Role of the MicroLab in Antimicrobial Stewardship Programs

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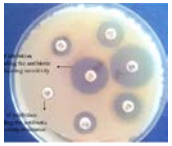
Diagnostic Microbiology Pathway

Sampling and transporting

This is the basis of the diagnostic pathway . Taking Good quality samples is fundamental to consider antimicroial adjustments.

Conventional (48-72h)



Rapid Diagnostics (1h – 6h)

Mass/Spect

ID Only

FilmArray

ID and resistance Markers.

Flow chip

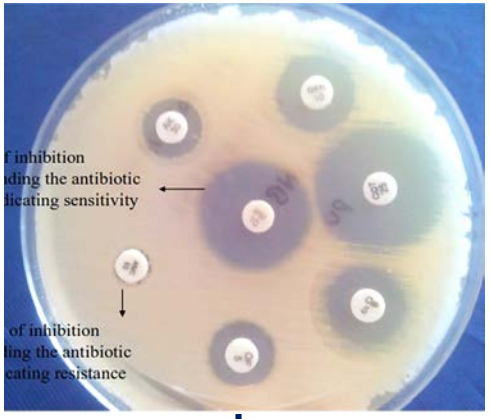
ID and resistance Markers.

Accelerate Phenosystem

ID and Complete AST with MICs

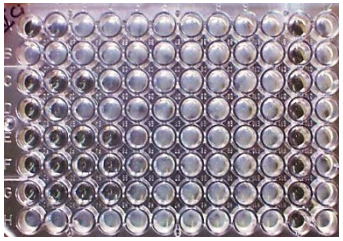
AST Methods are really different

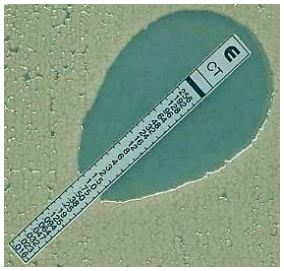
Qualitative Methods
Kirby Bauer

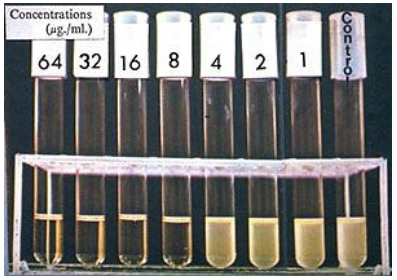


- It provides Categorical results like Susceptible, intermediate and resistant, **but it doesn´t tell you how much susceptible or resistant the bug is.**

Quantitative Methods
(MIC- minimal inhibitory concentration)



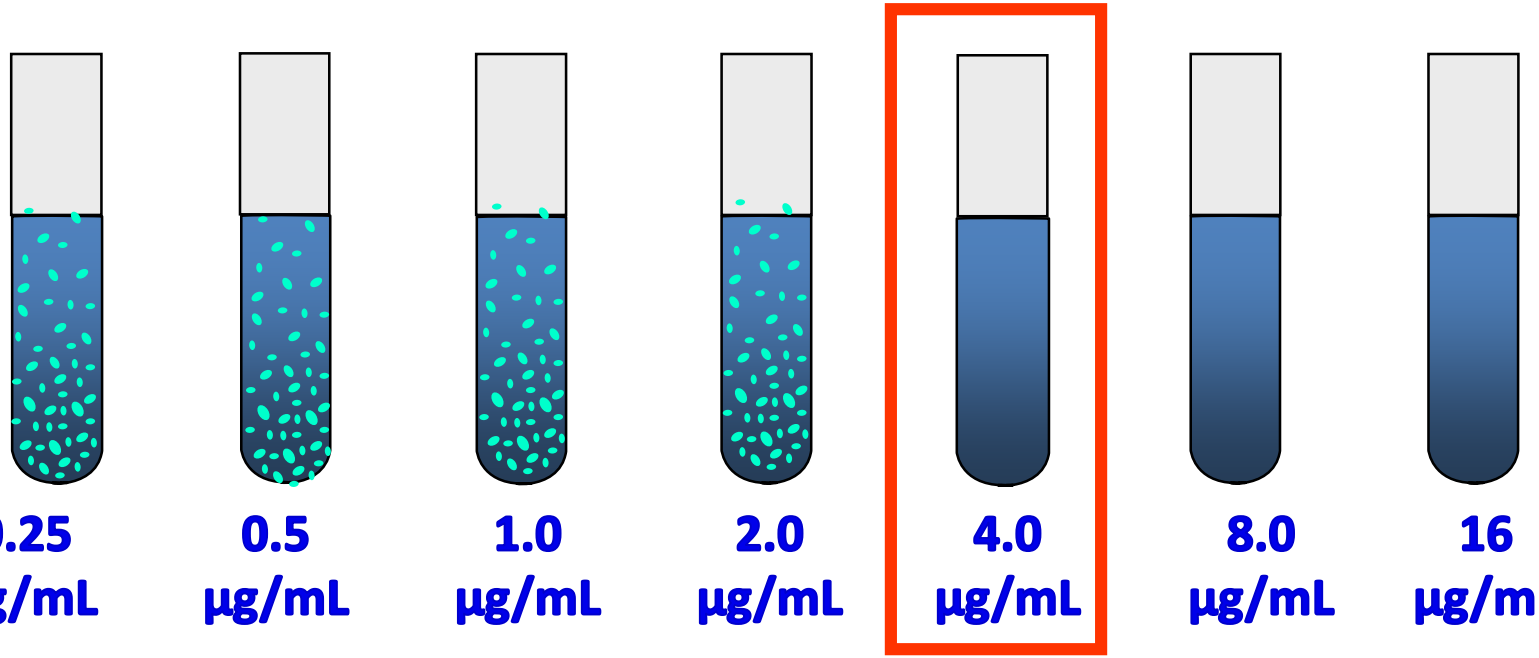




- Beside the categorical interpretation, the quantitative methods , provide the MIC what tells you **How much susceptible or resistant is a bug for a particular Antimicrobial**. It predicts better the clinical outcomes.

Minimal inhibitory concentration (MIC) from the technical perspective (Broth Microdilution)

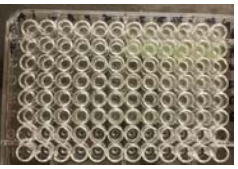
Inoculum, culture media and antibiotic dilutions are standardized



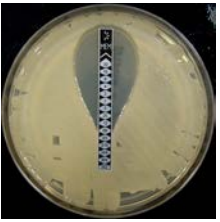
The antibiotic potency is expressed with the MIC
The MIC is the lowest concentration of antibiotic with inhibits the bacterial growth

J Antimicrob Chemother. 2018 Mar 1;73(3):564-568

Rationale to incorporate MICs in the Antimicrobial susceptibility reports

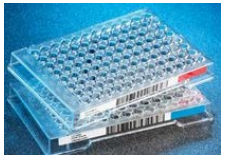


1. The MICs defines **the required antibiotic exposure** to guarantee that the patient can get the maximum clinical benefit.



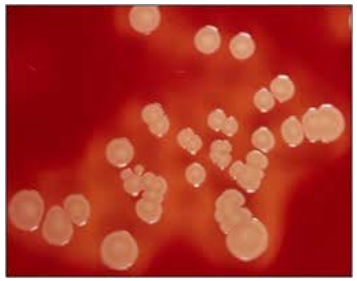
2. The MICs let you choose the antibiotic with the **highest probability of success**.
3. The MIC helps to monitor the presence of mechanism of resistance:

- Individually in a single AST report.
- In the hospital antibiogram, defining the most appropriate empiric therapy. (the one with the lowest MICs)



Bug/Drug combinations where reporting MICs is fundamental

S.aureus

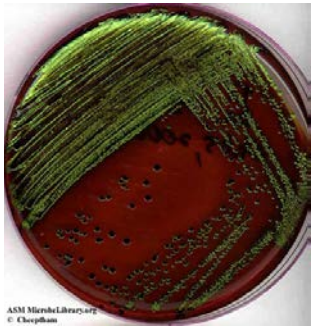


Vancomycin
Daptomycin
Ceftaroline

E.faecium

Daptomycin

Enterobacteriaceae

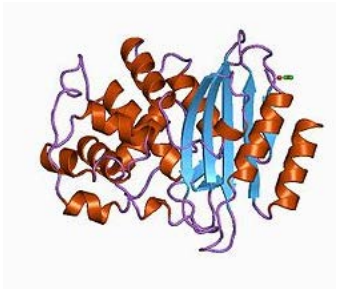


Cephalosporins
Carbapenems
Pip/tazo
Ceftolozane/tazo
Ciprofloxacin/Levoflox
Colistin
Tigecycline

P.aeruginosa

Cephalosporins
Carbapenems
Pip/tazo
Ceftolozane/tazo
Ciprofloxacin
Levofloxacin
Colistin

However, some times the MIC can´t predict antibiotic efficacy and the lab must look what is behind



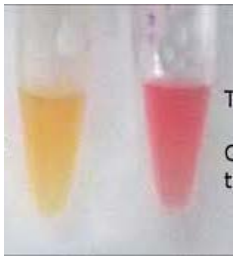
Issues with AST are related with :

- **The testing method:** Lots of varibility have been found between brands of different commercial methods. But also in Brands of Mueller Hinton agar, gradient diffusion strips etc.
- **The drug** : Some drugs are difficult to test because are unstable or require specific testing conditions. ie : Colistin.
- **The mechanism of resistance:** Despite *in vitro* susceptibility, there are reports of clinical failures/deaths related with some specific mechanisms. ie Carbapenemases.

Open Forum Infect Dis. 2018 May 23;5(6)
Antimicrob Agents Chemother. 2018 Jul 27;62(8).

Stewardship Approach from the MicroLab
Detection of AMR Mechanisms and application of "Expert Rules "

Carbapenemases in *Enterobacteriaeae*



If a Class A Carbapenemase is detected:

- Report Aminopenicillins, Cephalosporins, Pip/tazo Aztreonam and Ertapenem as Resistant. The Imi/Mero/Dori result can be reported as tested including a footnote that carbapenemases are present. Test CAZ/AVI

If a Class B Carbapenemase is detected:

- Report Aminopenicillins, Cephalosporins, Pip/tazo and Ertapenem as Resistant. The Aztreonam should be tested and reported itself. The Imi/Mero/Dori result can be reported as tested including a footnote that carbapenemase is present.

If a Class D Carbapenemase is detected:

- Report Aminopenicillins, 1º , 2º generation and 3º generation Cephalosporins, Pip/tazo, Aztreonam and Ertapenem as Resistant. . Cefepime and Imipenem, Meropenem, Doripenem, could be reported as tested with a footnote that a carbapenemase is present. Test CAZ/AVI

Expert rules Guidelines API - 2019

What is Hot in Antimicrobial Susceptibility testing and why you should TAKE CARE:

Piperacillin/Tazobactam Susceptible in ESBLs

MERINO trial showed higher mortality rates with Pip/tazo than Meropenem in Bacteremias by ESBL E.co and Kpn. Despite controversy, False susceptibility results had been reported with Pip/tazo in several methods (CLSI is addressing this)

Delete Pip/tazo susceptible result in Bacteremias and Pneumonias

Polymyxin Susceptibility

There is a disconnection between Colistin Susceptible results and clinical efficacy:

- Low serum levels.
- Use of Pro-drugs.
- Rapid selection of resistance.
- Drug instability .
- False S in commercial systems.

When a Polymyxin is required, Consider if posible to confirm Colistin results with a reference BMD method or use disk elution or supplemented agar.

Fosfomycin Susceptibility

There is controversy about Fosfomycin results for the treatment of UTIs:

- Broth microdilution is not accurate.
- Glucose 6 Phosphate is required for testing but it´s absent in bladder.
- Treatment is basically one dose.

Consider testing in specific situations using AD or DD

TESTING FOR NEW DRUGS

CREATING PROTOCOLS BETWEEN MICROLAB AND STEWARDSHIP COMMITTEES

CEFTOLOZANE/TAZOBACTAM

Very active for *P.aeruginosa* not producing Carbapenemases. But take into account:

- Susceptibility testing is required .
- Some brands of Gradient diffusion test are unreliable.
- Not available in all automated systems yet.

Consider testing in MDR *P.aeruginosa* with BMD/Disk or E-test®

CEFTAZIDIME/AVIBACTAM

Very active inhibitor for Class A (KPC) and Class D (OXA48) Carbapenemase producing *Enterobacteriaceae and P.aeruginosa*:
But take into account:

- Susceptibility testing is required .
- Disk diffusion is unreliable.
- It is not active against MBLs and there are reports of simultaneous production of Class A+B carbapenemases.
- There is not test accurate enough to detect ALL carbapenemases.

Consider in Carbapenem I/R *Enterobacteriaea* and MERO +CAZ R *P.aeruginosa* having a rapid phenotypic or molecular test for Carbapenemases other than Class B. Testing can be done with BMD or E-test®

Rapid Molecular Diagnostics

When, How and why important for Antimicrobial Stewardship

Mass/Spect

FilmArray

Flow chip

Accelerate Phenosystem

- They can help to **REDUCE THE GAP** between empiric and targeted therapy as could be performed directly on samples.
- Knowing your molecular epidemiology can assist you to develop your local guidelines for Antimicrobial prescribing and for Infection control purposes.

What is important here ?

1. To discover what is the patient profile to apply this methods (not all solutions are for all patients) you have to develop protocols. (**Diagnostic Stewardship**)
2. Include results in your guidelines. **You Will waste money if actions are not taken with this solutions**.

The results of your molecular diagnostic platform should be personalized with comments.

PCR RESULT®	Report	Suggested comments to be included
***S.aureus* (+) *mecA* (+)**	***Methicillin resistant S.aureus***	*Methicillin resistant S.aureus* is considered resistant to all betalactams except Ceftaroline. Consult the stewarship guidelines for treatment options.
***Serratia* Carbapenemases (-)**	***Serratia* species**	This organisms produces an inducible AmpC β-lactamase. The use of Aminopenicillins, Cephalosporins other than Cefepime and inhibitor combinations (Pip/tazo) could lead to clinical failures in high inoculum infections. Consult the stewarship guidelines for treatment options.
E.cloacae complex **Carbapenemases (-)**	***Enterobacter cloacae complex***	

Summary:

1. The role of the microlab in Antimicrobial Stewardship is ESSENTIAL to guarantee Good clinical outcomes and to reduce the selective pressure that generates resistance.
2. Incorporating MICs in the susceptibility reports, knowing the limitations of AST and editing results with expert rules is fundamental for Stewardship decisions.
3. Rapid diagnostic test can change the paradigm. But you need to stratify patients (who is the patient that most Benefit with this technology) and to choose a rapid molecular platform, to think in the principles of Diagnostic Stewardship : Right test, Right Patient, Right time and . Right Costs.

Thanks for your attention

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