40</td>
<td>20/20</td>
<td>10/10</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>66</td>
<td>60/50</td>
<td>70/50</td>
<td>50/50</td>
<td>40/40</td>
<td>20/20</td>
<td>10/10</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>71</td>
<td>80/70</td>
<td>90/80</td>
<td>70/70</td>
<td>60/60</td>
<td>40/40</td>
<td>20/20</td>
<td>10/10</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>E. cloacae</td>
<td>29</td>
<td>90/80</td>
<td>100/90</td>
<td>80/80</td>
<td>70/70</td>
<td>50/50</td>
<td>30/30</td>
<td>20/20</td>
<td>10/10</td>
<td>0/0</td>
</tr>
</tbody>
</table>

El análisis que podría hacerse es el siguiente:

El fenotipo observado en la tabla muestra un perfil elevado de multirresistencia en *Acinetobacter* spp, lo cual debe hacer sospechar la presencia de brotes; además se observa la presencia de BLEEs en *E. coli* y, en mayor proporción, en *K. pneumoniae*, con la probabilidad de carbapenemases. *P. aeruginosa* presenta un perfil de resistencia moderada a los antibióticos antipseudomonas, mientras que *E. cloacae* evidencia un perfil de de-represión de AmpC con cierre de porinas y/o carbapenemases.
Veamos el porcentaje de resistencia en Gram positivos:

Porcentaje de resistencia de las cinco bacterias Gram-positivas más frecuentemente aisladas en UCI de un hospital, entre enero y junio de 2015

<table>
<thead>
<tr>
<th>Microorganismo</th>
<th>n</th>
<th>Ampicilina%</th>
<th>Gentamicina Alta Carga%</th>
<th>Lincosida %</th>
<th>Dacilina %</th>
<th>Vancomicina%</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. aureus</em></td>
<td>51</td>
<td>0 (0/51)</td>
<td>63 (32/51)</td>
<td>0 (0/51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. epidermidis</em></td>
<td>34</td>
<td>0 (0/34)</td>
<td>79 (27/34)</td>
<td>0 (0/34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. hominis</em></td>
<td>19</td>
<td>0 (0/19)</td>
<td>53 (10/19)</td>
<td>0 (0/19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>E. faecalis</em></td>
<td>18</td>
<td>0 (0/18)</td>
<td>78 (14/18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>E. faecium</em></td>
<td>17</td>
<td>0 (0/17)</td>
<td>64 (0/17)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

El análisis que puede plantearse es el siguiente:

El perfil de resistencia observado en la tabla muestra al 63% de *S. aureus* resistentes a oxacilina; mientras que *E. faecium* presenta 14 casos de resistencia a vancomicina. Se presenta un (1) caso de resistencia a linezolid en *E. faecalis* que se recomienda re-confirmar.

También podemos observar la distribución de CIM de antibióticos de interés como vancomicina, para alguna de las bacterias más frecuentes como *S. aureus*:

En este caso podría decirse que:

El 55% de los aislamientos presentaron una CIM a vancomicina de 2 µg/ml mientras que el 39% de 1 µg/ml. Estos aislamientos requieren un seguimiento clínico de la respuesta terapéutica a vancomicina por su asociación con falla en neumonías y bacteriemias.

Distribución de las Concentraciones Inhibitorias Mínimas (CIM) para la población de *S. aureus* aislada en la UCI de un hospital, en el período de enero a junio de 2015.

Distribución de las Concentraciones Inhibitorias Mínimas (CIM) para la población de *P. aeruginosa* aisladas en la UCI de un hospital, en el período de enero a junio de 2015.
Para *P. aeruginosa*, doripenem mostró una “población no susceptible” del 14%. La implementación de los puntos de corte, propuestos por CLSI 2012, no afectará los porcentajes de resistencia en este caso.

Entre las recomendaciones que pueden darse para este hospital, teniendo en cuenta los datos presentados, están:

La presencia en *E. coli* BLEE, y en mayor proporción de BLEES y carbapenemasas en *K. pneumoniae*, requiere reforzar la implementación de un PROA, asociado a un buen diagnóstico del laboratorio. Se debe realizar el test de Hodge modificado en *K. pneumoniae* y *E. coli* para descartar la presencia de carbapenemasas, especialmente en infecciones severas como bacteriemia y neumonía. La confirmación de KPC y en general de carbapenemasas es importante ya que se ha asociado a mortalidad hasta del 60% cuando se usa monoterapia. Esto marca la diferencia frente a BLEE, en el que la monoterapia con carbapenémicos (incluyendo ertapenem) se asocia con mortalidad menor de 4%.

La presencia de *A. baumanii* multirresistente indica la existencia de brotes y probables carbapenemasas. La campaña de higiene de manos, limpieza y desinfección, que se llevará a cabo para las Enterobacteriaceas multirresistentes, deberá impactar también en la disminución de *A. baumanii*.

*P. aeruginosa* presenta un perfil moderado de multirresistencia para la mayoría de los antibióticos, incluyendo los carbapenémicos. Es importante realizar nuevamente una campaña de higiene de manos, limpieza y desinfección, ya que probablemente esta resistencia está asociada a brotes. Para evitar la presión selectiva por sobreuso de antibióticos *Anti-Pseudomonas* que puede contribuir a los perfiles de multirresistencia, deben usarse estos antibióticos de acuerdo con el protocolo institucional, siempre y cuando estén indicados.

El *S. aureus* presenta un perfil elevado de resistencia a oxacilina y con una CIM para vancomicina en su mayoría por encima de 1 µg/ml. Otro problema importante es el *Enterococcus* vancomicina-resistente. Esto requiere nuevamente la implementación de campañas para la higiene de manos y barreras de contacto, así como revisar los protocolos de desinfección y limpieza.
ANEXO 3: Ejemplo de manejo de la infección del tracto urinario complicada en Urgencias en el marco de un PROA

**Presencia de:***
- Alteraciones funcionales o Anatómicas Tracto urinario
- Genito masculino

**ITU complicada (Incluye polimicrobicós)***

**ITU no complicada***

**Síntomas del tracto urinario bajo intenso**
(Discreta, urgencia, disuria, dolor suprapúbico)

**Historia reciente de trauma o manipulación de tracto urinario con presencia de SRS (F<10^3 u>10^5,>50 Leucócitos/mm³, 1.000> Leucócitos/12.000)

**Urocultivo/Urinalisálil**
- Hemograma
- Creatinina
- Electrocardiograma (ECG)
- Hemocultivos
- Urografía/Endoscopia

**Factor de riesgo para infección por bacterias MDR***

**PR. P. aeruginosa***
- Uso de antibióticos antipseudomónicos en último mes
- Edad ≥75 años
- Hospitalización reciente en UCI
- Transferencia desde otras unidades hospitalarias
- Experiencia de uso de dispositivos invasivos (Ej: CVC)
- Exposición a definiciones antiguas

**PR. para Enterococcus spp***
- Edad >65 años
- Hospitalización reciente
- Urogastria urinaria
- Sonda urinaria a permanencia

**PR. para BLDs***
- Uso de β-lactámicos, Quinolonas y Piperacilina
- Infección en los últimos 3 meses
- Hemodinámica
- Infección genitourinaria
- Más de 3 episodios ITU en el último año
- Paciente en institución de cuidado permanente (Ej: hogar geriátrico)
- Sonda urinaria a permanencia
- Hospitalización reciente

**Considerar***
- Ceftriaxona 1 g/12h IV
- Cefotaxima 1-2 g/12h IV
- Ceftazidima 1,5 g/12h IV

**Desescazar una vez se tenga identificación y perfil de susceptibilidad***

**PR para Enterococcus spp***
- Vancomicina 1-3 g/12h IV
- Linezolid 600 mg/12h IV

**PR. para BLDs***
- Ceftriaxona 1 g/12h IV

*Para la selección de un esquema antibiótico tenga en cuenta el perfil epidemiológico local, el mecanismo de resistencia probable y la menor probabilidad de persistencia selectiva. MDR: Multirresistente, PR. Factor de Riesgo, BLDs: Betalactámicos de Spectrum extendido, Pip./Zar: Piperracilina/tazobactam, SRS: Síntomas de Respuesta Inflamatoria Sistémica.*
LECTURAS RECOMENDADAS


72. Soriano A. Relationship between Vancomycin Minimum Inhibitory Concentration and Antibiotic Efficacy in Methillin-resistant Staphylococcus aureus Bacteraemia. European Infectious Disease, 2009; 3(1):75-77


Table of Contents

Executive Summary ................................................. 2

Introduction ..................................................... 4

Goals

1. Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections ............................................ 11
2. Strengthen National One-Health Surveillance Efforts to Combat Resistance ......................................... 24
3. Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria ....................................... 36
4. Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines ........................................... 40
5. Improve International Collaboration and Capacities for Antibiotic-resistance Prevention, Surveillance, Control, and Antibiotic Research and Development ......................................... 49

Tables

1. National Targets for Combating Antibiotic-Resistant Bacteria ............................................. 6
2. Goals and Objectives ............................................. 9
3. Antibiotic-Resistant Threats in the United States ............................................. 60

Appendix .................................................................. 60
Executive Summary

Antibiotics have been a critical public health tool since the discovery of penicillin in 1928, saving the lives of millions of people around the world. Today, however, the emergence of drug resistance in bacteria is reversing the miracles of the past eighty years, with drug choices for the treatment of many bacterial infections becoming increasingly limited, expensive, and, in some cases, nonexistent. The Centers for Disease Control and Prevention (CDC) estimates that drug-resistant bacteria cause two million illnesses and approximately 23,000 deaths each year in the United States alone.

The National Action Plan for Combating Antibiotic-resistant Bacteria provides a roadmap to guide the Nation in rising to this challenge. Developed in response to Executive Order 13676: Combating Antibiotic-Resistant Bacteria—issued by President Barack Obama on September 18, 2014—the National Action Plan outlines steps for implementing the National Strategy for Combating Antibiotic-Resistant Bacteria and addressing the policy recommendations of the President’s Council of Advisors on Science and Technology (PCAST). Although its primary purpose is to guide activities by the U.S. Government, the National Action Plan is also designed to guide action by public health, healthcare, and veterinary partners in a common effort to address urgent and serious drug-resistant threats that affect people in the U.S. and around the world. Implementation of the National Action Plan will also support World Health Assembly resolution 67.25 (Antimicrobial Resistance), which urges countries to take urgent action at the national, regional, and local levels to combat resistance.

The goals of the National Action Plan include:

1. Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections.

By 2020, implementation of the National Action Plan will lead to major reductions in the incidence of urgent and serious threats, including carbapenem-resistant Enterobacteriaceae (CRE), methicillin-resistant Staphylococcus aureus (MRSA), and Clostridium difficile (see Table 1). The National Action Plan will also result in improved antibiotic stewardship in healthcare settings, prevention of the spread of drug-resistant threats, elimination of the use of medically-important antibiotics for growth promotion in food animals, and expanded surveillance for drug-resistant bacteria in humans and animals. Other significant outcomes include creation of a regional public health laboratory network, establishment of a specimen repository and sequence database that can be accessed by industrial and academic researchers, development of new diagnostic tests through a national challenge, and development of two or more
antibiotic drug candidates or non-traditional therapeutics for treatment of human disease. In addition, the effort to combat resistant bacteria will become an international priority for global health security.

Progress towards achieving these outcomes will be monitored by the U.S. Government Task Force that developed the National Action Plan. The Task Force, which is co-chaired by the Secretaries of Defense, Agriculture, and Health and Human Services, includes representatives from the Departments of State, Justice, Veterans Affairs, and Homeland Security, as well as the Environmental Protection Agency, the United States Agency for International Development, the Office of Management and Budget, the Domestic Policy Council, the National Security Council, the Office of Science and Technology Policy, and the National Science Foundation. Additionally, the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, created by Executive Order 13676, will provide advice, information, and recommendations to the Secretary of Health and Human Services regarding the National Action Plan’s programs and policies and their impact on the threat.

Implementation of the objectives and activities in the National Action Plan requires sustained, coordinated, and complementary efforts of individuals and groups around the world, including healthcare providers, healthcare leaders, veterinarians, agriculture industry leaders, manufacturers, policymakers, and patients. All of us who depend on antibiotics must join in a common effort to detect, stop, and prevent the emergence and spread of resistant bacteria.
Introduction

Vision: The United States will work domestically and internationally to prevent, detect, and control illness and death related to infections caused by antibiotic-resistant bacteria by implementing measures to mitigate the emergence and spread of antibiotic-resistance and ensuring the continued availability of therapeutics for the treatment of bacterial infections.

Antibiotics have been a critical public health tool since the discovery of penicillin in 1928, saving the lives of millions of people around the world. Today, however, the emergence of drug resistance in bacteria is reversing the gains of the past eighty years, with many important drug choices for the treatment of bacterial infections becoming increasingly limited, expensive, and, in some cases, nonexistent. The Centers for Disease Control and Prevention (CDC) estimates that each year at least two million illnesses and 23,000 deaths are caused by drug-resistant bacteria in the United States alone.

The loss of antibiotics that kill or inhibit the growth of bacteria means that we can no longer take for granted quick and reliable treatment of rare or common bacterial infections, including bacterial pneumonias, foodborne illnesses, and healthcare-associated infections. As more strains of bacteria become resistant to an ever larger number of antibiotics, we will also lose the benefits of a range of modern medical procedures—from hip replacements to organ transplants—whose safety depends on our ability to treat bacterial infections that may arise as post-surgical complications. Moreover, antibiotic-resistance also threatens animal health, agriculture, and the economy.

The National Action Plan for Combating Antibiotic-resistant Bacteria provides a roadmap to guide the Nation in rising to this challenge. The National Action Plan outlines steps for implementing the National Strategy for Combating Antibiotic-Resistant Bacteria and addressing the policy recommendations of the President’s Council of Advisors on Science and Technology. Although its primary purpose is to guide activities by the U.S. Government, the National Action Plan is also designed to guide action by public health, healthcare, and veterinary partners in a common effort to address urgent and serious drug-resistant threats (Table 3) that affect people in the U.S. and around the world.

Scope of the National Action Plan: “Antibiotic resistance” results from mutations or acquisition of new genes in bacteria that reduce or eliminate the effectiveness of antibiotics. “Antimicrobial resistance” is a broader term that encompasses resistance to drugs to treat infections caused by many different types of pathogens, including bacteria, viruses (e.g., influenza and the human immunodeficiency virus (HIV)), parasites (e.g., the parasitic protozoan that causes malaria), and fungi (e.g., Candida spp.). While all of these pathogens are dangerous to human health, the National Action Plan focuses on resistance in bacteria that present an urgent or serious threat to public health.
Goals of the National Action Plan

The National Action Plan—inaugurated by the guiding principles in Table 2—is organized around five goals for collaborative action by the U.S. Government, in partnership with foreign governments, individuals, and organizations aiming to strengthen healthcare, public health, veterinary medicine, agriculture, food safety, and research and manufacturing. Aggressive action will move the nation towards major reductions in the incidence of urgent and serious drug-resistant threats (Table 3), including carbapenem-resistant Enterobacteriaceae (CRE), methicillin-resistant Staphylococcus aureus (MRSA), and Clostridium difficile.

- Misuse and over-use of antibiotics in healthcare and food production continue to hasten the development of bacterial drug resistance, leading to loss of efficacy of existing antibiotics.
- Detecting and controlling antibiotic-resistance requires the adoption of a “One-Health” approach to disease surveillance that recognizes that resistance can arise in humans, animals, and the environment.
- Implementation of evidence-based infection control practices can prevent the spread of resistant pathogens.
- Interventions are necessary to accelerate private sector investment in the development of therapeutics to treat bacterial infections because current private sector interest in antibiotic development is limited.
- Researchers can use innovations and new technologies—including whole genome sequencing, metagenomics, and bioinformatic approaches—to develop next-generation tools to strengthen human and animal health, including:
  - Point-of-need diagnostic tests to distinguish rapidly between bacterial and viral infections as well as identify bacterial drug susceptibilities;
  - New antibiotics and other therapies that provide much needed treatment options for those infected with resistant bacterial strains; and
  - Antibiotic resistance is a global health problem that requires international attention and collaboration, because bacteria do not recognize borders.
Those goals include:

**GOAL 1: Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections.** Judicious use of antibiotics in healthcare and agricultural settings is essential to slow the emergence of resistance and extend the useful lifetime of effective antibiotics. Antibiotics are a precious resource, and preserving their usefulness will require cooperation and engagement by healthcare providers, healthcare leaders, pharmaceutical companies, veterinarians, the agricultural industry, and patients. Goal 1 activities include the optimal use of vaccines to prevent infections, implementation of healthcare policies and antibiotic stewardship programs that improve patient outcomes, and efforts to minimize the development of resistance by ensuring that each patient receives the right antibiotic at the right time at the right dose for the right duration. Prevention of resistance also requires rapid detection and control of outbreaks and regional efforts to control transmission across community and healthcare settings.

**GOAL 2: Strengthen National One-Health Surveillance Efforts to Combat Resistance.** Improved detection and control of drug-resistant organisms will be achieved through an integrated, “One-Health” approach that includes the enhancement and integration of data from surveil-
GOAL 3: Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria. Improved diagnostics for detection of resistant bacteria and characterization of resistance patterns will help healthcare providers make optimal treatment decisions and assist public health officials in taking action to prevent and control disease. Improved diagnostics will also help decrease unnecessary or inappropriate use of antibiotics. Goal 3 activities will accelerate the development of new diagnostics and expand their availability and use to improve treatment, enhance infection control, and achieve faster response to infections and outbreaks caused by resistant bacteria in hospitals and in the community.

GOAL 4: Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines. Despite the urgent need for new antibiotics, the number of products in the drug-development pipeline is small and commercial interest remains limited. The advancement of drug development—as well as non-traditional therapeutics and vaccines—will require intensified efforts to boost scientific research, attract private investment, and facilitate clinical trials of new drug candidates. Goal 4 activities will help accomplish these objectives by supporting basic and applied research, providing researchers with scientific services (e.g., specimens, sequence data, and regulatory guidance), and fostering public-private partnerships that strengthen the clinical trials infrastructure and reduce the risks, uncertainty, and obstacles faced by companies who are developing new antibiotics and/or other therapeutics and vaccines that can impact the use of antibiotics and the development of resistance.

GOAL 5: Improve International Collaboration and Capacities for Antibiotic-resistance Prevention, Surveillance, Control, and Antibiotic Research and Development. Antibiotic resistance is a worldwide problem that cannot be addressed by one nation in isolation. Goal 5 activities include working with foreign ministries of health and agriculture, the World Health Organization (WHO), the Food and Agriculture Organization (FAO), the World Organization for Animal Health (OIE), and other multinational organizations to enhance global capacity to detect, analyze, and report antibiotic use and resistance, create incentives for the development of therapeutics and diagnostics, and strengthen global efforts to prevent and control the emergence and spread of antibiotic-resistance. To advance these objectives, U.S. agencies will support development of a WHO Global Action Plan on Antimicrobial Resistance, enhance
international collaborations including cooperation under the European Union-United States Trans-Atlantic Task Force on Antimicrobial Resistance (TATFAR), and mobilize global health resources through the Global Health Security Agenda.

**Development of the National Action Plan**

The *National Action Plan* was developed in response to Executive Order 13676: Combating Antibiotic-Resistant Bacteria (Appendix 2), which was issued by President Barack Obama on September 18, 2014 in conjunction with the *National Strategy for Combating Antibiotic-Resistant Bacteria*.

The Executive Order calls for a U.S. Government Task Force to create a five-year action plan that lays out steps and milestones for achieving the Strategy’s goals and objectives (Table 2) and addressing the PCAST recommendations. The Task Force, which is co-chaired by the Secretaries of Defense, Agriculture, and Health and Human Services, includes representatives from the Department of State, the Department of Justice, the Department of Veterans Affairs, the Department of Homeland Security, the Environmental Protection Agency, the United States Agency for International Development, the Office of Management and Budget, the Domestic Policy Council, the National Security Council staff, the Office of Science and Technology Policy, and the National Science Foundation.

Development of the *National Action Plan* also supports World Health Assembly (WHA) resolution 67.25 (Antimicrobial Resistance), which was endorsed in May 2014 and urges countries to develop and finance national plans and strategies and take urgent action at the national, regional, and local levels to combat resistance. The resolution urges WHA Member States to develop practical and feasible approaches to, among other actions, extend the lifespan of drugs, strengthen pharmaceutical management systems and laboratory infrastructure, develop effective surveillance systems, and encourage the development of new diagnostics, drugs, and treatment options.

These recommendations are intended to inform the policy development process, and are not intended as a budget document. The commitment of resources to support these activities will be determined through the usual Executive Branch budget processes. Implementation of some of the actions in this report will require additional resources and these resources could be new or redirected from lower-priority Agency activities.

**Monitoring and Evaluation**

The Task Force created under Executive Order 13676 is charged with providing the President with annual updates on Federal Government actions to combat antibiotic resistance, including progress made in implementing the *National Action Plan*, plans for addressing obstacles and challenges, and recommendations for new or modified actions. The Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria will provide advice, information, and recommendations to the Secretary of Health and Human Services regarding the programs and policies developed in the National Action Plan.
Partnerships and Implementation

Implementation of the National Action Plan will require the sustained, coordinated, and complementary efforts of individuals and groups around the world, including public and private sector partners, healthcare providers, healthcare leaders, veterinarians, agriculture industry leaders, manufacturers, policymakers, and patients. All of us who depend on antibiotics must join in a common effort to detect, stop, and prevent the emergence and spread of resistant bacteria.

<table>
<thead>
<tr>
<th>TABLE 2: GOALS AND OBJECTIVES: Combating Antibiotic-Resistant Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GOAL 1: Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections</strong></td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
</tr>
<tr>
<td>1.1 Implement public health programs and reporting policies that advance antibiotic-resistance prevention and foster antibiotic stewardship in healthcare settings and the community.</td>
</tr>
<tr>
<td>1.2 Eliminate the use of medically-important antibiotics for growth promotion in food-producing animals and bring other agricultural uses of antibiotics, for treatment, control, and prevention of disease, under veterinary oversight.</td>
</tr>
<tr>
<td>1.3 Identify and implement measures to foster stewardship of antibiotics in animals.</td>
</tr>
<tr>
<td><strong>GOAL 2: Strengthen National One-Health Surveillance Efforts to Combat Resistance Objectives</strong></td>
</tr>
<tr>
<td>2.1 Create a regional public health laboratory network to strengthen national capacity to detect resistant bacterial strains and a specimen repository to facilitate development and evaluation of diagnostic tests and treatments.</td>
</tr>
<tr>
<td>2.2 Expand and strengthen the national infrastructure for public health surveillance and data reporting, and provide incentives for timely reporting of antibiotic-resistance and antibiotic use in all healthcare settings.</td>
</tr>
<tr>
<td>2.3 Develop, expand, and maintain capacity in State and Federal veterinary and food safety laboratories to conduct antibiotic susceptibility testing and characterize select zoonotic and animal pathogens.</td>
</tr>
<tr>
<td>2.4 Enhance monitoring of antibiotic-resistance patterns, as well as antibiotic sales, usage, and management practices, at multiple points in the production chain for food animals and retail meat.</td>
</tr>
<tr>
<td><strong>GOAL 3: Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria</strong></td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
</tr>
<tr>
<td>3.1 Develop and validate new diagnostics—including tests that rapidly distinguish between viral and bacterial pathogens and tests that detect antibiotic-resistance—that can be implemented easily in a wide range of settings.</td>
</tr>
<tr>
<td>3.2 Expand availability and use of diagnostics to improve treatment of antibiotic-resistant infections, enhance infection control, and facilitate outbreak detection and response in healthcare and community settings.</td>
</tr>
<tr>
<td><strong>GOAL 4: Accelerate Research to Develop New Antibiotics, Other Therapeutics, Vaccines, and Diagnostics</strong></td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
</tr>
<tr>
<td>4.1 Conduct research to enhance understanding of environmental factors that facilitate the development of antibiotic-resistance and the spread of resistance genes that are common to animals and humans.</td>
</tr>
<tr>
<td>4.2 Increase research focused on understanding the nature of microbial communities, how antibiotics affect them, and how they can be harnessed to prevent disease.</td>
</tr>
<tr>
<td>4.3 Intensify research and development of new therapeutics and vaccines, first-in-class drugs, and new combination therapies for treatment of bacterial infections.</td>
</tr>
<tr>
<td>4.4 Develop non-traditional therapeutics and innovative strategies to minimize outbreaks caused by resistant bacteria in human and animal populations.</td>
</tr>
<tr>
<td>4.5 Expand ongoing efforts to provide key data and materials to support the development of promising antibacterial drug candidates.</td>
</tr>
</tbody>
</table>
### TABLE 2: GOALS AND OBJECTIVES: Combating Antibiotic-Resistant Bacteria

#### GOAL 5: Improve international collaboration and capacities for prevention, surveillance and antibiotic research and development

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Surveillance</th>
<th>Research and Development</th>
<th>Prevention and Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1</td>
<td>Promote laboratory capability to identify at least 3 of the 7 WHO priority antimicrobial resistant (AMR) pathogens(^2) using standardized, reliable detection assays.</td>
<td>Establish and promote international collaboration and public-private partnerships to incentivize development of new therapeutics to counter antibiotic-resistance including new, next-generation, and other alternatives to antibiotics, vaccines, and affordable, rapidly deployable, point-of-need diagnostics.</td>
<td>Support countries to develop and implement national plans to combat antibiotic-resistance and strategies to enhance antimicrobial stewardship.</td>
</tr>
<tr>
<td>5.2</td>
<td>Collaborate with WHO, OIE, and other international efforts focused on the development of integrated, laboratory-based surveillance to detect and monitor antibiotic-resistance in relevant animal and human foodborne pathogens.</td>
<td></td>
<td>Partner with other nations to promote quality, safety, and efficacy of antibiotics and strengthen their pharmaceutical supply chains.</td>
</tr>
<tr>
<td>5.3</td>
<td>Develop a mechanism for international communication of critical events that may signify new resistance trends with global public and animal health implications.</td>
<td></td>
<td>Coordinate regulatory approaches by collaborating with international organizations such as FAO and OIE to harmonize international data submission requirements and risk assessment.</td>
</tr>
<tr>
<td>5.4</td>
<td>Promote the generation and dissemination of information needed to effectively address antibiotic-resistance.</td>
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</tbody>
</table>

\(^2\) The WHO priority AMR pathogens are a subset of the pathogens identified as urgent and serious threats in Table 3.
GOAL 1. Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections

Actions taken to achieve Goal 1 will fulfill:

- **Executive Order 13676, Sections 5 and 7:**
  - Improved Antibiotic Stewardship
  - Preventing and Responding to Infections and Outbreaks with Antibiotic-Resistant Organisms
- **Provisions in PCAST Recommendations #2, #6, and #7:**
  - Effective Surveillance & Response for Antibiotic-resistance
  - Improving Stewardship of Existing Antibiotics in Health Care
  - Limit the Use of Antibiotics in Animal Agriculture

Judicious use of antibiotics in healthcare and agricultural settings is essential to slow the emergence of resistance and extend the useful lifetime of effective antibiotics. Antibiotics are a precious resource, and preserving their usefulness will require cooperation and engagement by healthcare providers, healthcare leaders, pharmaceutical companies, veterinarians, the agricultural industry, and patients. Effective dissemination of information to the public is critical. Prevention of resistance also requires rapid detection and control of infections and outbreaks (see also Goal 2) and regional efforts to control transmission across community and healthcare settings.

Goal 1 includes activities to foster antibiotic stewardship by improving prescribing practices across all healthcare settings, prevent the spread of drug-resistant threats in healthcare facilities and communities, and reduce and eventually eliminate the use of medically-important antibiotics for growth promotion in animals.

By 2020, significant outcomes of Goal 1 will include:

- Establishment of antibiotic stewardship programs in all acute care hospitals and improved antibiotic stewardship across all healthcare settings.
- Reduction of inappropriate antibiotic use by 50% in outpatient settings and by 20% in inpatient settings.
- Establishment of State Antibiotic Resistance (AR) Prevention (Protect) Programs in all 50 states to monitor regionally important multidrug resistant organisms and provide feedback and technical assistance to healthcare facilities.
• Elimination of the use of medically-important antibiotics for growth promotion in food-producing animals.

• Requirement of veterinary oversight for use of medically-important antibiotics in the feed or water of food-producing animals.

1.1 Implement public health programs and reporting policies that advance antibiotic resistance prevention and foster antibiotic stewardship in healthcare settings and the community.

Perhaps the single most important action to slow the development and spread of antibiotic-resistant infections is to change the way antibiotics are used. Antibiotics are overprescribed in both human and animal settings, which makes everyone less safe. Investments in this area will be used to develop education and outreach programs to clarify and strengthen responsible, appropriate use of antibiotics in humans and animals. Efforts in this area will help greatly in slowing down the spread of resistant bacteria. This commitment to always use antibiotics appropriately and safely—to use the right antibiotic at the right time at the right dose for the right duration—is known as antibiotic stewardship.

Sub-Objective 1.1.1A: Strengthen antibiotic stewardship in inpatient, outpatient, and long-term care settings by expanding existing programs, developing new ones, and monitoring progress and efficacy.

The establishment and expansion of antibiotic stewardship programs will improve patient outcomes and minimize the development of resistance by ensuring judicious use of antibiotics.

Milestones for provision of educational materials to enhance antibiotic stewardship in outpatient settings are provided under Sub-Objective 1.1.1B.

Milestones

Within one year:

• The Departments of Health and Human Services (HHS), Defense (DOD), and Veterans Affairs (VA) will review existing regulations and propose new ones, as needed, requiring hospitals, ambulatory surgery centers, dialysis facilities, and other inpatient facilities to implement robust antibiotic stewardship programs that align with the CDC Core Elements. HHS, DOD, and VA will also work together to optimize standardization of stewardship programs and activities, including monitoring activities and reporting criteria.

• The National Healthcare Safety Network (NHSN) will begin tracking the number of healthcare facilities with stewardship policies and programs in place.

• DOD will establish a multidisciplinary group, under the purview of the Assistant Secretary of Defense for Health Affairs, to support and coordinate stewardship activities across DOD.
Within three years:

- All hospitals that participate in Medicare and Medicaid programs must comply with Conditions of Participation (COP). The Centers for Medicare & Medicaid Services (CMS) will issue new COPs or revise current COP Interpretive Guidelines to advance compliance with recommendations in CDC's Core Elements of Hospital Antibiotic Stewardship Programs. HHS, DOD, and VA will also implement policies that:
  - Encourage implementation of antibiotic stewardship programs as a condition for receiving Federal grants for health care delivery (e.g., in community healthcare centers).
  - Require health facilities operated by the U.S. Government to develop and implement antibiotic stewardship programs and participate in NHSN reporting (see Objective 2.2).

- All acute care hospitals governed by the CMS COP will implement antibiotic stewardship programs. CMS will expand COP requirements to apply to long-term acute care hospitals, other post-acute facilities, ambulatory surgery centers, and dialysis centers.

- CMS will revise existing Interpretive Guidelines (IGs), as needed, to include antimicrobial stewardship improvements. For example, IGs on Quality Assurance and Performance Improvement for hospitals may incorporate antibiotic-stewardship performance measures developed by the CDC, the Agency for Healthcare Research and Quality (AHRQ), or other professional organizations.

- Training webinars for CMS surveyors will be updated to include information on antibiotic utilization in nursing homes, in accordance with existing IGs in the Infection Control Nursing Home regulations.

- CDC, CMS, AHRQ, and other partners will issue guidance on antibiotic stewardship and best practices for ambulatory surgery centers, dialysis centers, nursing homes and other long-term care facilities, doctors’ offices and other outpatient settings, pharmacies, emergency departments, and medical departments at correctional facilities.

- At least 25 States, the District of Columbia, and Puerto Rico will establish or enhance antibiotic stewardship activities in inpatient healthcare delivery settings, in accordance with the CDC Core Elements. CDC will support these efforts via State AR Prevention (Protect) Programs for Healthcare (“AR Protect Programs”; see also Sub-Objective 1.1.2).

Within five years:

- DOD will support antibiotic stewardship programs and interventions critical for maintaining quality health care throughout the Military Healthcare System (MHS).

- CDC will work with select hospital systems to expand antibiotic use reporting and stewardship implementation, and will partner with nursing organizations to develop and implement stewardship programs and interventions in a set of nursing homes.

- All states will establish or enhance antibiotic stewardship activities in healthcare delivery settings.
Sub-Objective 1.1.1B: Strengthen educational programs that inform physicians, veterinarians, members of the agricultural industry, and the public about good antibiotic stewardship. Educational programs that promote good antibiotic stewardship in healthcare settings include:

- *Get Smart: Know When Antibiotics Work.* Many antibiotics prescribed in doctors’ offices, clinics, and other outpatient settings are not needed. This program focuses on appropriate antibiotic prescribing and use for common illnesses in children and adults.

- *Get Smart for Healthcare.* Many patients in hospitals, nursing homes, and other healthcare facilities receive antibiotics to fight infections, but these drugs are often prescribed incorrectly. This program helps clinicians prescribe the right drugs for the right patients at the right doses and times.

The United States Department of Agriculture (USDA), CDC, and the Food and Drug Administration (FDA) will also continue to work with partners in the agriculture industry to advance appropriate use of antibiotics in food animals and promote collaborations among partners in medicine, veterinary medicine, and public health.

Additional milestones for provision of educational materials to enhance antibiotic stewardship in agricultural settings are provided under Sub-Objectives 1.2.3 and 1.3.1.

**Milestones**

**Within one year:**

- CDC and VA will apply lessons learned from the CDC and VA pilot project to provide clinicians with support for making prescribing decisions based on judicious use of antibiotics and will submit a manuscript for publication describing initial research findings from this effort.

**Within three years:**

- CDC will support public health departments in establishing statewide programs for antibiotic stewardship and appropriate antibiotic use. These programs will identify healthcare facilities with high antibiotic-prescribing rates and use lessons learned from the CDC and VA pilot project (see above) and other best practices to improve antibiotic prescribing in these facilities. The success of these efforts will be assessed by measuring changes in prescribing rates and in clinicians’ understanding of antibiotic stewardship activities and programs.

- CDC will provide technical assistance to Federal facilities (e.g., those operated by DOD, the VA, and the Indian Health Service) and other large health systems in scaling up implementation and assessment of interventions to improve outpatient antibiotic prescribing, extending effective interventions to long-term care settings, and ensuring long-term sustainability of antibiotic stewardship efforts.

- DOD will initiate the planning and approval process to modify clinical decision-support interventions in DOD facilities in targeted regions.

- CDC, CMS, and partners will propose expanded quality measures for antibiotic prescribing.
CMS will expand the Physician Quality Reporting System (PQRS) to include quality measures that discourage inappropriate antibiotic use to treat non-bacterial infections, such as respiratory tract infections.

CDC will expand training and support to acute care facilities and nursing homes to improve antibiotic stewardship, as part of the Get Smart for Healthcare project.

Within five years:

- CDC will evaluate the impact of quality measures on antibiotic use and provide feedback to healthcare partners.

Additionally, CDC will continue to host a Get Smart About Antibiotics Week observance each November to raise public awareness about antibiotic-resistance and the importance of appropriate antibiotic prescribing.

Sub-Objective 1.1.2: Expand collaborative efforts by groups of healthcare facilities that focus on preventing the spread of antibiotic-resistant bacteria that pose a serious threat to public health (Table 3).

Public health action to prevent transmission of healthcare-associated infections—including drug-resistant bacterial infections—has traditionally been taken by individual healthcare facilities. However, drug-resistant organisms—including multidrug resistant organisms (MDROs) such as CRE and MRSA, and Clostridium difficile infections that are associated with antibiotic use (Table 3)—can spread regionally from one healthcare facility to another when patients colonized or infected with resistant bacteria move between hospitals or long-term care facilities within a state or locality. It is therefore imperative that healthcare facilities work together, in close partnership with state health departments, to implement effective interventions that slow the regional spread of drug-resistant pathogens.

Milestones

Within one year:

- The DOD Multidrug-Resistant Organism Repository & Surveillance Network (MRSN) will expand its detection and reporting capabilities to include *Clostridium difficile* and other high-risk drug-resistant pathogens.

Within three years:

- At least 25 states, the District of Columbia, and Puerto Rico will establish or enhance State AR Prevention (Protect) Programs to improve antibiotic use and reduce transmission of resistant pathogens. Activities will include measuring the incidence of at least one regionally important MDRO, providing healthcare facilities with feedback on local and regional MDRO rates, and providing healthcare facilities with technical assistance to advance MDRO prevention. CDC and CMS Quality Improvement Networks (QINs) will work with state and large local health...
departments to advance these efforts. QINs are groups of health quality experts, clinicians, and consumers who help improve the care delivered to people with Medicare.

- At least 20 state health departments will maintain advanced capacity for rapid response to drug-resistant gonorrhea, including capacity to detect, diagnose, and investigate suspected resistant cases within their state or region and assist healthcare providers in providing appropriate treatment of infected patients.

Within five years:

- CDC will expand capacity to prevent the importation of cases of multidrug resistant Tuberculosis (TB) (MDR-TB) by doubling TB screening among migrants from high-incidence countries from 500,000 to 1 million persons per year.
- State AR Prevention (Protect) Programs will be in place in all 50 states, as well as the District of Columbia and Puerto Rico.

**Sub-Objective 1.1.3:** Implement annual reporting of antibiotic use in inpatient and outpatient settings and identify geographic variations and/or variations at the provider and/or patient level that can help guide interventions.

Antibiotic resistance in healthcare settings is a significant threat to public health. Because nearly all Americans receive care in a healthcare setting at some point in their lives, the problem can affect anyone. Patients undergoing chemotherapy for cancer and very sick patients in intensive care units are at special risk, because they are already vulnerable due to weakened immune systems and underlying illness.

Through its antibiotic use (AU) and antimicrobial resistance (AR) modules, the National Health Safety Network (NHSN) receives hospital data on:

- Amounts of specific antibiotics used to treat hospitalized patients (AU reporting).
- Cases of drug-resistant disease (AR reporting).

The AU and AR data allow healthcare facilities to target areas of concern, make needed improvements, and track the success of their efforts. NHSN data also allow CDC to track regional and national trends in drug resistant diseases and provide hospitals with feedback about prescribing practices and antibiotic stewardship.

Milestones for AU reporting are provided below, as part of the effort to foster antibiotic stewardship. Additional milestones for AR reporting and for strengthening the public health surveillance infrastructure that supports AU and AR reporting are provided in Goal 2.
Milestones: Reporting Antibiotic Use in Inpatient Settings

Within one year:

- CDC will finalize arrangements for the purchase of proprietary data on inpatient antibiotic use to supplement NHSN data until a larger number of hospitals begin to utilize the NHSN module for antibiotic use reporting.
- CDC will work with healthcare and public health partners to propose new healthcare-facility antibiotic use measures to the National Quality Forum (NQF; see also Sub-Objective 2.2.1).

Within three years:

- CDC will use data collected through the NHSN AU module to provide annual national estimates of aggregated inpatient antibiotic use and feedback to healthcare facilities on antibiotic use, indicating whether antibiotic use rates are above or below the national average.
- CDC will establish routine reporting of antibiotic use and resistance data from select hospital systems via the NHSN AU and AR modules (see Objective 2.2).
- DOD will centralize its reporting of inpatient antibiotic use to NHSN.

Within five years:

- CDC will provide estimates of inappropriate inpatient antibiotic prescribing rates by state and region and use this data to target and prioritize intervention efforts.

Milestones: Reporting Antibiotic Use in Outpatient Settings

Within one year:

- CDC will report outpatient prescribing rates for 2011 and 2012 and use this data to target and prioritize intervention efforts.
- CDC will establish a benchmark (in terms of prescriptions per population) for reduction in antibiotic use.

Within three years:

- Starting in 2016, CDC will issue yearly reports on progress in meeting the national target of 50% reduction in inappropriate use of antibiotics in outpatient settings (see above), as well as on overall trends in antibiotic prescribing.
- DOD will establish goals for reducing antibiotic use in DOD facilities that provide outpatient care for military personnel and their families.
- DOD will centralize reporting of outpatient antibiotic use and issue annual summary reports.
Sub-Objective 1.1.4: Develop and pilot new interventions to address geographic, socio-cultural, policy, economic, and clinical drivers of the emergence and spread of antibiotic-resistance and misuse or overuse of antibiotics.

Milestones

Within one year:

- The Agency for Healthcare Research and Quality (AHRQ) and CDC will host a meeting of experts and stakeholders to consider knowledge gaps for prevention of antibiotic-resistant, healthcare-associated infections and identify potential interventions for development, field testing, and eventual widespread implementation.
- CDC Emerging Infections Program (EIP) sites will perform assessments of antibiotic use and resistance to allow updating of national estimates of antibiotic-resistant, healthcare-associated infections and of antibiotic-resistance threats in the United States.
- CDC EIP sites will solicit applications for funding large-scale interventions to reduce *C. difficile* infections through enhanced antibiotic stewardship programs.

Within three years:

- The CDC Prevention Epicenters Program will evaluate one or more novel antibiotic-resistance prevention tools for use in diverse healthcare settings.
- CDC EIP sites will initiate large-scale demonstration projects to field-test AR interventions developed by the Prevention Epicenters Program.
- AHRQ will sponsor research to develop improved methods and approaches for combating antibiotic-resistance and conducting antibiotic stewardship activities in multiple healthcare settings, with a focus on long-term and ambulatory care centers, as well as acute care hospitals. AHRQ will support translation of research findings into antibiotic-resistance prevention tools that can be implemented by healthcare providers in long-term and ambulatory care settings, as well as in hospitals.
- CDC will perform two randomized control trials to test improved treatment methods to prevent the spread of MDR-TB.

Within five years:

- CDC will finalize data collection to validate new antibiotic-resistance prevention tools tested by the EIP sites and transition validated interventions to ongoing State AR Prevention (Protect) Programs.
Sub-Objective 1.1.5: Streamline regulatory processes for updating and approving or clearing antibiotic susceptibility testing devices, as appropriate, so that clinicians receive up-to-date interpretive criteria to guide antibacterial drug selection.

Manufacturers of antibiotic susceptibility testing (AST) devices provide interpretive criteria that are used by healthcare providers to categorize a bacterial isolate as “susceptible” or “resistant” to particular antibiotics. However, when bacteria develop new means of resistance, the interpretive criteria may no longer be clinically useful. Rapid updating of interpretive criteria in AST devices—by manufacturers or by standards development organizations (SDOs)—is therefore essential to provide accurate information to guide appropriate drug treatment.

Milestones

Within one year:

- FDA will provide technical assistance, as appropriate, on legislative proposals being considered to streamline updating of interpretive criteria for AST devices.

Within five years:

- FDA will update AST interpretive criteria more efficiently and rapidly (e.g., by adopting criteria developed by SDOs rather than including interpretive guidelines on labels).

1.2 Eliminate the use of medically important antibiotics for growth promotion in food-producing animals and bring under veterinary oversight other in-feed and in-water uses of antibiotics that are medically important for treatment, control, and prevention of disease.

FDA’s strategy to ensure the judicious use of medically important antibiotics in animal agriculture is outlined in two guidance documents:

- FDA Guidance for Industry (GFI) #209—The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals—is intended to limit medically important antimicrobial drugs to uses in animals that (1) are considered necessary for assuring animal health, and (2) include veterinary oversight or consultation.

- FDA Guidance for Industry (GFI) #213—New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209—calls for:
  - Voluntary revision of the FDA-approved use conditions on the labels of medically important antibiotics to remove production indications, such as increased rate of weight gain and improved feed efficiency.
— Phasing in veterinary oversight of the remaining therapeutic uses of medically important antibiotics in feed or water by changing the current over-the-counter status of these drugs. Because antibiotics in feed or water are typically administered to herds or flocks of food-producing animals, in-feed or in-water antibiotic use leads to an increased risk of selecting for resistance.

**Sub-Objective 1.2.1:** Implement FDA GFI #213 to eliminate the use of medically important antibiotics for growth promotion in animals and bring other in-feed and in-water uses of medically important antibiotics under veterinary oversight. FDA should evaluate the adoption of the proposed changes under GFI #213 after the three-year implementation period and take further action as appropriate.

**Milestones**

**Within one year:**
- FDA will finalize changes to the Veterinary Feed Directive (VFD) regulation to encourage manufacturers to transition the dispensing status of in-feed antibiotics covered by GFI #213 from over-the-counter (OTC) to VFD status, which requires veterinary oversight. FDA will publish an enhanced summary report of antibiotics sold or distributed for use in food-producing animals from 2009 to 2013. This report will support the effort to monitor the antibiotic usage aspects of Guidance #213 (see also Objective 2.2.4).

**Within three years:**
- FDA, in partnership with animal drug sponsors, will complete all changes recommended by GFI #213 and GFI #209. Once these changes are complete, growth promotion uses of medically important antibiotics will no longer be permitted, and the use of medically important antibiotics in the feed or water of food-producing animals will require veterinary oversight.

**Sub-Objective 1.2.2:** Assess progress toward eliminating the use of medically important antibiotics for growth promotion in food-producing animals through enhanced data collection on antibiotic sales and use.

**Milestones**

**Within five years:**
- FDA, in partnership with USDA and the animal agricultural industry, will evaluate and report on the impact of GFI #213 by analyzing data on antibiotic use, including total sales of antibiotics in animal agriculture and types and prevalence of antibiotic-resistance among selected foodborne pathogens and commensals isolated from retail meat and farm animals.
Milestones for enhancing collection of data to monitor the impact of GFI #213 in fostering the judicious use of antibiotics in food-producing animals are provided under Objective 2.4.

**Sub-Objective 1.2.3:** Develop and implement educational outreach efforts to ensure that veterinarians and animal producers receive information and training to support implementation of these changes.

**Within three years:**
- FDA will collaborate with veterinary organizations, animal producer organizations, the animal feed industry, and others to develop and implement educational outreach efforts to ensure that veterinarians and animal producers receive the necessary information and training to support implementation of GFI #213 (see also: Sub-Objective 1.3.1).

**Sub-Objective 1.2.4:** Optimize public awareness about progress toward eliminating the use of medically important antibiotics for animal-growth promotion.

**Within one year:**
- FDA will publish and maintain a public web listing of products affected by GFI #213.
- FDA will begin publishing periodic updates summarizing progress in adoption of the changes proposed in GFI #213.

**Within three years:**
- FDA will publish a final assessment of the progress of GFI #213 on eliminating the use of medically important antibiotics for animal-growth promotion.

**1.3 Identify and implement measures to foster stewardship of antibiotics in animals.**

**Sub-Objective 1.3.1:** Develop, implement, and measure the effectiveness of evidence-based educational outreach to veterinarians and animal producers to advance antibiotic stewardship and judicious use of antibiotics in agricultural settings.

**Milestones**

**Within one year:**
- FDA and USDA will consult with livestock and veterinary organizations on the development of educational outreach materials on judicious use of antibiotics and antibiotic stewardship, and
will meet with the American Veterinary Medical Association and the American Association of Veterinary Medical Colleges to consider the incorporation of additional material on antibiotic resistance and antibiotic stewardship into the curricula of U.S. veterinary colleges.

- USDA will conduct assessments in various animal production and veterinary settings to identify priority areas in which research is needed to support the development and validation of stewardship activities to assure judicious antibiotic use.

- USDA will solicit applications to the USDA Antimicrobial Resistance Initiative Program, which aims to advance development and use of antibiotic stewardship practices that assure judicious use of antibiotics in agriculture. Applicants may propose a combination of activities, including research studies and development of educational and outreach materials. Projected outcomes of the educational and outreach activities include better preparation of the next generation of veterinarians and laboratory scientists. Projected outcomes of the research activities include development of sustainable strategies to mitigate antibiotic resistance (see Objective 4).

**Within 3 years:**

- USDA will support the distribution of educational and outreach materials on antibiotic stewardship and judicious use of antibiotics that target veterinarians, producers, educators, and consumers. These activities will be accomplished through the Antimicrobial Resistance Initiative awardees whose integrated projects are linked to the Cooperative Extension System for education and extension/outreach activities.

**Sub-Objective 1.3.2:** Foster collaborations and public-private partnerships with public health, pharmaceutical, and agricultural stakeholders to facilitate identification and implementation of interventions (e.g., good husbandry practices) to reduce the spread of antibiotic-resistance.

**Milestones**

**Within one year:**

- FDA and USDA will identify priority areas for research to develop and validate stewardship activities to reduce the spread of antibiotic-resistance.

- FDA and USDA will work with livestock and veterinary organizations to consider ways to develop, update, and incorporate assessments of antibiotic stewardship activities into quality assurance programs.

**Within three years:**

- FDA and USDA will support applied research in field settings to demonstrate the feasibility and effectiveness of stewardship programs and test and validate alternatives to traditional uses of antibiotics in agriculture.
Within five years:

- FDA and USDA will identify validated interventions to reduce the spread of antibiotic resistance and work with public and private sector partners to incorporate them into veterinary practice.

**Sub-Objective 1.3.3:** Identify, develop, and revise key agricultural practices that allow timely and effective implementation of interventions that improve animal health and efficient production.

**Milestones**

Within three years:

- FDA and USDA will support drivers-of-change studies to determine which stewardship materials and educational approaches are most effective in improving antibiotic use practices.

**Sub-Objective 1.3.4:** Develop appropriate metrics to gauge the success of stewardship efforts and guide their continued evolution and optimization.

**Milestones**

Within three years:

- FDA and USDA will:
  - Collect additional data regarding antibiotic use and resistance in food-producing animals. These data will supplement existing surveillance data used to evaluate the impact of GFI #213 on use practices and resistance trends over time.
  - Measure changes in antibiotic stewardship programs and practices as part of quality assurance programs in cattle operations and swine and broiler chicken production.
  - Use baseline data from the National Animal Health Monitoring System (NAHMS), where available, to evaluate changes over a 5-year time horizon.
GOAL 2. Strengthen National One-Health Surveillance Efforts to Combat Resistance

Actions taken to achieve Goal 2 will fulfill:

- **Executive Order 13676, Section 6:**
  - Strengthening National Surveillance Efforts for Resistant Bacteria
- **Provisions in PCAST Recommendations #2 and #6:**
  - Effective Surveillance & Response for Antibiotic Resistance
  - Improving Stewardship of Existing Antibiotics in Health Care

The “One-Health” approach to disease surveillance for human and animal pathogens is critical to combat antibiotic-resistance. Improved detection and control can be achieved through enhancement and integration of data from surveillance systems that monitor human pathogens and commensals—including NHSN, the Emerging Infections Program (EIP), and the National Antimicrobial Resistance Monitoring System (NARMS)—with data from surveillance systems that monitor animal pathogens—including the National Animal Health Monitoring System (NAHMS), the National Animal Health Laboratory Network (NAHLN), and the Veterinary Laboratory Investigation and Response Network (Vet-LIRN). These activities will provide high-quality data, including detailed genomic data, and other information necessary to track resistant bacteria in diverse settings in a timely fashion.

Goal 2 activities include creation of a Detect Network of Antimicrobial Resistance (AR) Regional Laboratories that will provide a standardized platform for resistance testing and advanced capacity for genetic characterization of resistant bacteria, including whole genome sequencing. In addition, Goal 2 activities will enhance monitoring of antibiotic sales, usage, resistance and management practices at multiple points along in the food-production chain, from farms to processing plants to supermarkets.

By 2020, significant outcomes of Goal 2 will include:

- Creation of a regional public health network—the Detect Network of AR Regional Laboratories—for resistance testing, a specimen repository for resistant bacterial strains, and a National Sequence Database of Resistant Pathogens.
- Routine reporting of antibiotic use and resistance data to NHSN by 95% of Medicare-eligible hospitals, as well as by DOD and VA healthcare facilities.
- Routine testing of zoonotic and animal pathogens for antibiotic susceptibility at ten to twenty NAHLN and Vet-LIRN member laboratories, using standardized testing methods and data-sharing practices.
• Publication of enhanced summary reports on the sale and distribution of antibiotics approved for use in food-producing animals, issued on an annual basis.

2.1 Create a regional public health laboratory network to strengthen national capacity to detect resistant bacterial strains, and create a specimen repository to facilitate development and evaluation of diagnostic tests and treatments.

Sub-Objective 2.1.1: Create a regional public health laboratory network that uses standardized testing platforms to expand the availability of reference testing services, characterize emerging resistance patterns and bacterial strains obtained from outbreaks and other sources, and facilitate rapid data analysis and dissemination of information.

Milestones

Within one year:

• CDC will develop an implementation plan for the Detect Network of AR Regional Laboratories that considers all aspects of operation, including specimen transport, testing, reporting, and data-sharing.

• Multidrug-resistant Organism Repository & Surveillance Network (MRSN) will be formally recognized as a reference laboratory network with responsibility for reporting data on antibiotic resistance and antibiotic use in military treatment facilities. It will expand its mission to include rapid characterization of emerging resistance patterns, laboratory support during outbreak investigations, and reporting of clinically relevant bacterial pathogens for facilities that serve military service members and their families.

Within three years:

• CDC will designate at least five public health laboratories as part of the Detect Network of Regional AR Laboratories, which is charged with rapid detection of outbreaks caused by drug-resistant pathogens, characterization of resistance mechanisms, and tracking resistance trends and identifying emerging forms of resistance. CDC will work with DOD and USDA to share resistance detection strategies and protocols.

• CDC will work with the Association of Public Health Laboratories (APHL), state and local health laboratories, and other partners to provide technical assistance and guidance to the Regional AR Laboratories, as needed.

Sub-Objective 2.1.2: Link data generated by the regional public health laboratory network to existing public health surveillance networks so that antibiotic susceptibility testing data
are immediately available to local, state, and Federal public health authorities as they detect and investigate outbreaks, as well as to veterinary diagnostic and food safety laboratory databases and/or surveillance systems, as needed.

**Milestones**

**Within three years:**

- The five designated Detect Network Regional AR Laboratories (Sub-Objective 2.1.1) will be integrated into an AR communications network that posts early warning alerts and reports urgent results and trends.
- The AR communication network will establish linkages with DOD and VA clinical, veterinary, and food safety laboratories.

**Sub-Objective 2.1.3:** Create a repository of resistant bacterial strains (an “isolate bank”) and maintain a well-curated reference database that describes the characteristics of these strains. The repository will aid biotechnology and pharmaceutical companies that develop new antibiotics and therapeutics and/or design next-generation tests, diagnostic test developers and regulatory agencies who evaluate these tests, government facilities, academic labs, and pharmaceutical companies that test antibiotics for clinical effectiveness and researchers, regulators, and others who assess the effectiveness of interventions to prevent resistance.

**Milestones**

**Within one year:**

- CDC and FDA will develop a defined set of microorganisms to be included in a repository of resistant bacterial strains, including the urgent and serious threats listed in Table 1, and a bioinformatics database to maintain detailed information on the drug susceptibilities and resistance mechanisms of each repository strain.
- The DOD will post data on a representative sample of characterized isolates on a website that can be accessed by authenticated users.

**Within three years:**

- CDC and FDA will create the repository and database for resistant bacterial strains and, in conjunction with DOD, will provide isolates to diagnostic test manufacturers and research laboratories, as needed.
• DOD will continue to maintain its repository of resistant bacterial strains within the MRSN, update procedures for specimen collection, storage, and data-sharing, and share information, as appropriate, with industry, academic, non-profit, and government stakeholders.

Annually thereafter:
• CDC and FDA will update the repository of bacterial strains, incorporating isolates with new resistance mechanisms or emerging resistance patterns identified by the national infectious disease surveillance system.
• CDC, FDA, and DOD will update procedures for strain collection, storage, and data-sharing.

**Sub-Objective 2.1.4:** Develop and maintain a national sequence database of resistant pathogens.

**Milestones**

**Within one year:**
• FDA and the National Institutes of Health (NIH) will pilot-test a sequence database containing more than 550 drug-resistant bacterial strains, with accompanying clinical and demographic data (“metadata”). The entries will cover a range of organisms selected by CDC to assist in diagnostic development.
• NIH and partners will sequence additional high-priority, drug-resistant strains to add to the database.
• DOD will stand up its diagnostic sequence database, inclusive of genomic information (including raw reads and interpretations/annotations) and relevant phenotypic metadata for access by authenticated users.

**Within three years:**
• FDA and NIH will review the pilot project to address challenges and identify lessons learned concerning data standards, analysis tools, and data-sharing (see also Objective 4.2).
• As new strains are added to the repository of resistant strains described in Sub-Objective 2.1.3, NIH, FDA, and CDC will work with public and private sector partners to add the genomic sequences of each isolate to the database.
• NIH will expand the pilot project database into a National Database of Resistant Pathogens (NDRP) that will continue to incorporate information on newly identified bacterial strains. The database entries will be cross-referenced with entries in the bioinformatics database described in Sub-Objective 2.1.3.
2.2 Expand and strengthen the national infrastructure for public health surveillance and data reporting, and provide incentives for timely reporting of antibiotic-resistance and antibiotic use in all healthcare settings.

The milestones below cover improvements in reporting infrastructure that pertain to both antibiotic resistance (AR) reporting and antibiotic use (AU) reporting. Additional milestones for AU reporting are provided under Objective 1.1.3 as part of the effort to advance antibiotic stewardship in healthcare facilities.

Sub-Objective 2.2.1: Enhance reporting infrastructure and provide incentives for reporting (e.g., require reporting of antibiotic-resistance data to NHSN as part of the CMS Hospital Inpatient Quality Reporting Program).

Within one year:

- CDC will submit proposals for new measures for hospital reporting of data on antibiotic use to the National Quality Forum (NQF).
- CDC will create a user-friendly electronic portal that makes aggregated NHSN data publicly available and facilitates integrated analyses of state and regional trends and practices.

Within three years:

- CDC will submit proposals for new measures for hospital reporting of data on antibiotic resistance to NQF.
- CDC will work with CMS and public health partners to minimize the regulatory burden and maximize the health utility of requiring hospitals to report antibiotic use and resistance to NHSN as part of the CMS Hospital Inpatient Quality Reporting (IQR) Program. Data will be reported through the NHSN AU and AR modules.
- Once the analysis has been completed and new NQF measures have been approved, CMS will begin the process of proposing new IQR rules.
- CDC will work with DOD and VA to define steps and resource needs to support NHSN data submission by DOD and VHA facilities and ensure timely analysis of trends in antibiotic use and antibiotic resistance.
- CDC will expand user-support and validation programs to accommodate expected increases in hospital reporting through the NHSN AU and AR modules during 2017-2019.

Within five years:

- CDC will work with hospital consortiums and state-based hospital networks to determine whether additional reporting incentives are needed in place of (or in addition to) reporting required by CMS.
Sub-Objective 2.2.2: Add electronic reporting of antibiotic use and resistance data in a standard file format to the Stage 3 Meaningful Use certification program for electronic health record systems.

To qualify for an incentive payment through the CMS Medicare Electronic Health Records (EHR) Incentive Program, eligible hospitals must adopt certified EHR technology and use it to achieve specific objectives. The objectives for Stage 1 were data capture and data sharing. The objective for Stage 2 was advance clinical processes. The objective for Stage 3, improved outcomes, can be achieved by using EHR to report antibiotic use and resistance data to CDC via the NHSN AU and AR modules.

Milestones

Within one year:
- CDC will provide technical assistance to hospitals across the nation that report drug-resistance data to NHSN via the NHSN AU and AR modules.

Within three years:
- CMS will finalize a tool to help software developers certify electronic health records and other health IT software, as appropriate, for recording and submitting AU data.
- CMS will complete an analysis of standards and terminologies for AU reporting to ensure alignment between NHSN reporting and IQR reporting and to support local clinical decision-making.

Within five years:
- CDC and partners will develop an AU electronic clinical-quality NHSN-reporting measure in a standard file format that hospitals can use to achieve the Stage 3 Meaningful Use objective and accelerate reporting. The timing of this activity will depend on the timeframe of the CMS Meaningful Use certification program.
- Once an AU electronic clinical-quality NHSN-reporting measure has been developed, it will be submitted to NQF for review and endorsement and to CMS for consideration as a reporting requirement of the CMS Hospital Inpatient Quality Reporting Program.

Sub-Objective 2.2.3: Expand the activities and scope of the Emerging Infections Program (EIP) to include monitoring of additional urgent and serious bacterial threats (see Table 3) and evaluating populations at risk across community and healthcare settings.

The EIP, a network of 10 state health departments,3 conducts active, population-based surveillance for infectious diseases of public health importance. AR surveillance is conducted for ten of the 15 urgent and serious threats listed in Table 1:
- *Clostridium difficile* (10 sites)

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3 The ten EIP sites are: California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon and Tennessee.
NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

- Carbapenem-resistant Enterobacteriaceae (CRE; 8 sites)
- Multidrug-resistant Acinetobacter (8 sites)
- Drug-resistant Candida (4 sites)
- Methicillin-resistant Staphylococcus aureus (MRSA; 9 sites)
- Drug-resistant Streptococcus pneumoniae (10 sites)
- Drug-resistant foodborne pathogens, including Campylobacter, Shigella, Salmonella Typhi, and non-typhoidal Salmonella (10 sites)

Milestones

Within one year:
- CDC will host a meeting of EIP Principal Investigators to consider ways to improve EIP surveillance for drug-resistant threats. The outcomes of this meeting will include refined protocols and standard operating procedures to enable EIP surveillance of additional threats in additional EIP sites.
- CDC EIP sites will pilot methodology to incorporate at least one additional urgent or serious threat into surveillance activities.

Within three years:
- CDC will establish up to 10 additional EIP sites, including sites in the West and Midwest that will monitor drug-resistant pathogens. CDC will evaluate the contribution of these new sites to collection of data that better represents the incidence and prevalence of drug-resistant disease in the United States.
- CDC EIP sites will initiate a study to evaluate populations at risk for CRE.
- CDC will work with research partners and EIP sites to validate molecular assays to support surveillance for drug-resistant gonorrhea.

Within five years:
- CDC will expand EIP activities to include surveillance for additional urgent and serious AR threats (Table 3).
- EIP will help coordinate a public health surveillance study to explore the impact of bacterial populations within the human microbiome on attack rates of drug-resistant pathogens (e.g., C. difficile, CRE, MRSA, Candida, Salmonella, Shigella, Campylobacter, and S. pneumoniae).
- CDC will analyze the resistance of bacteria in the intestines of healthy people with a variety of diets, lifestyles, and antibiotic-use histories.
Over the following years:

- The EIP network will continue to conduct active surveillance for drug-resistant bacteria, provide data to inform CDC’s AR threat reports, identify populations at special risk, and test interventions to reduce the emergence and spread of AR threats.

### 2.3 Develop, expand, and maintain capacity in veterinary and food safety laboratories to conduct standardized antibiotic susceptibility testing and characterize select zoonotic and animal pathogens.

Surveillance for antibiotic-resistant zoonotic and animal pathogens may be enhanced nationwide by building capacity among member laboratories of the USDA National Animal Health Laboratory Network (NAHLN), the FDA Veterinary Laboratory Investigation and Response Network (Vet-LIRN), and USDA-Food Safety and Inspection Service (FSIS) Field Service Laboratories. NAHLN is managed by the National Veterinary Services Laboratories (NVSL).

**Sub-Objective 2.3.1:** Expand and maintain veterinary and food safety laboratory infrastructure for the identification of select zoonotic and animal health pathogens through the implementation of new diagnostic technologies (see also Goal 3).

**Milestones**

**Within one year:**

- USDA and FDA will assess current capacities and protocols within NAHLN and Vet-LIRN member laboratories and identify capacity development needs to support nationwide AR surveillance for zoonotic pathogens and pathogens of importance to animal health.

**Within three years:**

- USDA and FDA will support capacity development in ten selected NAHLN and Vet-LIRN member laboratories by providing training in standardized methodologies for antibiotic-susceptibility testing.
- USDA and FDA will provide support to five or more NAHLN and/or Vet-LIRN member laboratories for next-generation sequencing equipment and training on the use of whole-genome sequencing techniques and bioinformatics.

**Within five years:**

- Ten to twenty NAHLN and Vet-LIRN member laboratories will establish capacity and infrastructure for antibiotic susceptibility testing of bacterial isolates using standardized testing methods (involving WGS or other techniques) and data-sharing mechanisms.
Sub-Objective 2.3.2: Accelerate and standardize antibiotic susceptibility testing and bacterial characterization for select zoonotic and animal health pathogens, coordinating with appropriate stakeholder groups.

Milestones

Within one year:
- USDA and FDA will develop standardized protocols for assessing proficiency in susceptibility testing.

Within three years:
- USDA and FDA will launch pilot projects in three to five NAHLN and/or Vet-LIRN laboratories to establish proficiency in conducting standardized antibiotic susceptibility testing.

Within five years:
- Ten to twenty NAHLN and/or Vet-LIRN member laboratories will actively conduct antibiotic susceptibility testing using standardized methodologies.

Sub-Objective 2.3.3: Enhance communications and identify mechanisms for sharing and reporting antibiotic-susceptibility data on select zoonotic and animal health pathogens collected by veterinary diagnostic and food safety laboratories. These data should be stored in a centralized repository that can be linked with relevant public health databases, as appropriate, while maintaining source confidentiality.

Milestones

Within one year:
- USDA and FDA will initiate discussions with veterinary diagnostic and food safety laboratories to identify opportunities and incentives to share antibiotic-susceptibility data and consider barriers such as confidentiality concerns that would prevent or incentives that would encourage this type of data sharing among NAHLN and Vet-LIRN laboratories.

Within three years:
- USDA and FDA will identify requirements for a system to facilitate national collection, analysis, and reporting of antibiotic-susceptibility testing data by NAHLN and/or Vet-LIRN laboratories, develop guidelines for data collection and for sharing metadata, and generate mechanisms and criteria for linking veterinary data to public health data (e.g., by entering veterinary data into the NARMS database).
USDA and FDA will launch pilot projects in three to five NAHLN and/or Vet-LIRN laboratories for data collection and sharing.

Within five years:

USDA and FDA will establish an IT system that links NAHLN and Vet-LIRN laboratories that conduct antibiotic susceptibility testing and facilitates sharing, analysis, and reporting of veterinary AR data through a centralized repository.

2.4. **Enhance monitoring of antibiotic-resistance patterns, as well as antibiotic sales, usage, and management practices, at multiple points in the production chain for food animals and retail meat.**

Additional baseline information regarding on-farm use of antibiotics is urgently needed to:

- Monitor the impact of FDA Guidance for Industry #213 in fostering the judicious use of antibiotics in food-producing animals (see Goal 1.2).
- Investigate whether certain antibiotic use practices in food production facilitate the development of resistance.

Currently, NAHMS collects voluntary information on on-farm use and resistance patterns on a periodic basis. However, there is increased need for on-farm antibiotic-use data, and the relationship between use and resistance requires enhanced data collection. As yet, no system is in place to provide detailed surveillance data on the use of antibiotics in agriculture or associations between antibiotic use and the development of resistance.

**Sub-Objective 2.4.1:** Enhance surveillance of antibiotic resistance in animal and zoonotic pathogens and commensal organisms by strengthening the National Antimicrobial Resistance Monitoring System (NARMS) and leveraging other field- and laboratory-based surveillance systems.

**Milestones**

Within one year:

- USDA will develop a plan to enhance efforts to monitor the occurrence of drug-resistant zoonotic pathogens in food animals on farms and at slaughter.

Within three years:

- CDC will decrease by 50% the time required to detect and characterize drug-resistant enteric pathogens through NARMS surveillance, and communicate results to stakeholders.
- CDC will improve the detection, investigation, and mitigation of multistate outbreaks caused by resistant enteric bacteria through a 25% reduction in time from the initial notification to NARMS to reporting of susceptibility testing results.
• CDC will gather risk factor information, including data on recent antibiotic use, foreign travel, medical conditions, non-food exposures, and health outcomes for patients with drug-resistant infections. This data (including information about sources of infection) will be used to help improve antibiotic prescribing practices, reduce invasive infections, and decrease hospitalization rates.

• CDC will identify resistance patterns for Salmonella by analyzing near-real-time data from all Salmonella isolates sent to public health laboratories. This activity will help detect outbreaks earlier and faster, improve health outcomes, and avert large food recalls.

• CDC will conduct susceptibility testing on an increased proportion of Campylobacter isolates to help identify outbreaks and determine the sources of drug-resistant Campylobacter infections.

• USDA will implement routine susceptibility testing of veterinary diagnostic isolates and report its findings.

• USDA-FSIS will expand its meat sample and cecal sample surveillance for antibiotic resistance, in collaboration with FDA, NARMS, and other USDA offices.

• FDA will expand retail meat sampling to improve the representativeness of surveillance data on bacterial contamination of meat products.

Within five years:

• NARMS will partner with NHSN to obtain drug-resistance data from clinical laboratories on bacteria isolated from persons with invasive Salmonella, Campylobacter, or Shigella infections. Analysis of this data will provide much-needed information about the burdens and outcomes of drug-resistant enteric infections.

• CDC will begin a pilot project to evaluate the association between antibiotic-resistant urinary tract infections and foodborne bacteria.

Sub-Objective 2.4.2: Enhance collection and reporting of data regarding antibiotic drugs sold and distributed for use in food-producing animals.

Milestones

Within one year:

• FDA will publish enhanced annual summary reports on the sale and distribution of antibiotics approved for use in food-producing animals. An FDA summary report for 2009-2013 will provide baseline information regarding antibiotic sales for the period preceding the implementation of FDA Guidance for Industry #213.

• FDA will publish a proposed regulation that includes additional proposed reporting requirements for sponsors of antibiotics approved for use in food-producing animals.

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4. Cecal samples are taken from the large intestines of swine, cattle, and poultry. The cecum is a pouch at the beginning of the large intestine.
**Sub-Objective 2.4.3:** Implement voluntary monitoring of antibiotic use and resistance in pre-harvest settings to provide nationally representative data while maintaining producer confidentiality.

**Milestones**

**Within one year:**
- USDA and FDA will seek public input on a plan for collecting drug use and resistance data on farms.

**Within 3 years:**
- CDC and FDA will work with EPA to evaluate the risk of environmental uses of antibiotics on human health.
- USDA and FDA will initiate collection of drug use and resistance data on farms. This information will be used to determine baselines and trends in drug use and resistance.

**Sub-Objective 2.4.4:** Collect quantitative data on antibiotic-resistance and management practices along various points at pre-harvest, harvest, and processing stages, in collaboration with producers and other stakeholders, and disseminate information as appropriate.

**Milestones**

**Within one year:**
- USDA will develop a plan for expanded monitoring of resistant bacteria throughout the food production continuum (e.g., pre-harvest, harvest, and processing of food products). On-farm sampling will be voluntary.

**Within three years:**
- USDA will implement collection of data on antibiotic-resistance and management practices during pre-harvest, harvest, and processing of food products. On-farm sampling will be voluntary. This information will be used to monitor trends in drug-resistant bacteria and identify potential mitigation strategies for further investigation.
- USDA will begin coordinated investigations of emerging zoonotic antibiotic resistant pathogens on the farm and at slaughter.
Goal 3: Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria

Actions taken to achieve Goal 3 will fulfill:

- **Executive Order 13676, Section 8:**
  - Promoting New and Next Generation Antibiotics and Diagnostics
- Provisions in PCAST Recommendations #5 and #6 that concern:
  - International collaboration to promote diagnostic development
  - Prizes for the development of breakthrough diagnostics

Today’s researchers are taking advantage of new technologies to develop rapid “point-of-need” diagnostic tests that can be used during a healthcare visit to distinguish between viral and bacterial infections and identify bacterial drug susceptibilities—an innovation that could significantly reduce unnecessary antibiotic use. The availability of new rapid diagnostic tests, combined with ongoing use of culture-based assays to identify new resistance mechanisms, will advance the detection and control of resistant bacteria, including the priority pathogens listed in Table 1.

By 2020, significant outcomes of Goal 3 will include:

- Development and dissemination of authorized point-of-need diagnostic tests that rapidly distinguish between bacterial and viral infections.
- Validation of diagnostic tests that rapidly determine the antibiotic-resistance profiles of bacteria of public health concern (Table 1).

To advance these outcomes, HHS agencies will award a prize for development of a rapid diagnostic test that can improve treatment of drug-resistant infections and facilitate antibiotic stewardship.
Objectives

3.1 Develop and validate new diagnostics—including tests that rapidly distinguish between viral and bacterial pathogens and tests that detect antibiotic-resistance—that can be implemented in a wide range of settings.

Federal departments and agencies will work with domestic and international partners to develop rapid diagnostic tests that can identify clinical illnesses that may benefit from treatment with antibiotics, detect invasive bacterial pathogens in blood, cerebrospinal fluid, synovial fluid, and urine, and provide information to guide decisions on treatment and control of CRE, Neisseria gonorrhoeae, and other multidrug-resistant organisms.

Within three years:

- NIH will fund at least five new projects aimed at the development of rapid diagnostics, including:
  - Point-of-need diagnostic tests that rapidly distinguish between bacterial and viral infections.
  - Tests that can rapidly determine the antibiotic-resistance profiles of resistant bacterial threats of high importance to public health (Table 3), including CRE, MRSA, and ceftriaxone-resistant N. gonorrhoeae.

- The Assistant Secretary for Preparedness and Response (ASPR)/Biomedical Advanced Research and Development Authority (BARDA) will fund at least three new diagnostic development projects that involve next-generation sequencing, multiplex molecular assays, or other new technologies that shorten the time needed for reliable and accurate detection of drug resistance.

- NIH and ASPR/BARDA will establish a prize for development of a rapid diagnostic test that can improve treatment of drug-resistant infections and facilitate antibiotic stewardship.

- DOD will fund projects to develop:
  - A functional (phenotypic) antibiotic susceptibility test that provides results more quickly than conventional susceptibility tests. This project will be conducted in collaboration with CDC.
  - A set of assays that can characterize the drug-resistance profile of any bacterial isolate.
  - An innovative method for antibiotic susceptibility testing (AST) aimed at eliminating the need to perform AST in centralized microbiology laboratories and enabling rapid AST in non-traditional healthcare settings.

- DOD will also fund at least one project involving next-generation sequencing technologies or bioinformatics platforms or tools that can be leveraged to improve diagnostics for drug-resistant or multidrug resistant pathogens.
Within five years:

- At least one new diagnostic product, the development of which was facilitated by NIH or ASPR/BARDA, will be submitted for FDA approval or clearance.
- NIH and ASPR/BARDA will manage and administer a prize contest (see above) for development of a rapid diagnostic test that can improve treatment of drug-resistant infections and facilitate antibiotic stewardship.

### 3.2 Expand the availability and use of diagnostics to improve treatment of antibiotic-resistant bacteria, enhance infection control, and facilitate outbreak detection and response in healthcare and community settings.

FDA and CMS are working with industry partners to streamline development and uptake of new diagnostic tests and facilitate their use to improve patient treatment and achieve public health goals. A major aim of these efforts is to develop well-defined reimbursement policies and incentives that encourage routine use of diagnostics in clinical settings to distinguish between bacterial and viral infections and identify the antibiotic susceptibilities of bacteria.

FDA and CMS signed a Memorandum of Understanding (MOU) on June 18, 2010 that facilitates inter-agency efforts to streamline regulatory processes in ways that reduce costs and timelines. New projects include the **FDA-CMS Parallel Review**, a pilot program that permits concurrent (rather than sequential) product reviews by FDA and CMS (i.e., while FDA reviews pre-market submissions for approval or clearance of diagnostic tests, CMS determines whether the tests will be covered by Medicare). Other projects designed to facilitate innovation include:

- **FDA Entrepreneur in Residence Program**, which provides technical support to small businesses who may lack the expertise to navigate the FDA approval or clearance process.
- **FDA Medical Device Innovation Consortium**, a partnership between a nonprofit organization and FDA to advance medical device regulatory science. Members include representatives of organizations involved in:
  - Medical and/or medical device research, development, treatment, or education
  - Promotion of public health
  - Regulatory science
- **FDA Medical Device Reimbursement Task Force**, which is pilot-testing a formal process that allows a device company to request a pre-submission meeting with FDA staff and one or more third-party payers to discuss reimbursement issues.

### Milestones

Within one year:

- FDA and CMS will evaluate the potential impact of innovative regulatory pathways currently under development to foster the development of diagnostic tests by addressing issues related to Medicare reimbursement and coding.
Within three years:

- HHS will establish a process that allows product developers to provide data to CMS for use in developing Interpretive Guidelines that facilitate the use of tests for patient treatment, hospital infection control, and reporting of cases of disease during outbreaks.

Within five years:

- HHS will issue technical assistance and education modules and materials that assist health-care providers and health systems in using diagnostic tests to improve patient management, enhance hospital infection control, and facilitate outbreak detection and response.
GOAL 4. Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines

Actions taken to achieve Goal 4 will fulfill

- **Executive Order 13676, Section 8:**
  - Promoting New and Next Generation Antibiotics and Diagnostics.
- **Provisions in PCAST Recommendations #3, #4, and #5:**
  - Fundamental Research
  - Clinical Trials with New Antibiotics
  - The Federal Government should Significantly Increase Economic Incentives for Developing Urgently Needed Antibiotics

Antibiotics that lose their effectiveness for treating human disease through antibiotic-resistance must be replaced with new drugs; alternatives to antibiotics are also needed in veterinary medicine. The advancement of drug development requires intensified efforts to boost basic scientific research, attract greater private investment, and facilitate clinical trials of new antibiotics. These activities are imperative to increase the number of antibiotic drug candidates in the drug-development pipeline.

Goal 4 activities will also advance the discovery and development of other tools to combat resistance, including vaccines, alternatives to (or improved uses of) antibiotics in food animals, and non-traditional therapeutics to improve human health, including products that preserve or restore beneficial bacteria that live in human gastrointestinal tracts.

By 2020, significant outcomes of Goal 4 will include:

- Characterization of the gut microbiome—the communities of microorganisms that live within the gastrointestinal tract—of at least one animal species raised for food. This outcome will help us understand how antibiotic treatments disrupt normal gut bacteria and how animal growth might be promoted—and bacterial diseases might be treated—without using antibiotics.
- Advancement of at least two new antibiotic drug candidates, non-traditional therapeutics, and/or vaccines from pre-clinical testing to clinical trials for treatment or prevention of human disease.
- Development of at least three new drug candidates or probiotic treatments as alternatives to antibiotics for promoting growth or preventing disease in animals.
- Creation of a biopharmaceutical incubator—a consortium of academic, biotechnology and pharmaceutical industry partners—to promote innovation and increase the number of antibiotics and antibodies in the drug-development pipeline.

**Objectives**

4.1 **Conduct research to enhance understanding of environmental factors that facilitate the development of antibiotic-resistance and the spread of resistance genes that are common to animals and humans.**

**Sub-Objective 4.1.1:** Support basic research to exploit powerful new technologies, including systems biology, to advance the study of antibiotic-resistance and address the special problems posed by resistant Gram-negative pathogens such as CRE.

**Milestones**

**Within one year:**

- FDA, USDA, CDC, and NIH will host a roundtable of private and public sector experts to gather input on strategies to advance collaborative research to develop tools to combat antibiotic resistance using systems biology and other new technologies.

**Within three years:**

- A National Institute of Mathematical and Biological Synthesis (NIMBioS) working group will develop an analytic modeling framework for assessing the relationship between antibiotic use in livestock (measured at the population level) and the development of antibiotic resistance.

**On an annual basis:**

- HHS, NIH, FDA, USDA, CDC, DOD, and EPA will conduct a review to ensure that U.S. Government research resources are focused on high-priority antibiotic resistance issues (including basic research on the emergence and spread of resistance genes) and facilitate use of advanced technologies in research on antibiotic resistance (e.g., whole genome sequencing, proteomics, metagenomics, structural biology, bioinformatics).

Additional milestones related to basic research are provided under Objective 4.2.

**Sub-Objective 4.1.2:** Leverage existing partnerships, such as the NIH Antibacterial Resistance Leadership Group (ARLG), and international collaborations to reduce obstacles faced by pharmaceutical companies that are developing new antibiotics, other therapies,
and vaccines. Partnerships will help identify human subjects qualified for enrollment in clinical trials of vaccines to prevent and antibiotics to treat resistant bacterial infections that occur sporadically, episodically, and/or in limited populations, generate and apply common clinical test protocols to multiple test groups of patients while sharing a common control group, and conduct other research-support activities as needed.

Milestones

Within one year:

- NIH will work with FDA and partners in industry and academia to:
  - Explore features necessary for developing a more robust clinical trials infrastructure for antibacterial product development.
  - Assess the feasibility of applying common clinical protocols for evaluation of multiple products while sharing a common control group. This approach may facilitate clinical testing of drugs to treat Gram-negative infections such as CRE that occur sporadically or episodically in limited populations (e.g., during hospital outbreaks).

- NIH will expand and strengthen the ARLG network, which facilitates clinical testing and validation of new antibacterial products and conducts studies to determine how existing products can be used in optimal ways to improve the treatment of resistant infections.

- FDA, USDA, CDC, and NIH will bring together experts in food production, agriculture, and public health to encourage collaborative research—from basic research to clinical testing—on antibiotic resistance.

Additional milestones related to fostering public/private partnerships and attracting greater private investment in antibiotics development are provided in Objective 4.6 and 4.7.

4.2 Increase research focused on understanding the nature of microbial communities, how antibiotics affect them, and how they can be harnessed to prevent disease.

Milestones

Within three years:

- USDA, NIH, and CDC will support research on the spread of resistance genes between zoonotic pathogens and the commensal microbiota that live in the gastrointestinal tracts of animals and humans (i.e., in animal and human microbiomes).

- USDA, in consultation with NIH and CDC, will support research to map the gut microbiome of at least one food animal, using metagenomic techniques and “big data” analysis tools. This research will advance understand antibiotic treatments disrupt the normal gut microbiome and
how animal growth may be promoted without antibiotics. It may also suggest ways to treat bacterial animal diseases without using antibiotics.

4.3 **Intensify research and development of new therapeutics and new and improved vaccines, first-in-class drugs, and new combination therapies for treatment of bacterial infections.**

**Milestones**

**Within one year:**

- The Chemical and Biological Defense Program/Defense Threat Reduction Agency (CBDP/DTRA) will:
  - Submit an Investigational New Drug (IND) application to FDA to initiate the clinical investigation of an antibiotic developed with DOD funding.
  - Award two new contracts to industry partners to accelerate advancement of novel small-molecule antibiotic therapies that circumvent known resistance mechanisms or potentiate the therapeutic efficacy of existing antibiotics (e.g., combination therapies). This activity will leverage ongoing efforts to develop treatments for infections caused by Select Agents (pathogens that might be used as biological weapons).

**Within three years:**

- NIH will arrange for clinical trials networks such as the Antibacterial Resistance Leadership Group (ARLG), (see Objective 4.1.2) to test a Gram-negative therapeutic agent with the goal of addressing use in a limited-population setting such as a hospital.
- NIH will launch a research program that uses systems biology to identify new drug targets that can be used to develop antibiotic drugs with new modes of action that make the development of resistance less likely.
- NIH will assist research partners who are developing novel classes of antibacterial drugs in submitting IND applications to FDA.

**Within five years:**

- NIH will support initial testing and validation of two new products (antibacterial drugs, novel therapeutics, or vaccines) to treat or prevent multidrug resistant Gram-negative pathogens. Once validated, these products will be transitioned to ASPR/BARDA or pharmaceutical companies for advanced development, including clinical efficacy trials (see also Objective 4.4).
- CBDP/DTRA will complete pre-clinical testing of an additional antibiotic drug and will support clinical trials of two new products to treat infections with Select Agents.
Additional milestones related to development of vaccines and combination therapies to address antibiotic resistance are provided under Objective 4.4.

4.4 Develop non-traditional therapeutics, vaccines, and innovative strategies to minimize outbreaks caused by resistant bacteria in human and animal populations.

The development of non-traditional approaches that are less likely to drive resistance is an important step in breaking the cycle of drug development immediately followed by the development of resistance.

Examples of non-traditional therapeutic strategies include:

- Targeting bacterial virulence factors to prevent disease without killing bacteria.
- Using phage and phage-derived lysins to kill specific bacteria while preserving the microbiota.
- Creating vaccines that prevent infection with drug-resistant pathogens.
- Creating therapeutic products involving monoclonal or polyclonal antibodies.
- Developing products that restore or preserve beneficial bacteria in human and animal microbiomes and prevent colonization with harmful bacteria (e.g., probiotics, prebiotics, or synthetic microbiota).
- Identifying natural compounds with antibiotic activity (e.g., phytochemicals, essential oils, organic acids, animal-derived lytic enzymes, and small interfering RNAs).
- Developing combination therapies and dosing strategies that slow the emergence of resistance.

Milestones: Therapeutics and strategies for use in humans

Within one year:

- NIH will fund new projects to support the discovery and development of new types of antibacterial products (e.g., monoclonal antibodies, vaccines, or microbiota-based therapeutics), as well as adjunctive therapies to restore the activity of existing antibiotic drugs.
- DOD will implement laboratory use of new microfluidic technologies to detect antibodies that inhibit antibiotic-resistant bacteria.
- DOD will award:
  - Two new contracts focused on development of non-traditional therapeutics that are less likely to lead to the development of resistance (e.g., immunomodulators, therapeutic antibodies, or host-directed therapies).
  - Two new contracts focused on evaluating drug combinations that may decrease the emergence of drug resistance.
Two new contracts to explore revitalization and/or reformulation of antibacterial drug candidates that have failed to enter preclinical or clinical development due to undesirable characteristics related to solubility, pharmacokinetics, or toxicity.

Within three years:

- NIH, with guidance from FDA, will support development and evaluation of novel approaches for treatment of drug-resistant infections.
- DOD will investigate genes encoding antibodies that target drug-resistant bacteria and might be used in immunoprophylactic treatments.

Within five years:

- NIH will support the identification of alternative dosing strategies (e.g., combination therapies and shortened durations) that improve treatment for two bacterial pathogens of public health concern.
- NIH will launch clinical trials for two new products to treat or prevent high-priority bacterial pathogens and transition them to ASPR/BARDA or pharmaceutical companies for advanced development.
- Scientists at the Walter Reed Army Institute of Research will transition one antibiotic drug candidate to advanced development.

Milestones: Therapeutics and strategies for use in animals

Within one year:

- USDA, in collaboration with NIH, FDA, and the agriculture industry, will develop a research and development strategy to promote understanding of antibiotic-resistance and the creation of alternatives to (or improved uses of) antibiotics in food animals.
- USDA will solicit proposals that comprehensively develop research and outreach programs targeting development of novel alternatives to antibiotics for use in animals.

Within three years:

- USDA-funded research teams will develop three candidate alternatives to antibiotics used for promoting growth in animals (e.g., drugs or probiotic treatments) that do not disrupt the normal flora of the gut of food animals and enhance animal immune systems and resistance to disease.

Within five years:

- USDA-funded research teams will develop non-traditional alternatives to antibiotics that can be used (alone or in combination with existing antibiotics) to treat at least three priority bacterial pathogens of livestock and poultry.
USDA-supported researchers will study genes that confer resistance to high-priority agricultural animal diseases (e.g., Bovine Respiratory Disease Complex) to facilitate genetic selection for animals with less susceptibility to infections whose treatments typically require significant use of antibiotics.

4.5 **Expand ongoing efforts to provide key data and materials to support the development of promising antibacterial drug candidates and promising vaccines that can reduce the need to treat bacterial infections.**

**CARB Economic Incentives Working Group**

Economic incentives for product development are critical to ensuring diverse and robust pipeline of antibiotics. The PCAST report provides several key recommendations on economic incentives.

In response to these recommendations, the Office of Science and Technology Policy (OSTP) and National Security Council (NSC) staff of the Executive Office of the President convened a working group to conduct an analysis of these potential economic incentives. Efforts to attract more private investment will reflect the recommendations of the CARB Economic Incentives Working Group.

**Milestones**

**Within one year:**

- NIH and ASPR/BARDA will implement a strategy for assisting research partners who are developing novel classes of antibacterial drugs in fulfilling the requirements of FDA IND applications.

- NIH and ASPR/BARDA will meet on a semi-annual basis with investigators who participate in the Antibiotic Resistance Biopharmaceutical Incubator (see Objective 4.7) to evaluate progress in providing technical resources for *in vitro* and *in vivo* screening of resistant pathogens of public health concern.

- Agencies with existing capabilities will ensure that genomic sequence data, proteomic data, and other related AR data sets generated with U.S. Government funding will be made publically available in a manner consistent with protecting personally identifiable information.

- DOD will develop three specimen panels as a critical resource for evaluating the efficacy of novel antibiotic therapies against multidrug-resistant Select Agents. The panels will include: (1) resistant bacterial isolates suitable for work in lower-level (BSL-2) biocontainment laboratories, (2) multidrug resistant strains of Select Agents, and (3) attenuated strains of multidrug resistant Select Agents. The panels will be maintained within DOD and will be available through the Select Agent Core Antibiotic Screening Program.
Within three years:

- NIH and ASPR/BARDA will identify at least twelve candidate products for preclinical development support and support three candidate products from preclinical development through IND submission (see also Objective 4.4).

Within five years:

- All agencies will ensure that genomic sequence data, proteomic data, and other related AR data sets generated with U.S. Government funding will be made publicly available in a manner consistent with protecting personally identifiable information.

### 4.6 Enhance opportunities for public-private partnerships to accelerate research on new antibiotics and other tools to combat resistant bacteria

HHS is partnering with pharmaceutical and biotechnology companies to advance the development of antibiotics through a “portfolio approach” in which companies investigate multiple drug candidates at the same time. This approach balances risk (for the companies and the government) by increasing the likelihood that one or more drug candidates will advance from preclinical testing to commercial use.

#### Milestones

**Within one year:**

- The HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) will ensure coordination with the U.S. Task Force for Combating Antibiotic-Resistant in promoting public-private partnerships to develop new and next-generation countermeasures to target antibiotic-resistant bacteria that present a serious or urgent threat to public health.

- ASPR/BARDA will create at least one additional portfolio partnership with a pharmaceutical or biotechnology company to accelerate development of antibacterial drugs.

**Within three years:**

- At least two antibiotic drugs developed by portfolio partners for treatment of an urgent or serious pathogen (Table 1) will enter Phase III clinical investigation.

**Within five years:**

- IND applications for at least two additional antibiotic drugs developed by portfolio partners will be submitted for FDA approval.
4.7 Create a biopharmaceutical incubator—a consortium of academic, biotechnology and pharmaceutical industry partners—to promote innovation and increase the number of antibiotics in the drug-development pipeline.

ASPR/BARDA, in collaboration with NIH, will establish a pharmaceutical incubator that brings inventors and researchers together with start-up companies to explore creative ideas that could lead to the development of new antibiotics or non-traditional therapies. Like the ARLG network described in Objective 4.1.2 and the “portfolio partnerships” described in Objective 4.6, the biopharmaceutical incubator will help attract greater private investment by reducing the risks and obstacles faced by drug companies who are developing new antibiotics.

Milestones

Within one year:

- ASPR/BARDA and NIH will work with a consortium of industry partners to develop a strategy for establishing the Antibiotic Resistance Biopharmaceutical Incubator (ARBI).

Within three years:

- The ARBI will be operational, with technical services in place to facilitate toxicology studies, animal challenge studies, and other activities needed to accelerate drug development.

On an annual basis:

- ASPR/BARDA and NIH will assess progress in meeting ARBI’s five-year goals: identifying at least five targets for novel therapeutics, generating in vivo data to validate at least three of these targets, generating at least three antibacterial drug candidates, and transitioning at least two of these candidates from preclinical testing to submission of an FDA IND application to begin clinical trials.
GOAL 5. Improve International Collaboration and Capacities for Antibiotic-resistance Prevention, Surveillance, Control, and Antibiotic Research and Development

Actions taken to achieve Goal 5 will fulfill

- **Executive Order 13676, Section 9:**
  - *International Cooperation*
- **Provisions in PCAST Recommendation #8:**
  - *Ensure Effective International Coordination*

Antibiotic resistance is a global problem that requires global solutions. The United States, led by the Secretaries of State, USDA, and HHS and the Administrator of USAID, will engage in international action with foreign ministries of health and agriculture, the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO), the World Organization for Animal Health (OIE), and other domestic and international stakeholders to strengthen national and international capacities to detect, monitor, analyze, and report antibiotic resistance, provide resources and incentives to spur the development of therapeutics and diagnostics for use in humans and animals, and strengthen regional networks and global partnerships that help prevent and control the emergence and spread of resistance. The United States will support the development of the *WHO Global Action Plan on Antimicrobial Resistance*, strengthen cooperation under the European Union-United States Trans-Atlantic Task Force on Antimicrobial Resistance (TATFAR), promote antibiotic resistance as an international health priority, and mobilize resources for global activities through bilateral, regional, and multilateral venues such as the Global Health Security Agenda.

By 2020, significant outcomes of Goal 5 will include:

- Elevation of antibiotic resistance as an international priority for global health and security.
- Enhanced capacity to identify antimicrobial-resistant pathogens in more than fifteen partner countries.
- Establishment of a common U.S.-European Union (EU) system for sharing and analyzing bacterial resistance patterns for priority pathogens.
- Development of a global database to collect harmonized quantitative data on the use of antibacterial agents in animals.
- Development of national plans to combat antibiotic resistance and improve antibiotic stewardship in low- and middle-income countries.
- Strengthened regulatory and supply chain systems that assure the quality, safety, and efficacy of antibiotics used in low- and middle-income countries.

Objectives

Surveillance: Establish capacity to detect, analyze, and report antibiotic resistance, in order to make available information needed for evidence-based decision making in individual countries and globally.

5.1 Promote laboratory capability to identify at least three of the seven WHO priority antimicrobial resistant (AMR) pathogens using standardized, reliable detection assays.

The WHO AMR Pathogens and types of resistance of concern include:

- *Escherichia coli*: resistance to 3rd generation cephalosporins and to fluoroquinolones
- *Klebsiella pneumoniae*: resistance to 3rd generation cephalosporins and to carbapenems
- *Staphylococcus aureus*: methicillin resistance, or MRSA
- *Streptococcus pneumoniae*: resistance (non-susceptibility) to penicillin
- *Non-typhoidal Salmonella (NTS)*: resistance to fluoroquinolones
- *Shigella species*: resistance to fluoroquinolones
- *Neisseria gonorrhoeae*: reduced susceptibility to 3rd generation cephalosporins

Milestones

Within one year:

- CDC and USAID will work with ministries of health in at least twelve to fifteen countries to complete laboratory proficiency assessments, and will assess expansion of bilateral relationships to additional countries.
- DOD will work with international partner laboratories to identify and enhance local proficiency and capabilities and will conduct assessments on an annual basis.

Within three years:

- CDC and USAID will provide technical assistance to foreign ministries of health on developing national plans for strengthening laboratory-based surveillance for antimicrobial resistance, and will complete assessments of laboratory capacity in additional counties.

5 The WHO priority AMR pathogens are a subset of the pathogens identified as urgent and serious threats in Table 3.
Within five years:

- Public health laboratories in at least fifteen partner countries will be able to identify at least three of the seven WHO priority AMR pathogens and will report their results to WHO, to international surveillance networks, and—in the case of a public health emergency of international concern—to International Health Regulations (IHR) focal points.

5.2 Collaborate with WHO, OIE, and other international efforts focused on the development of integrated, laboratory-based surveillance to detect and monitor antibiotic resistance in relevant animal and human foodborne pathogens.

Milestones

Within one year:

- USDA, FDA, and CDC will develop a plan, in partnership with WHO, the Pan American Health Organization, and other international organizations to identify key partner laboratories that conduct AMR testing of animal foodborne pathogens.

Within three years:

- USDA and FDA, in conjunction with CDC and international partners, will:
  - Develop a process for assessing national and regional capabilities for surveillance of antibiotic resistance in animal and human foodborne pathogens.
  - Identify challenges to harmonizing AMR data requirements and collection methods on an international scale.
  - Assess the current status of national capabilities for molecular diagnostics and epidemiology and address the need for access to these capacities.
  - Identify additional partners who can assess laboratory testing proficiencies and provide training for technology transfer.
  - Work with regional partners to monitor the emergence and spread of resistance genes in animal and foodborne pathogens on an ongoing basis, using molecular techniques.
  - Expand activities conducted through other USG-funded activities (e.g., the Asia-Pacific Economic Cooperation) to inventory existing worldwide laboratory resources and assess the need for national and regional improvements to support surveillance for drug-resistant animal and human foodborne pathogens. These efforts will include expansion of training opportunities in pathogen characterization and diagnostics.
- DOD will develop a scalable, evidence-based database of global information on antimicrobial resistance and issue annual reports of findings.
Within five years:

- USDA, FDA, and CDC will initiate regional collaborations to monitor the emergence and spread of resistance genes in food, animal, and human foodborne pathogens, using genome sequencing techniques.

- USDA and FDA will work with CDC and international partners to provide training in laboratory methodologies (in-country or within the U.S.) and initiate collaborations to promote training as opportunities arise.

- USDA, FDA, and CDC will work through existing laboratory and public health networks—such as PulseNet International and the Red Interamericana de Laboratorios de Análisis de Alimentos (RILAA)—to transfer technology and train local partners.

5.3 Develop a mechanism for international communication of critical events that may signify new resistance trends with global public and animal health implications.

Milestones:

Within one year:

- CDC will work with TATFAR partners to develop a common U.S.-E.U. system for sharing and analyzing bacterial resistance patterns for pathogens identified as urgent and serious threats in Table 1.

- HHS/OGA, USDA, FDA and CDC will work with TATFAR partners to address TATFAR Recommendation #18, which calls for the formation of an international working group to identify key knowledge gaps about transmission of drug-resistant bacteria in animals and the use of antibiotics in animal agriculture.

Within three years:

- CDC will work with WHO and other partners to develop a secure website for real-time sharing of international surveillance data on antimicrobial resistance in order to facilitate early warning and notification of significant events to WHO, regional and international disease surveillance networks (e.g., European Centre for Disease Prevention and Control), and IHR. These efforts will make use of data-sharing practices developed by the U.S. and TATFAR (see above). Steps include developing terms of reference, assessing IT requirements, and identifying mechanisms for validating and sharing information.

- CDC will deploy the website in partnership with the international community and will help test, monitor, evaluate, and improve its utility.

- USDA will identify next steps in addressing knowledge gaps about development and spread of antibiotic resistance in animals, based on the conclusions of the work group formed in fulfillment of TATFAR Recommendation #18 (see above).
Within five years:

- CDC and other U.S. agencies will help ensure access to—and full participation by—public health authorities in all WHO member countries.
- USDA will engage TATFAR and other regional partners in sharing information about drug-resistance trends with implications for animal health.

5.4 Promote the generation and dissemination of information needed to effectively address antibiotic-resistance.

Sub-Objective 5.4.1: Support consistent international standards for determining whether bacteria are resistant to antibiotics.

Milestones

Within one year:

- U.S. agencies, led by CDC and USAID, will engage stakeholders in establishing harmonized definitions of drug resistance for surveillance purposes (e.g., by standardizing interpretive criteria for analyzing the results of antibiotic susceptibility tests).
- As part of these efforts, DOD will continue to engage and support existing and newly-identified international partners through sharing of technological packages for surveillance and reporting purposes.

Within three years:

- U.S. agencies, led by CDC, will work with the six WHO regional surveillance networks to implement harmonized definitions of resistance for surveillance programs integrating data on WHO and CDC priority pathogens.

Sub-Objective 5.4.2: Develop international collaborations to gather country-specific and regional information on drivers of antibiotic resistance, identify evidence-based interventions, adapt these strategies to new settings, and evaluate their effectiveness.

Within one year:

- U.S. agencies, led by the Department of State and HHS, will develop a strategy for working with partner countries to elevate the issue of antibiotic resistance as an international priority for global health security.
- U.S. agencies, led by HHS/OGA, will support development of the *WHO Global Action Plan on Antimicrobial Resistance*. As part of this effort, U.S. agencies will support the inclusion of provi-
sions that require open access to research data on factors that drive the emergence of resistance and strategies to prevent its spread.

Within three years:

- The Department of State, HHS, and other agency partners will convene a group of international stakeholders to discuss best practices for research collaborations on antimicrobial resistance, including methodologies, data-sharing policies, management plans and interoperability.
- U.S. agencies will work with WHO, FAO, and OIE to support implementation of the *WHO Global Action Plan on Antimicrobial Resistance* by:
  - Assessing country-specific and regional factors that drive the development of antimicrobial resistance, building on existing risk management frameworks such as the Codex Alimentarius.
  - Establishing a global database to collect harmonized quantitative data on the use of antibacterial agents in animals.
  - Forging partnerships aimed at reducing the use of medically-important antibiotics for growth promotion in food animals.

Over five years:

- The Department of State, HHS, and other agency partners will continue to promote antibiotic resistance as an international health priority by raising the issue of antibiotic resistance during bilateral consultations and multilateral forums and by advancing implementation of the Global Health Security Agenda (GHSA) Antimicrobial Resistance Action Package.

**Sub-Objective 5.4.3:** Provide technical assistance as needed to underdeveloped and developing nations to improve their capacity to detect and respond effectively to antibiotic resistance.

**Milestones**

Within three years:

- CDC will develop bilateral agreements with twelve to fifteen countries to develop country-specific surveillance strategies, and will assess expansion of these activities to additional countries (see also Objective 5.1).
- CDC and other U.S. agencies will assist partner countries with development and implementation of national strategies for infection prevention and control in healthcare facilities.
NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

Within five years:

- CDC and other U.S. agencies will assist at least fifteen countries with collection of resistance surveillance data and data-sharing with stakeholders.

Research and Development: Incentivize development of therapeutics and diagnostics for humans and animals.

5.5 Establish and promote international collaboration and public-private partnerships to incentivize development of new therapeutics to counter antibiotic resistance, including new, next-generation, and other alternatives to antibiotics, vaccines, and affordable, rapidly deployable, point-of-need diagnostics.

Milestones

Within one year:

- U.S. agencies, led by HHS, will work with WHO, FAO, OIE, and other international partners to accelerate investment in research to develop point-of-care diagnostics, vaccines, and drugs to combat resistant bacteria, as well as to investigate the microbiomes of food animals. For example, U.S. agencies and partners in industry and academia will work with TATFAR partners to advance collaborations with EU nations to facilitate translational and clinical research on tools to slow the emergence and spread of antimicrobial resistance. U.S. agencies will also explore collaborations with the New Drugs 4 Bad Bugs (ND4BB) programs of the Innovative Medicines Initiative.

Within three years:

- U.S. agencies and partners in industry and academia will establish or expand additional international partnerships to advance research to reduce antibacterial resistance through the development of point-of-care diagnostics, vaccines, and drugs.

- USDA will establish or expand five collaborative international partnerships to facilitate research regarding development of alternatives to antibiotics, as well as vaccines and new antimicrobial drugs that are less likely to develop resistance.
**Prevention and Control:** Strengthen systems in countries, regional networks, and global partnerships to prevent and control the emergence and spread of antibiotic resistance through evidence-based interventions, and monitor and evaluate the effectiveness of interventions.

### 5.6 Support countries to develop and implement national plans to combat antibiotic resistance and strategies to enhance antimicrobial stewardship.

**Milestones**

**Within one year:**
- U.S. agencies, led by HHS/OGA, will collaborate with the global community to ensure that the *WHO Global Action Plan on Antimicrobial Resistance* incorporates approaches and interventions that benefit all healthcare programs and calls for the development of national plans to combat antibiotic resistance (see also Sub-Objective 5.4.2).

**Within three years:**
- CDC and USAID will provide technical assistance to foreign ministries of health and agriculture to advance the use of tools and interventions that have proven successful at slowing the spread of resistance in healthcare and agricultural settings (e.g., infection prevention and control and antibiotic stewardship programs in hospitals).
- U.S. agencies, led by USAID and CDC, will support at least four Low and Middle Income Countries (LMICs) in developing and/or operationalizing national antimicrobial resistance containment plans, national healthcare-facility infection prevention and control plans, antimicrobial stewardship strategies, or comparable packages of interventions.

**Within five years:**
- U.S. agencies, led by USAID and CDC, will:
  - Support at least three additional LMICs in developing and/or operationalizing national antimicrobial resistance containment plans, national healthcare facility infection prevention and control plans, antimicrobial stewardship strategies, or comparable packages of interventions.
  - Support the implementation of national infection prevention and control programs in at least twenty priority healthcare facilities in eight LMICs.
  - Support operational research that leads to remedial actions and improved antibiotic use in at least eight healthcare facilities in 4 LMICs.
  - Develop and disseminate at least four global technical leadership documents/reports for use by LMICs and the global community, that review approaches, results, lessons learned, and recommendations related to key antibiotic containment strategies.
• U.S. agencies, led by HHS/OGA, the Department of State and USAID, will support international advocacy and coordination to contain the common threat of antimicrobial resistance, through collaboration with WHO and other partners and participation in multilateral forums, such as the 4th Conference on Improving Use of Medicines (ICIUM).

• USDA will use Veterinary Accreditation training modules—including the Judicious Use Module—to assist countries in at least three WHO regions in developing sustainable veterinary service capacity to monitor and slow antibiotic resistance and to report outbreaks of drug resistant disease to WHO, international surveillance networks, collaborative reporting structures, or (when appropriate) to International Health Regulations (IHR) focal points.

• USDA will translate the Judicious Use Module into three other languages.

A milestone on development of national plans for strengthening laboratory-based surveillance for antibiotic resistance is provided under Objective 5.1.

5.7 Partner with other nations to promote quality, safety, and efficacy of antibiotics and strengthen their pharmaceutical supply chains.

Milestones

Within three years:

• U.S. agencies, led by USAID, will support country systems to enhance access to and appropriate use of quality-assured, safe, effective essential antibiotics through improved medicines, regulatory capacity and quality assurance systems, modern procurement practices, reliable and secure supply chains, and equitable pharmaceutical services in at least four LMICs.

Within five years:

• U.S. agencies, led by USAID, will:
  − Support country systems that enhance access to quality-assured, safe, effective essential antibiotics in at least eight LMICs.
  − Develop and disseminate at least four global technical leadership documents/reports, for use by LMICs and the global community, that review approaches, results, lessons learned, and recommendations on access to quality-assured, safe, effective antibiotics and issues related to regulation, quality assurance, and patient safety in the use of antibiotics.
5.8 Coordinate regulatory approaches by collaborating with international organizations such as FAO and OIE to harmonize international data submission requirements and risk assessment guidelines related to the licensure and/or approval of veterinary medicinal products, including antibacterial agents, vaccines, and diagnostics, to the extent possible.

U.S. agencies are working in partnership with TATFAR, the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the International Cooperation on Harmonization of Technical Requirements for Veterinary Medicinal Products (VICH), the Institute for International Cooperation in Animal Biologics (IICAB), and the International Medical Device Regulators Forum (IMDRF) to facilitate the development of antibacterial drugs for human and agricultural use, diagnostic tests for human and animal bacterial diseases, vaccines for human and animal bacterial diseases, and risk assessments on the use of medically-important antibacterial drugs in agriculture.

Milestones

Within one year:

- FDA and USDA will contribute to and participate in global or regional cooperation with international organizations, including AGISAR, VICH, IICAB, and IMDRF, regarding development of vaccines, antibacterial drugs, and diagnostic tests for use in agriculture, and regarding risk assessments of the use of medically-important antibiotics in agriculture.
- USDA will maintain the U.S. commitment to VICH and IICAB, expanding the Global Outreach Forum to:
  - Promote the use of VICH guidance for safety, quality, potency and effective use of vaccines outside of the three cooperating major regions (the U.S., Japan, and the European Union).
  - Facilitate input from a broadened base of participating countries and economies.
- USDA will plan and participate in at least three VICH Global Outreach Forums over the first two years.
- USDA will hold at least one international meeting in collaboration with IICAB to discuss U.S. regulatory policy in a workshop setting.

Within three years:

- FDA and USDA will consult with regional health authorities about their processes for achieving regulatory approval of new antibacterial drugs, diagnostics, and vaccines for use in medicine and agriculture and for conducting risk assessments on the use of medically-important antibiotics in agriculture.
Within five years:

- FDA and USDA will engage China and additional interested partner countries to exchange technical information and harmonize approaches for risk assessment and regulation of veterinary medicinal products.
- FDA and USDA will work with OIE and other international partners on development of standardized methods of reporting antimicrobial drug use in animals.
Appendix

TABLE 3: CDC’s Antibiotic-Resistant Threats in the United States, 2013

<table>
<thead>
<tr>
<th>URGENT Threat Level Pathogens (3)</th>
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<tbody>
<tr>
<td><strong>Clostridium difficile</strong></td>
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<tr>
<td>250,000 infections per year requiring hospitalization or affecting hospitalized patients.</td>
</tr>
<tr>
<td>14,000 deaths per year.</td>
</tr>
<tr>
<td>At least $1 Billion in excess medical costs per year.</td>
</tr>
<tr>
<td><em>C. difficile</em> deaths increased 400% between 2000-2007 because of the emergence of a strain resistant to a common antibiotic class (fluoroquinolones).</td>
</tr>
<tr>
<td>Almost half of infections occur in people younger than 65, but more than 90% of deaths occur in people 65 and older.</td>
</tr>
<tr>
<td>Half of <em>C. difficile</em> infections first show symptoms in hospitalized or recently hospitalized patients, and half show symptoms in nursing home patients or in people recently cared for in doctors’ offices and clinics who received antibiotics.</td>
</tr>
<tr>
<td>The majority (71%) of pediatric <em>Clostridium difficile</em> infections, which are bacterial infections that cause severe diarrhea and are potentially life-threatening, occur among children in the general community, 73% were found to have recently taken antibiotics prescribed in doctor’s offices for other outpatient settings.</td>
</tr>
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<tr>
<th>Carbapenem-Resistant Enterobacteriaceae*</th>
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</thead>
<tbody>
<tr>
<td>Out of ~140,000 healthcare-associated <em>Enterobacteriaceae</em> infections per year, more than 9,000 are caused by CRE (7,900 CR-<em>Klebsiella</em> spp; 1,400 CR-<em>E. coli</em>).</td>
</tr>
<tr>
<td>44 States have had at least one type of CRE confirmed by CDC testing.</td>
</tr>
<tr>
<td>CRE are resistant to nearly all antibiotics including carbapenems—the antibiotic of last resort.</td>
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<tr>
<th>Neisseria gonorrhoeae* (Notifiable to CDC)</th>
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<tbody>
<tr>
<td><em>Neisseria gonorrhoeae</em> causes gonorrhea, is the second most common reportable infection in the United States, and is developing resistance to the cephalosporin antibiotics, the last line treatment option for this infection.</td>
</tr>
<tr>
<td>Of the 820,000 cases per year, 30% (246,000) now demonstrate resistance to at least one antibiotic.</td>
</tr>
<tr>
<td>If cephalosporin-resistant <em>N. gonorrhoeae</em> becomes widespread, the public health impact during a 10-year period is estimated to be 75,000 additional cases of pelvic inflammatory disease, 15,000 cases of epididymitis, and 222 additional HIV infections, with an estimated direct medical cost of at least $235 million.</td>
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<tr>
<th>SERIOUS Threat Level Pathogens (12)</th>
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</thead>
<tbody>
<tr>
<td>Multidrug-Resistant Acinetobacter</td>
</tr>
<tr>
<td>12,000 healthcare-associated <em>Acinetobacter</em> infections occur in the U.S. of which 7,000 are multidrug-resistant</td>
</tr>
<tr>
<td>~ 500 deaths per year.</td>
</tr>
<tr>
<td>At least three different classes of antibiotics no longer cure resistant <em>Acinetobacter</em> infections.</td>
</tr>
</tbody>
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<thead>
<tr>
<th>Drug-Resistant Campylobacter</th>
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<tbody>
<tr>
<td><em>Campylobacter</em> causes ~1.3 Million infections, 13,000 hospitalizations and 120 deaths each year; 310,000 (25%) drug-resistant <em>Campylobacter</em> infections are found each year.</td>
</tr>
<tr>
<td><em>Campylobacter</em> drug resistance increased from 13% in 1997 to 25% in 2011.</td>
</tr>
<tr>
<td><em>Campylobacter</em> spreads from animals to people through contaminated food, particularly raw or undercooked chicken and unpasteurized milk.</td>
</tr>
<tr>
<td>Antibiotic use in food animals can results in resistant <em>Campylobacter</em> than can spread to humans.</td>
</tr>
</tbody>
</table>

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<tr>
<th>Fluconazole-Resistant Candida</th>
</tr>
</thead>
<tbody>
<tr>
<td>Out of 46,000 <em>Candida</em> yeast infections per year, 3,400 (30%) of patients with bloodstream infections with drug-resistant (DR)-<em>Candida</em> die during their hospitalization.</td>
</tr>
<tr>
<td>CDC estimates that each case of <em>Candida</em> infection results in 3-13 days of additional hospitalization and a total of $6,000-$25,000 in direct healthcare costs per patient.</td>
</tr>
</tbody>
</table>

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### TABLE 3: CDC’s Antibiotic-Resistant Threats in the United States, 2013

**SERIOUS Threat Level Pathogens (12), continued**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Incidence</th>
<th>Drug Resistance/Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extended Spectrum β-Lactamase (ESBL) Producing Enterobacteriaceae</strong>*</td>
<td></td>
<td><strong>Extended Spectrum β-Lactamase (ESBL) is an enzyme that allows bacteria to become resistant to a wide spectrum of penicillins and cephalosporins.</strong> Of 140,000 <em>Enterobacteriaceae</em> infections per year, 26,000 are drug resistant causing 1,700 deaths. 26,000 healthcare-associated <em>Enterobacteriaceae</em> infections are caused by ESBL-Enteobacteriaceae. 26,000 healthcare-associated <em>Enterobacteriaceae</em> infections are caused by ESBL-Enteobacteriaceae.</td>
</tr>
<tr>
<td><strong>Vancomycin-Resistant Enterococcus</strong></td>
<td></td>
<td>Of 66,000 <em>Enterococcus</em> infections per year, 20,000 are drug resistant causing 1,300 deaths. <em>Enterococcus</em> strains resistant to vancomycin leave few or no treatment options.</td>
</tr>
<tr>
<td><strong>Multidrug-Resistant <em>Pseudomonas aeruginosa</em></strong></td>
<td></td>
<td>Of 51,000 <em>Pseudomonas</em> infections per year, 6,700 are multidrug resistant causing 440 deaths. 13% of severe healthcare-associated infections caused by <em>Pseudomonas</em> are multidrug resistant, meaning nearly all or all antibiotics no longer cure these infections.</td>
</tr>
<tr>
<td><strong>Drug-Resistant Non-Typhoidal <em>Salmonella</em></strong> (Notifiable to CDC)</td>
<td></td>
<td>Non-typhoidal <em>Salmonella</em> causes 1.2 million infections per year, of which 100,000 are drug-resistant resulting in 23,000 hospitalizations and 450 deaths each year. Non-typhoidal <em>Salmonella</em> results in higher number of hospital stays, length of stay, and treatment costs.</td>
</tr>
<tr>
<td><strong>Drug-Resistant <em>Salmonella typhi</em></strong> (Notifiable to CDC)</td>
<td></td>
<td>Of 21.7 M <em>Salmonella typhi</em> infections worldwide, 5,700 illnesses in the U.S. with 3,800 (67%) of infections are drug-resistant resulting in 620 hospitalizations each year. Before the antibiotic era or in areas where antibiotics are unavailable, <em>Salmonella typhi</em> results in up to 20% deaths.</td>
</tr>
<tr>
<td><strong>Drug-Resistant <em>Shigella</em></strong> (Notifiable to CDC)</td>
<td></td>
<td><em>Shigella</em> causes ~ 500,000 illnesses, 5,500 hospitalizations, and 40 deaths each year in the U.S. Since 2006, <em>Shigella</em> resistance to traditional first-line antibiotics has become so high that physicians must now rely on alternative drugs (ciprofloxacin and azithromycin) to treat infections.</td>
</tr>
<tr>
<td><strong>Methicillin-Resistant <em>Staphylococcus aureus</em></strong> (MRSA)**</td>
<td></td>
<td>Over 80,000 invasive MRSA infections and 11,285 related deaths per year (in 2011). Severe MRSA infections most commonly occur during or soon after inpatient medical care. Between 2005 and 2001, overall rates of invasive MRSA dropped 31% predominantly due to appropriate medical procedures implemented in central-line maintenance.</td>
</tr>
<tr>
<td><strong>Drug-Resistant <em>Streptococcus pneumoniae</em></strong> (Notifiable to CDC)</td>
<td></td>
<td>Of 4 million disease incidents and 22,000 deaths; 1.2 M are drug resistant (to amoxicillin and azithromycin (Z-Pak) resulting in 19,000 excess hospitalizations and 7,900 deaths. In 30% of <em>S. pneumoniae</em> cases, the bacteria are fully resistant to one or more antibiotics causing complications in treatment and death. Pneumococcal pneumonia accounts for 72% of all direct medical costs for treatment of pneumococcal disease and in excess of $96 million in medical costs per year. Pneumococcal conjugate vaccine (PCV) prevents disease, reduces antibiotic-resistance by blocking the transmission of resistant <em>S. pneumoniae</em> strains, and protects against 13 strains of <em>Streptococcus</em>.</td>
</tr>
</tbody>
</table>
## Table 3: CDC’s Antibiotic-Resistant Threats in the United States, 2013

### Serious Threat Level Pathogens (12), continued

**Drug-Resistant Tuberculosis** *(Notifiable to CDC)*

- Tuberculosis is among the most common infectious diseases and cause of death worldwide.
- Of 10,528 Tb cases in the U.S. in 2011, 1,042 (9.9%) were resistant to antibiotics resulting in 50 deaths.
- CDC manages 5 Tb Regional Training and Medical Consultation Centers (RTMCCs) and ongoing surveillance for drug-resistant Tb in all 50 states and DC using the National Tuberculosis Surveillance System (NTSS).

### Of Concern Threat Level Pathogens (3)

**Vancomycin-Resistant Staphylococcus aureus** *(Notifiable to CDC)*

- Few cases thus far (13 cases in 4 States since 2002).
- Staph strains resistant to vancomycin leave very few or no treatment options.

**Erythromycin-Resistant Group A Streptococcus**

- Group A Strep (GAS) causes many illnesses including strep throat (up to 2.6 M cases per year), toxic shock syndrome, and “flesh-eating” disease (necrotizing fasciitis, 25-35% fatal).
- Erythromycin-resistant GAS causes 1,300 illnesses and 160 deaths.
- Current concern is the increase in bacteria that show resistance to clindamycin—which has a unique role in treatment of GAS infections.

**Clindamycin-Resistant Group B Streptococcus**

- Of 27,000 Group B Strep (GBS) cases, 7,600 illnesses are drug-resistant resulting in 440 deaths in the U.S. each year.