The Essential Role of Clinical Microbiology in Antimicrobial Stewardship: Harnessing AST Data as a Driver of Successful Programs

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Disclosures

Consulting: ThermoFisher, Accelerate Diagnostics, Pattern, IHMA, Next Gen Dx, QPex

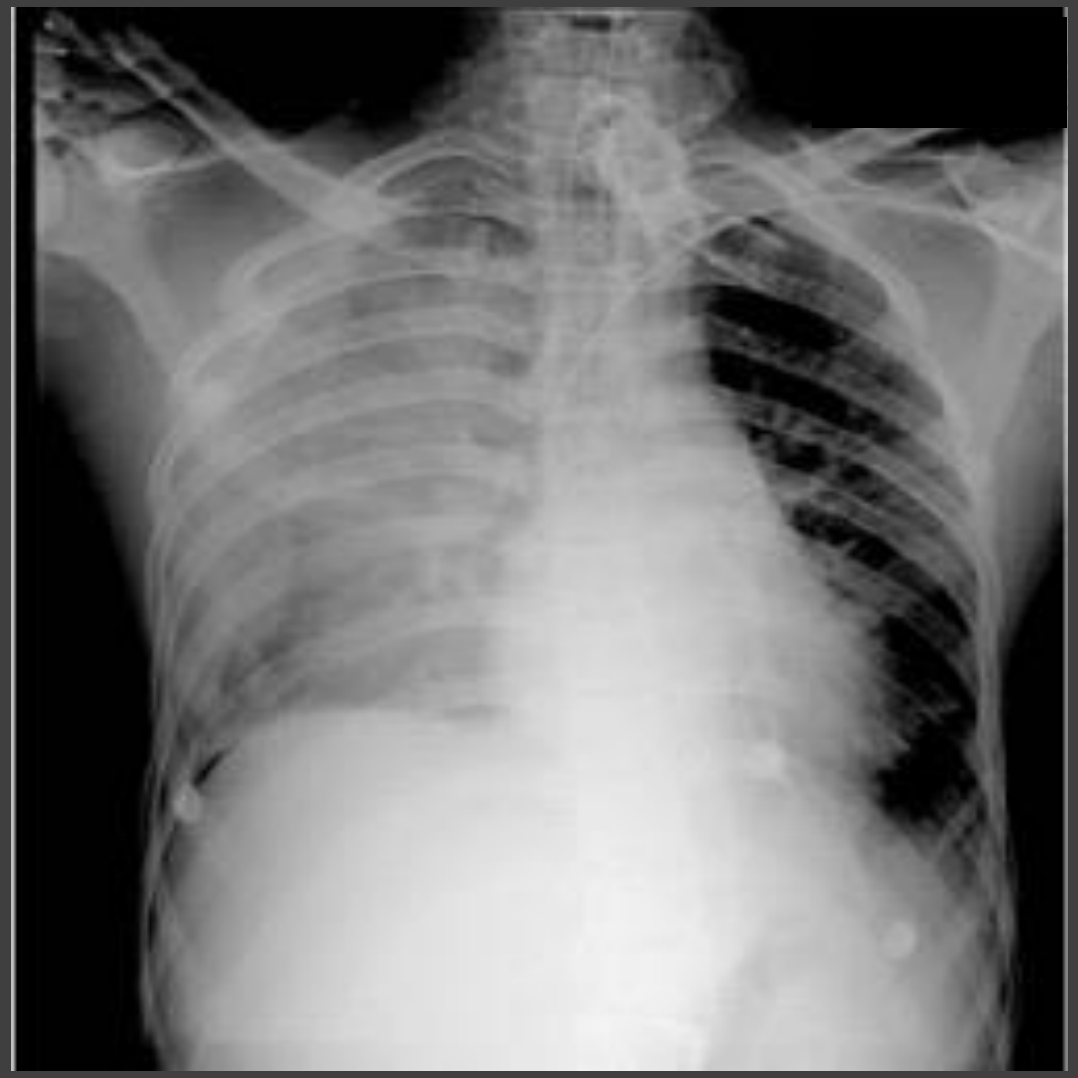
Objectives

1. Understand the impact clinical microbiology laboratory data can have on accurate treatment decisions and better management of critically ill patients
2. Describe the impact that COVID-19 has had on antimicrobial resistance
3. Review antimicrobial testing challenges in critically ill patients
4. Outline the role the microbiology lab plays to support antimicrobial stewardship during a pandemic

August 2020:VUMC

- 65 YO man
- Diagnosed with COVID-19 at outside hospital
- intubated, high ventilation settings, deep sedation, paralysis
- Completed dexamethaxone, remdesivir, vancomycin & piperacillin-tazobactam

- Transferred to VUMC at family's request
- Arrives septic, sputum produced with deep in-line suctioning



Respiratory cultures

HEAVY GROWTH OF *ACINETOBACTER BAUMANNII*

AST RESULTS

ANTIMICROBIAL	MIC	Interpretation
Amikacin	32	R
Amp/sulbactam	>16	R
Cefepime	>32	R
Ceftazidime	>32	R
Ciprofloxacin	>4	R
Doxycycline	>16	R
Gentamicin	>16	R
Meropenem	>16	R
Pip-tazobactam	>128	R
Tobramycin	>16	R
Trimeth-Sulfa	>4	R

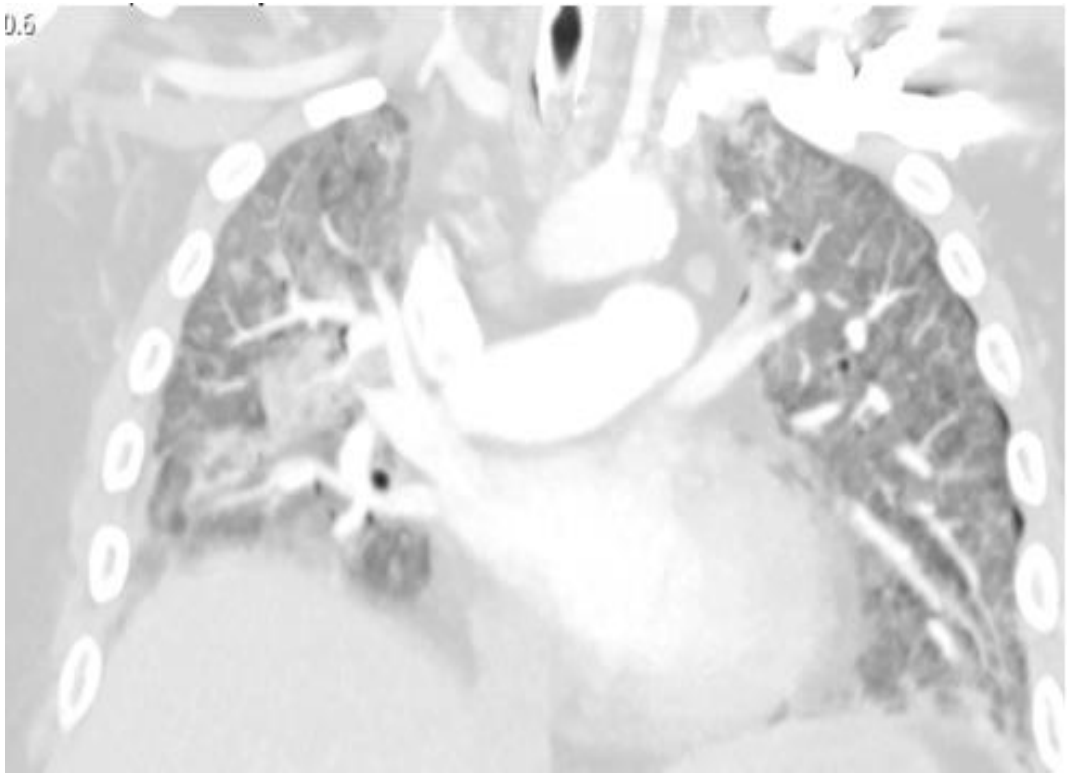
Adapted from Tamma P & Hsu AJ. 2019. J Ped Infect Dis. 8:251.

What are our treatment options?

Agent	Activity vs. MDR A. baumannii	Isolate MIC (mcg/mL)
Ceftazidime-avibactam	Limited	>16
Cefotolozane-tazobactam	No	>32
Imipenem-relebactam	Limited	>16
Meropenem-vaborbactam	No	>16
Cefiderocol	Yes	0.5*
Plazomicin	Yes	?
Tigecycline	No	4

***result from reference lab**

February 2021



- 56 YO man, type II diabetes, Crohn's and asthma
- Early January: COVID-19
  - Receives remdesiver, decadron, convalescent plasma therapy
- Intubated mid-January, transferred to VUMC
- Infectious complications:
  - *C. glabrata* fungemia
  - VAP due to carbapenem resistant *E. cloacae*

E. cloacae

Susceptibility

	Carbapenem-resistant Enterobacter species MIC	
Amikacin	<=8	Susceptible
Avycaz (Ceftazidime/Avibactam)	2/4	Susceptible
Cefepime	>16	Resistant
Ciprofloxacin	>2	Resistant
Ertapenem	>2	Resistant
Gentamicin	>8	Resistant
Levofloxacin	>4	Resistant
Meropenem	>8	Resistant
Piperacillin/Tazobactam	>64/4	Resistant
Tobramycin	>8	Resistant
Trimethoprim/Sulfa	>2/38	Resistant

CPO Detect Result:

“Class A Beta-lactamase”

PCR: KPC +

Treated with ceftazidime-avibactam

Patient story, continued

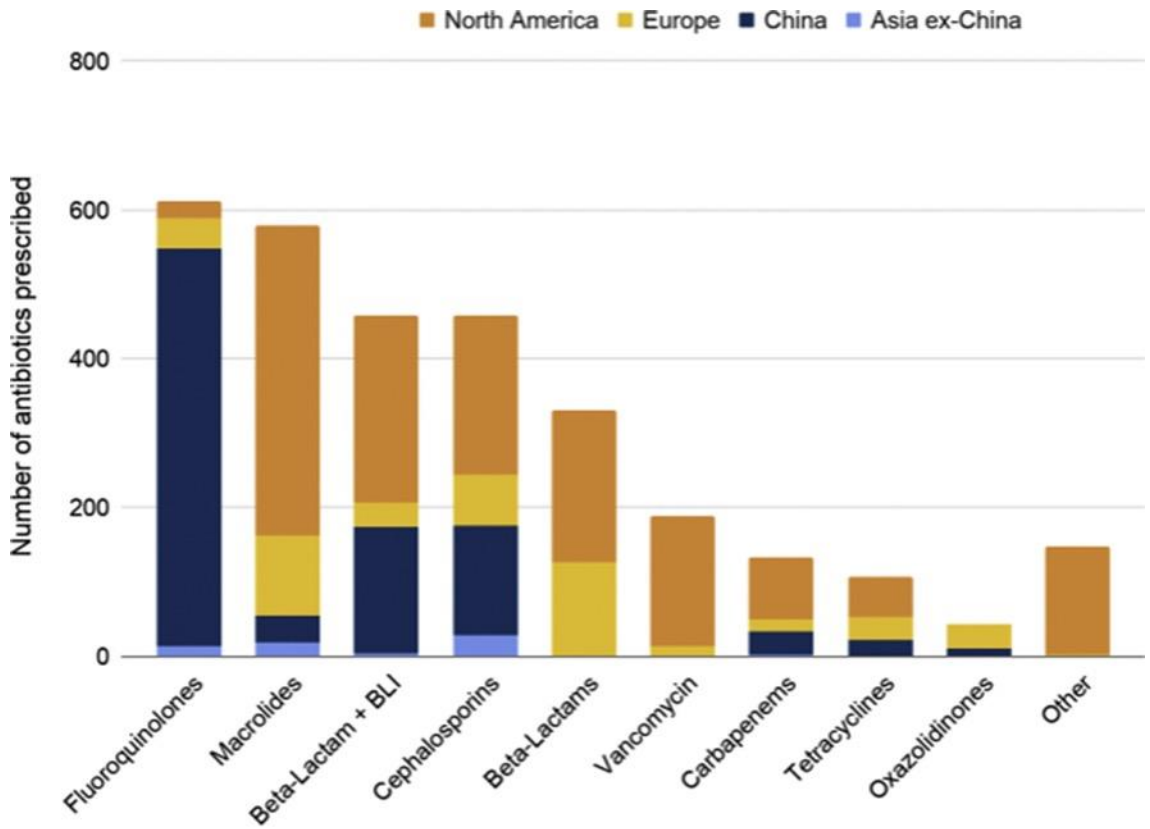
- 2 weeks post-ceftazidime-avibactam, isolate reoccurs
- Isolate is now “R” to ceftazidime-avibactam, “S” to meropenem
- Still has KPC → mutation to KPC that leads to resistance to avibactam
- Patient treated with meropenem-vaborbactam

Antimicrobial resistance and COVID-19

- A lot of reason for concern:
  - ~74% of COVID-19 patients received an antimicrobial prescription
  - Only 4% have a true bacterial infection
  - ~15% of hospitalized patients develop bacterial secondary infection
- Outside the US, huge emphasis on use of antibiotics (e.g., azithromycin) to prevent or treat COVID-19
  - Medical mis-information
- Some evidence of increase in resistance:
  - 10% increase at one institution

Langford et al. 2021. Clin Microbiol. Infect. 1:18; Nori et al. 2020 Infect Control Epidem. 1-5; Monnet et al 2020 Euro Surveillance 25: 2001886

Antimicrobial use in COVID-19

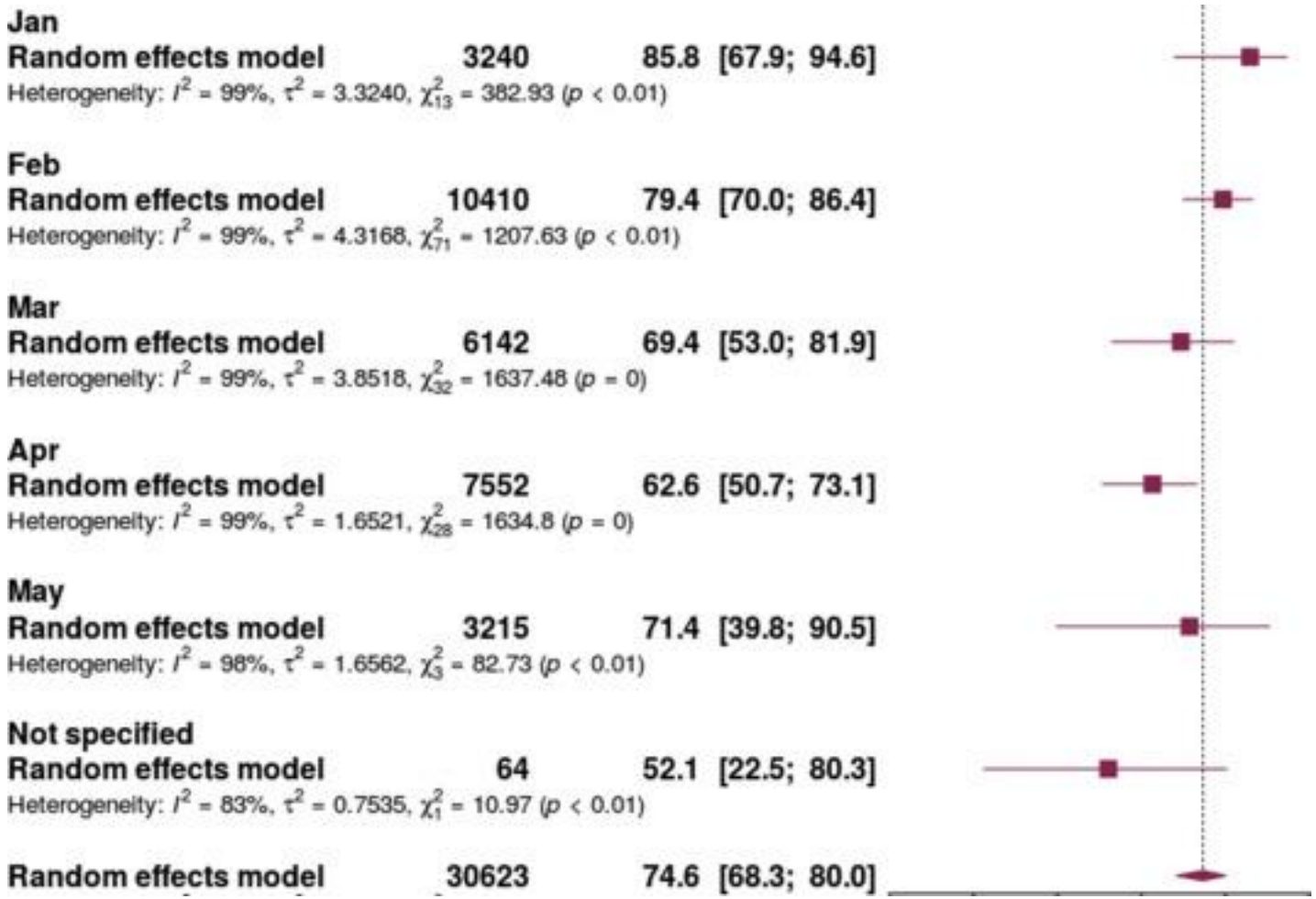


- Fluoroquinolones very commonly used in China
- Macrolides more common in USA

- Most common prescriptions in the ICU (86.4%) vs. outpatients (59%)

Langford et al. 2021. Clin Microbiol. Infect. 1:18

Trends towards less antimicrobials in later months of pandemic



Langford et al. 2021. Clin Microbiol. Infect. 1:18

Secondary bacterial infections in viral pandemics

2009 Influenza

- Community-acquired pneumonia
  - Nasopharyngeal colonizers cause secondary infections
  - *S. aureus, S. pneumoniae, S. pyogenes*

COVID-19

- Hospital / Ventilator Acquired Pneumonia
  - Hospital pathogens cause secondary infections
- Gram negative bacteria
- *S. aureus*
- Fungi*?*

Antimicrobial resistance is a huge concern

Rice et al. Crit Care Med 2012 1487
Clancy et al. Clin Infec Dis 2020. in press

Comparing viral pandemics

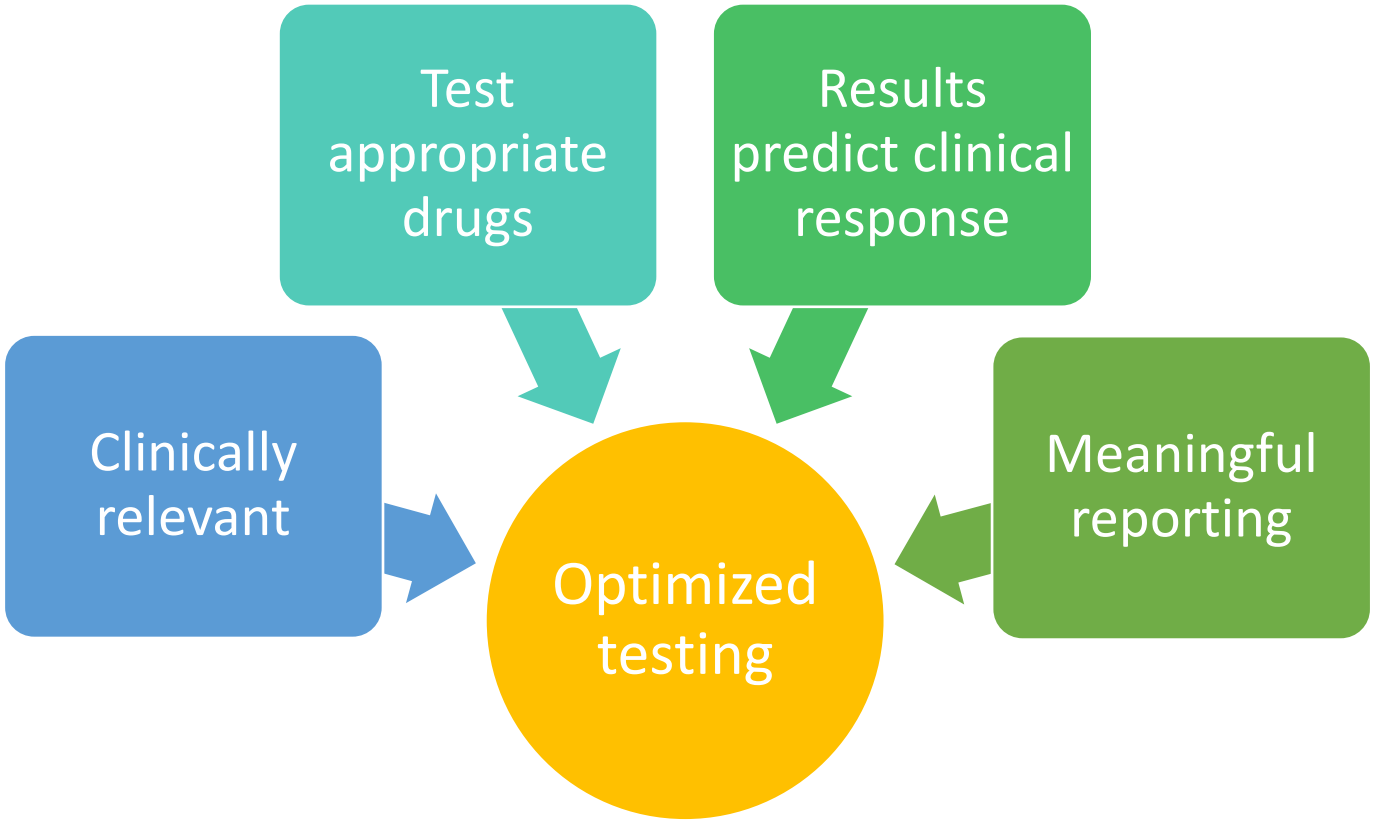
COVID-19	Influenza
8% secondary bacterial infections	23% secondary bacterial infection
75% receive antibiotics	65% receive antibiotics

Langford et al. 2021. Clin Microbiol. Infect. 1:18

What ways can this be mitigated?

- Continued support of antibiotic stewardship
- Appropriate use of diagnostic testing
  - Many patient with COVID-19 never get a sputum culture done; often rejected by lab due to poor quality
- Fewer outpatient physician visits: decreased use of antimicrobials in outpatient domain
- Increased emphasis on hand hygiene, masking, social distancing

Can can the laboratory do?



1. Clinically relevant testing

Perform AST on clinically relevant bacteria only

When should we be performing AST?

- Clinically meaningful isolates
  - Don’t test colonizers
  - Don’t test contaminants
  - If >2 potential pathogens… hard to know what’s relevant
- Only when susceptibility is not predicted
- When there are clinical breakpoints
  - Some exceptions here, but generally hard to interpret and AST should be done only in rare instances if there are not breakpoints

Example: Single set of blood cultures with coagulase-negative *Staphylococcus*

- Coagulase negative staphylococci are the most common contaminant of blood cultures
- VUMC has a high rate of contaminated blood cultures
- Intervention was performed to stop performing AST on single set of skin flora contaminants
    - Significant reduction in use of vancomycin for these patients in the ICU
    - Study conducted in September 2020… at a high COVID time

See Austin Ing's poster on this study at WFM 2021… and oral presentation

Test relevant antimicrobials

Ensure your testing meets your patient population:

- Broad spectrum (newer) agents for resistant organisms

Infectious Diseases Society of America Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Published by IDSA, 9/8/2020

A Focus on Extended-Spectrum β-lactamase Producing Enterobacterale
Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Di
(DTR-*P. aeruginosa*)

Pranita D. Tamma*, Samuel L. Aitken, Robert A. Bonomo, Amy J. Mather
J. Clancy

**Corresponding Author*

Treatment of choice includes many newer agents

CRE (with and without carbapenemase)
- ceftazidime-avibactam
- imipenem-relebactam
- meropenem-vaborbactam
- cefiderocol,
- eravacycline

Pseudomonas aeruginosa
- Ceftolozane-tazobactam
- Ceftazidime-avibactam
- imipenem-relebactam
- cefiderocol

Not on the list? Colistin!!

Testing newer agents: GNRs

Agent	Test			
	Disk	Gradient strip	Automated Systems	Manual MIC
Ceftazidime-avibactam	✓	✓	✓	✓
Cefotolozane-tazobactam	✓	✓	✓	✓
Imipenem-relebactam	Hardy	Etest, MTS	Sensititre, Vitek 2	Sensititre
Meropenem-vaborbactam	✓	✓	✓	✓
Cefiderocol	Hardy	-	Sensititre	Sensititre
Eravacycline	Hardy	Etest, MTS	Mscan, Sensititre, Vitek 2	Sensititre
Plazomicin	Hardy	Etest, MTS	Sensititre	Sensititre

Labs should be testing ceftazidime-avibactam and ceftolozane-tazobactam in house at this point

Labs should identify where to send for other tests… if you cannot do in house

Figure this out in advance, so you can be expedient when they are needed

*based on 510(k) summary search on fda.gov Oct 26 2020

✓ Available on most platforms

Value of testing newer agents in-house

- In absence of AST data:
  - Clinicians may use the drug empirically with no information
  - Clinicians may choose to use a sub-optimal drug (e.g., colistin)
- risk is unexpected resistance for these new agents

Risk of resistance for MDR Gram negative bacteria vs. newer antimicrobial agents

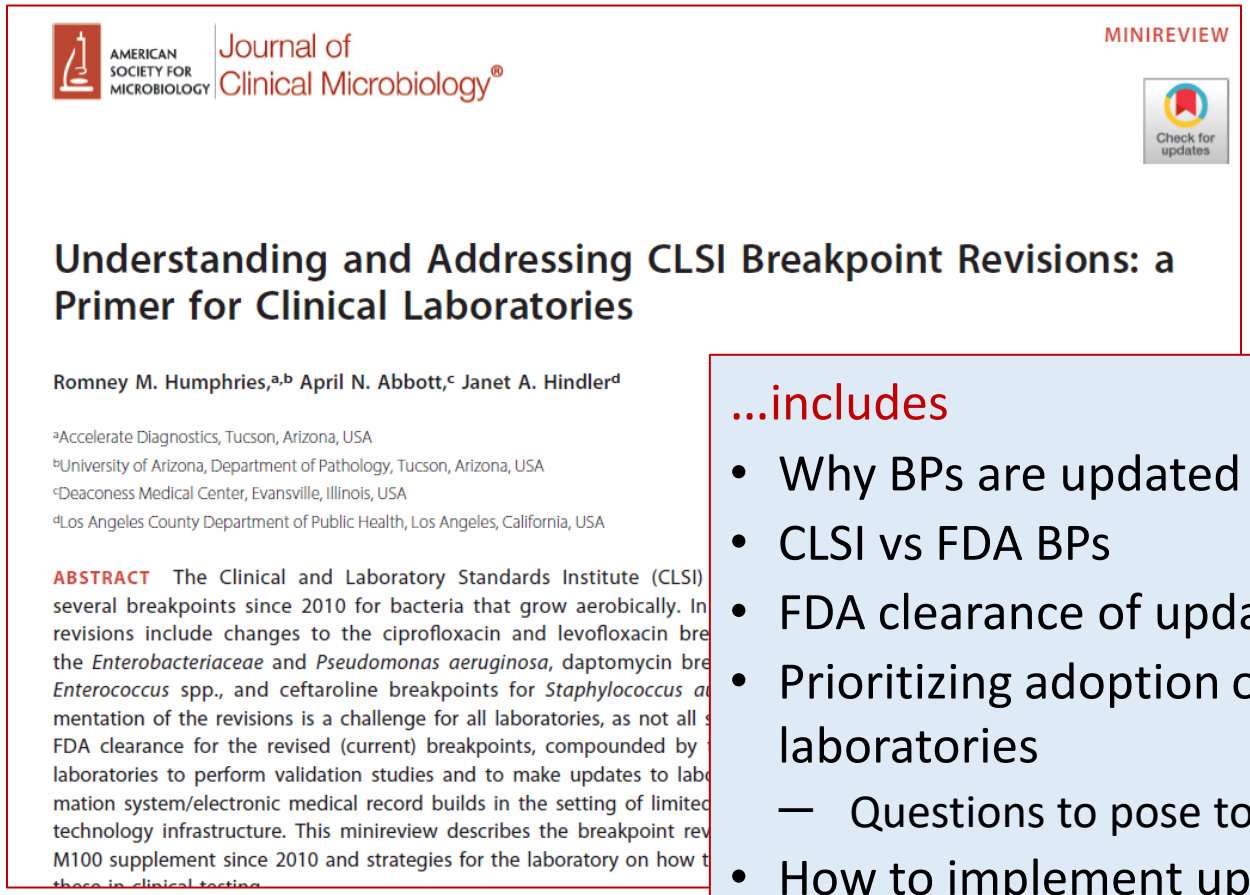
Antimicrobial	Enterobacterales	P. Aeruginosa	A. Baumannii
Ceftaz-avibactam	Low risk	Moderate risk	N/A
Ceftol-tazobactam	High risk	Moderate risk	N/A
Meropenem-vabor	Low risk	N/A	N/A
Imipenem-rel	Low risk	Low risk	N/A
Cefiderocol	Low risk	Low risk	? low risk

* Low risk : <5%; moderate risk, 20-30%; high risk: >50%

Make sure your tests are using up-to-date breakpoints!

Best predictor of clinical response to the MIC/ disk tests

Good reference to help with breakpoints changes:



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MINIREVIEW

Understanding and Addressing CLSI Breakpoint Revisions: a Primer for Clinical Laboratories

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[d]Los Angeles County Department of Public Health, Los Angeles, California, USA

ABSTRACT The Clinical and Laboratory Standards Institute (CLSI) several breakpoints since 2010 for bacteria that grow aerobically. In revisions include changes to the ciprofloxacin and levofloxacin bre the *Enterobacteriaceae* and *Pseudomonas aeruginosa*, daptomycin bre *Enterococcus* spp., and ceftaroline breakpoints for *Staphylococcus a* mentation of the revisions is a challenge for all laboratories, as not all FDA clearance for the revised (current) breakpoints, compounded by laboratories to perform validation studies and to make updates to labo mation system/electronic medical record builds in the setting of limited technology infrastructure. This minireview describes the breakpoint rev M100 supplement since 2010 and strategies for the laboratory on how t

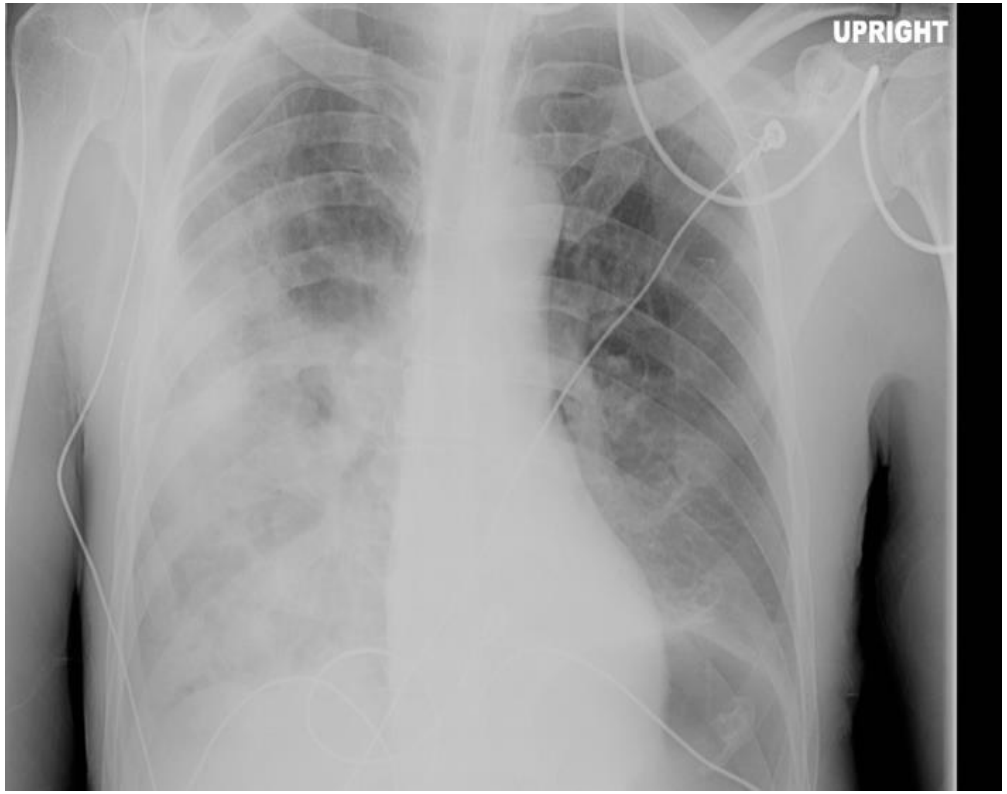
…includes

- Why BPs are updated
- CLSI vs FDA BPs
- FDA clearance of updated BPs on cASTs
- Prioritizing adoption of updated BPs in clinical laboratories
  - Questions to pose to stakeholders
- How to implement updated BPs
- Verification / validation for “off-label” BPs

Humphries et al. 2019. JCM. 57:e00203-19.

Case 3

- 48 year old male , No past medical history, admitted 3 weeks ago to OSH with ischemic bowel
- Resection of bowel, re-anatamosis but poor return of GI function
- Today: febrile, intubated, multiple pressors, new leukocytosis, renal failure, shock
- Outside hospital blood culture results: *K. pneumoniae*



Antimicrobial	Susceptibility
Ciprofloxacin	R
Pip/Tazobactam	R
Gentamicin	R
TMP-SMX	R
Meropenem	S
Tigecycline	R

Treated with meropenem + gentamicin

Case 3 continued

- 1 day after transfer:
  - Still on pressors, max ventilation, sputum production
- Local lab, blood cultures:
  - *K. pneumoniae* with KPC!!
    - Meropenem MIC = 4 µg/mL R
    - Phone outside lab, using obsolete breakpoints, no molecular testing

Why is it critical to use current carbapenem breakpoints (Enterobacterales)?

- CDC considers carbapenem-resistant *Enterobacteriaceae* (CRE), including carbapenemase producing CRE (CP-CRE) an urgent threat to the public's health as there are limited options for treating infections due to CRE.[1,2,3]
- Approximately 20% of CRE would be misclassified by use of outdated breakpoints.[5,6]
- Outdated breakpoints can direct treating physicians to inappropriate antimicrobial therapy, contributing to preventable patient morbidity and mortality.[2,3]
- Outdated breakpoints hinder the ability to identify CRE, impairing infection control initiatives and fueling the spread of CRE.[5]

1.CDC. Antibiotic Resistance Threats in the United States, 2019. CDC, Atlanta, GA.
2.Patel TS et al. 2015. *J Clin Microbiol.* 53:201-205.
3.Esterly JS et al. 2012. *Antimicrob Agents Chemother.* 56:4885-4890.
4.Marquez P et al. 2013. *Infect Control Hosp Epidemiol.* 34:144-150.
5.Bartsch SM et al. 2016. *J Clin Microbiol.* 54:2757-2762.
6.Humphries RM et al. 2018. *Clin Infect Dis.* 66:1061-1067.

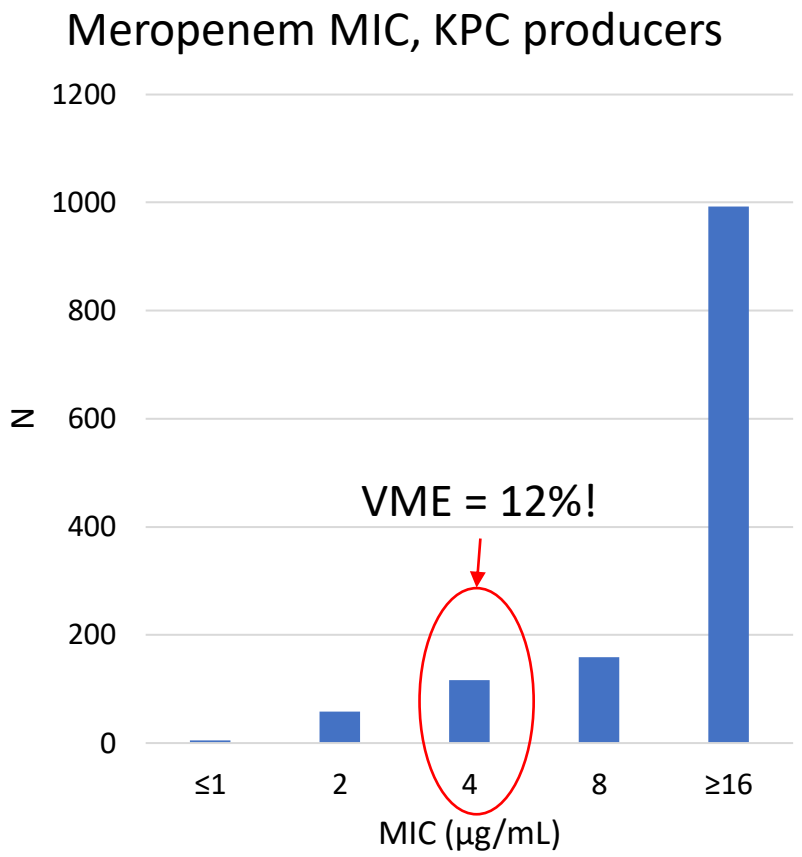
“Risk” of Using Obsolete Breakpoints

- To date, all CLSI BP updates involved “lowering” the BP
- If use obsolete BPs, there is a risk reporting “False “S” every time isolate is “R” by obsolete BPs and “S” with Updated BPs

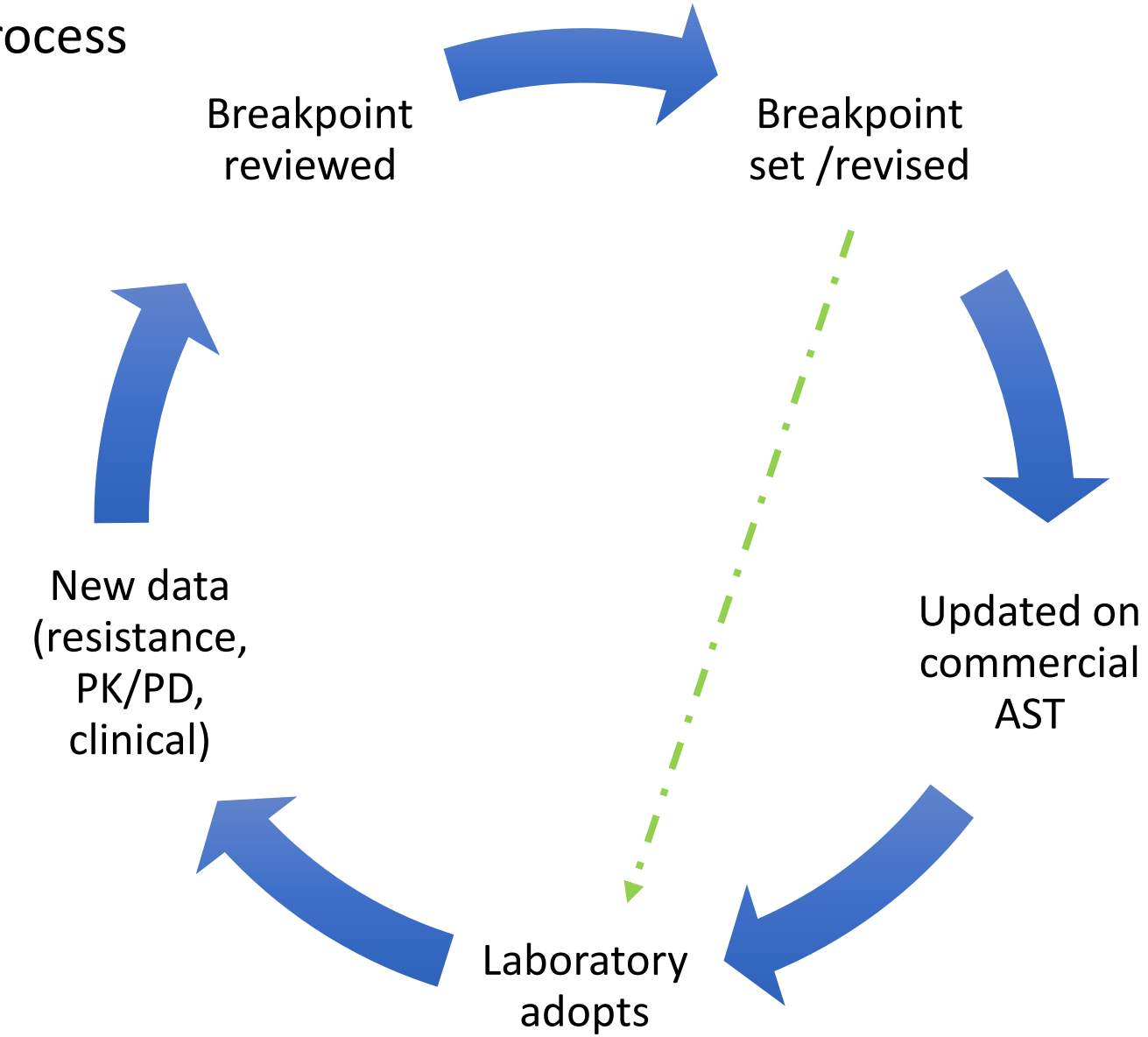
Enterobacterales

Agent	Obsolete Breakpoints (µg/ml)			Current Breakpoints (µg/ml)		
	S	I	R	S	I	R
Meropenem	≤4	8	≥16	≤1	2	≥4

Error	Results		Acceptable Error Rate
	Reference	New Test	
Very major	R	S	≤1.5%
Major	S	R	≤3.0%



Breakpoint update process



May take Years!

Why does it take years?

1. FDA cleared devices MUST use FDA breakpoints
    1. Delay between CLSI publication and FDA recognition
2. Companies need to update their tests for the new breakpoint
    1. Add dilutions, change software
    2. Do a new clinical trial
    3. Get new FDA clearance
3. Labs can validate their tests off-label for the breakpoints
    1. Must do a verification study (see M52)
    2. Labor intensive
    3. Confusing

Prioritizing Breakpoint Implementation

Priority	Considerations	Breakpoints Affected
1	If not implemented can result in: • Serious patient care concerns • Serious public health concerns	Carbapenems – GNRs Cephems – *Enterobacterales* Pip-tazo – *P. aeruginosa* Fluoroquinolones - *Salmonella*
2	• May not apply to your institution • May be handled with comments on report, alternative strategies	Cefazolin – *Enterobacterales* Fluoroquinolones – *Enterobacterales* & *P. aeruginosa* Daptomycin - *Enterococcus*
3	Related to drugs infrequently used or to doses not used in USA	Colistin – GNR Piperacillin, ticarcillin, ticar-clav – *P. aeruginosa* Ceftaroline – *S. aureus*

*these are just breakpoint *updates* since 2010… new breakpoints not covered herein

Humphries et al. 2019. JCM. 57:e00203-19.

Establishing Priorities for Updating BPs at Your Institution

Based on institutional-level practices, you should determine:

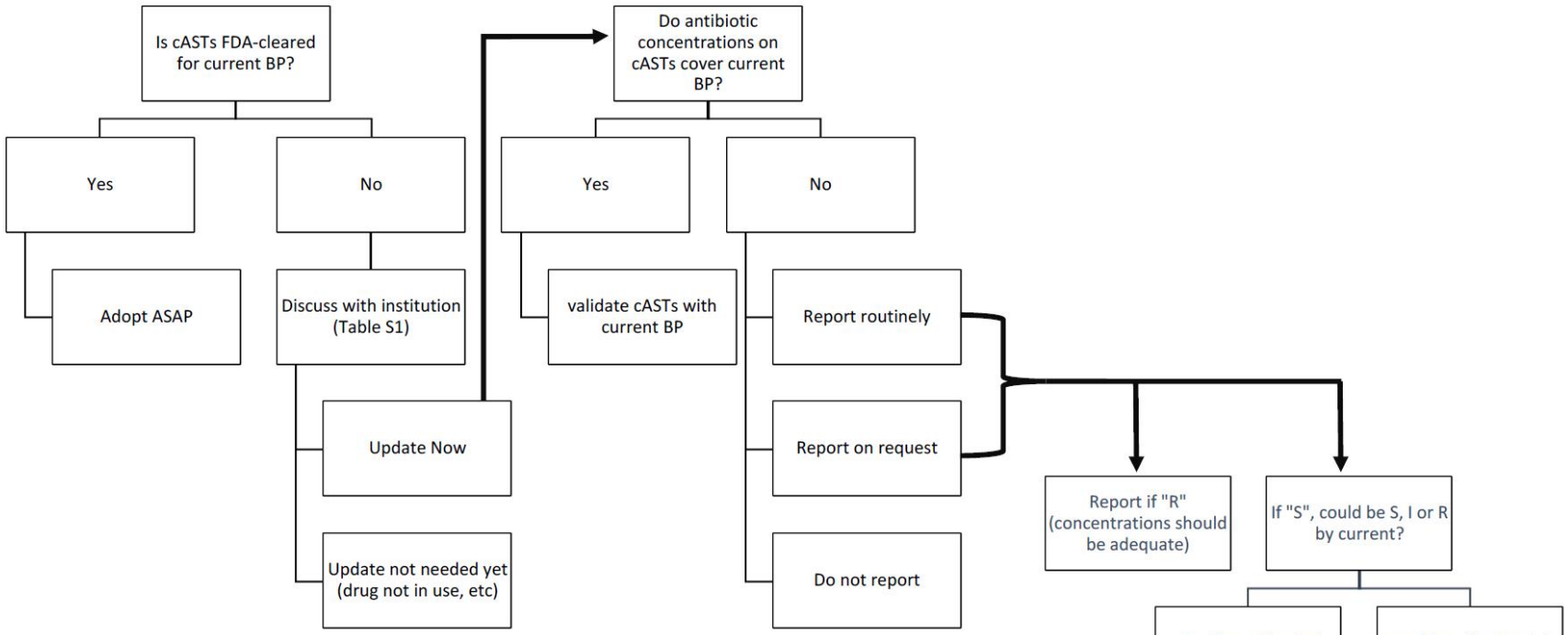
- the clinical use of the antimicrobial
- which testing options are available and most appropriate (for MIC tests, the concentrations encompassing lowered breakpoints must be available)
- which breakpoint(s) should be implemented
- if current breakpoints are not yet FDA-cleared on a cASTs, their use would be considered “off label” and a verification / validation is required for implementation

Work with stakeholders…antibiotic stewardship team, pharmacy, infectious diseases (ID), infection control and others, as appropriate

Humphries et al. 2019. JCM. 57:e00203-19.

Decision tree for revised BP adoption on cASTs…

Figure S1. Proposed decision tree for revised breakpoint adoption on cASTs



cASTs, commercial antimicrobial susceptibility test system; BPs breakpoints
Alternative test method options: disk diffusion (if test method appropriate for drug/organism combination); gradient diffusion; other

Humphries et al. 2019. JCM. 57:e00203-19.

Meaningful reporting

Supporting antibiotic stewardship: cascade / selective reporting

	Cascade Reporting	Selective reporting
Definition	Reporting broader antimicrobials only if more narrow spectrum agents are “R”	Suppressing select agent results from the laboratory reports based on ASP needs (e.g., formulary, select suppressions etc)
Example	Only report ertapenem if ceftriaxone is “R”	Suppress fluoroquinolone results from urine cultures to support ASP initiative to decrease their use in treatment of cystitis

The VERY basics: AST restrictions

- Make sure your AST reports are not doing potential harm:
  - Do not report drugs with “WARNINGS” in M100 Table 1
  - Be cautious of body-site specific restrictions:
    - Don’t report daptomycin on respiratory sources
    - Don’t report nitrofurantoin only on urine cultures
    - Don’t report clindamycin on urine cultures
    - CSF restrictions (below)
    - Etc

Based on pharmacokinetics

Search “warning” in M100 electronic document to find these easily!

Some institutions may expand on M100 (examples):
- Pip-tazo not reported on CSF
- Tigecycline not on blood/urine

“Warning”: The following antimicrobial agents that are included in this document should not be routinely reported for bacteria isolated from CSF. These antimicrobial agents are not the drugs of choice and may not be effective for treating CSF infections caused by these organisms (ie, the bacteria included in Tables 2A through 2J):

- Agents administered by oral route only
- 1st- and 2nd-generation cephalosporins and cephamycins
- Clindamycin
- Macrolides
- Tetracyclines
- Fluoroquinolones

The VERY basics: AST restrictions

- Make sure not reporting intrinsically "R" organisms as "S"
  - *Pseudomonas aeruginosa* and ertapenem, SXT, tetracyclines
  - *Salmonella*/*Shigella* and 1st/2nd generation cephalosporins
    - These will test "S" but are inactive clinically!
  - *Enterococcus* spp. and clindamycin, cephs, SXT
  - Etc

Go to Appendix B of the CLSI M100 document

Often, AST device "expert rules" will suppress these for you

They don't ALWAYS test "R"… for lots of reasons

More sophisticated: cascade reporting

- Requires buy-in from institution – antibiotic stewardship team
- There is no “one” right approach
  - Will vary based on lab formulary, patient population, provider biases etc
- Good places to start:
  - CLSI guidelines
  - Clinical guidelines (Sanford, IDSA treatment recommendations, etc)
- It is not easy to implement!
  - Rules may be in place at level of test platform, LIS or even EMR
  - Coordination and testing required!
  - If cascade reporting implemented, technologists MUST review the suppressed results too – to check for test system issues

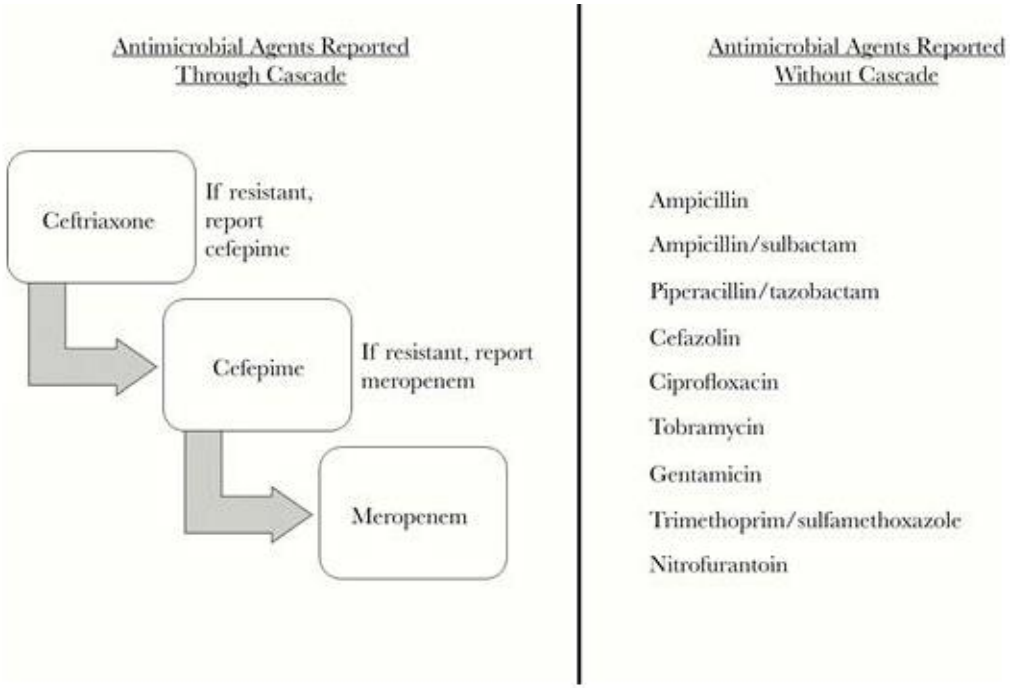
Impact of cascades

EDITOR'S CHOICE

Out of Sight—Out of Mind: Impact of Cascade Reporting on Antimicrobial Usage

Siyun Liao, Judith Rhodes, Roman Jandarov, Zachary DeVore, Madhuri M Sopirala

Open Forum Infectious Diseases, Volume 7, Issue 2, February 2020, ofaa002,
https://doi.org/10.1093/ofid/ofaa002
Published: 08 January 2020 **Article history ▾**



Days of therapy

Antibiotic	Baseline	Post-Cascade	P value
Pip-tazo	1.0	0.99	0.9
Cefepime	1.23	0.81	<0.0001
Cipro	0.86	0.96	0.028
Ceftriaxone	1.48	1.66	0.004

* Also noted a significant reduction in LOS (14 vs 10.8 days)

Resources

Public Health Ontario | Santé publique Ontario

Antimicrobial Stewardship Strategy:
Cascading microbiology susceptibility reporting

The selective suppression of an organism's susceptibility to broader-spectrum or more expensive secondary agents when it is susceptible to preferred primary agents.

https://www.publichealthontario.ca/-/media/documents/A/2016/asp-cascading-microbiology-reporting.pdf?la=en

Commentary

Selective reporting of antibiotic susceptibility testing results: less is more

Gunnar Kahlmeter [1,2], Nathalie Thilly [3,4], Céline Pulcini [3,5,*]

DOI:https://doi.org/10.1016/j.cmi.2020.11.017

Clinical Infectious Diseases

IDSA GUIDELINE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

Tamar F. Barlam,[1,a] Sara E. Cosgrove,[2,a] Lilian M. Abbo,[3] Conan MacDougall,[4] Audrey N. Schuetz,[5] Edward J. Septimus,[6] Arjun Srinivasan,[7] Timothy H. Dellit,[8] Yngve T. Falck-Ytter,[9] Neil O. Fishman,[10] Cindy W. Hamilton,[11] Timothy C. Jenkins,[12] Pamela A. Lipsett,[13] Preeti N. Malani,[14] Larissa S. May,[15] Gregory J. Moran,[16] Melinda M. Neuhauser,[17] Jason G. Newland,[18] Christopher A. Ohl,[19] Matthew H. Samore,[20] Susan K. Seo,[21] and Kavita K. Trivedi[22]

Summary

- AMR is a global, slow-burning pandemic
- The laboratory can help mitigate rising AMR by ensure testing practices best suit patient needs

Thank you!

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Clinical Microbiology VUMC