

# 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

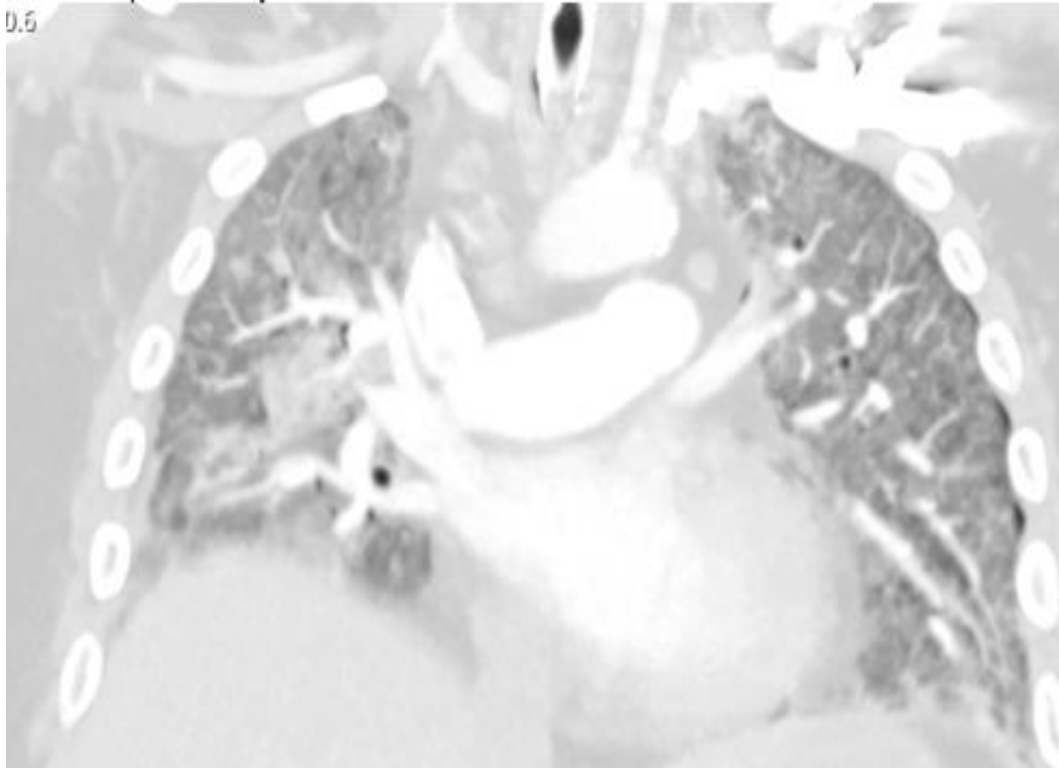
| ANTIMICROBIAL  | MIC  | Interpretation |
|----------------|------|----------------|
| Amikacin       | 32   | R              |
| Amp/sulbactam  | >16  | R              |
| Cefepime       | >32  | R              |
| Ceftazidime    | >32  | R              |
| Ciprofloxacin  | >4   | R              |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

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<br>Enterobacter species<br>MIC |             |
|-----------------------------------|-----------------------------------------------------|-------------|
| Amikacin                          | <=8                                                 | Susceptible |
| Avycaz<br>(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



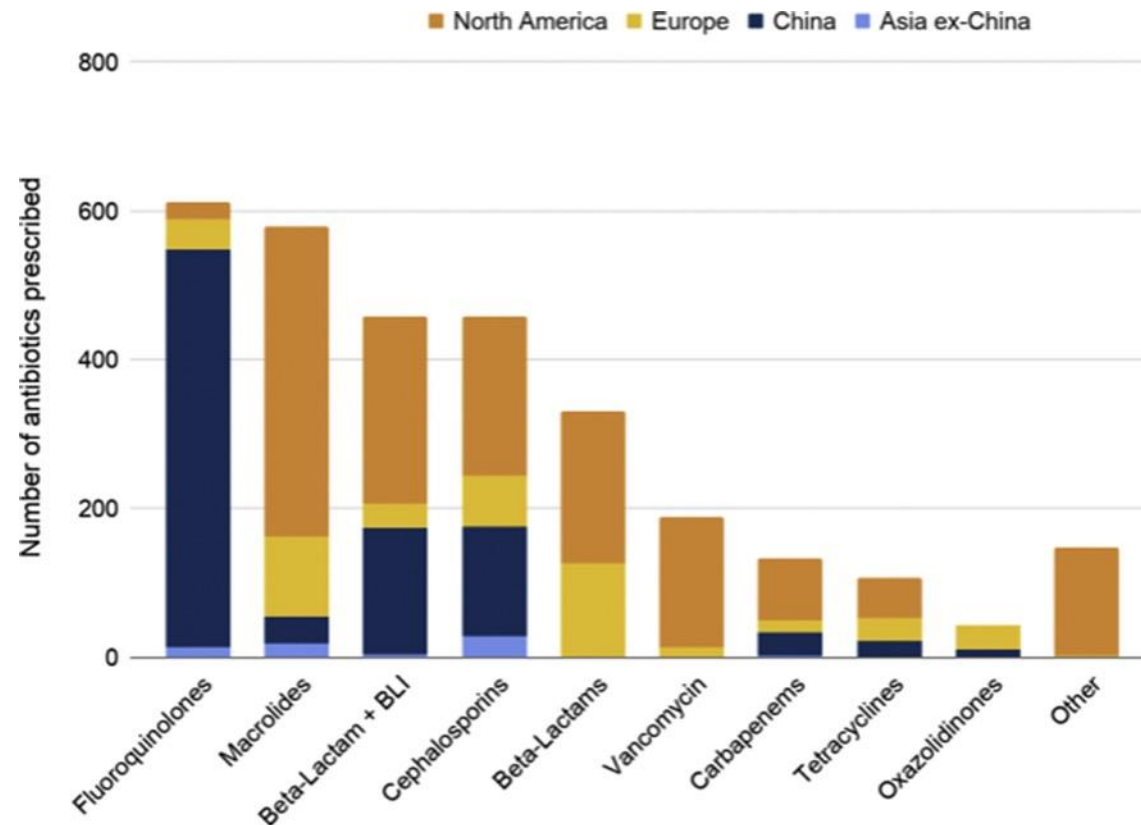
# Patient story, continued

- 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

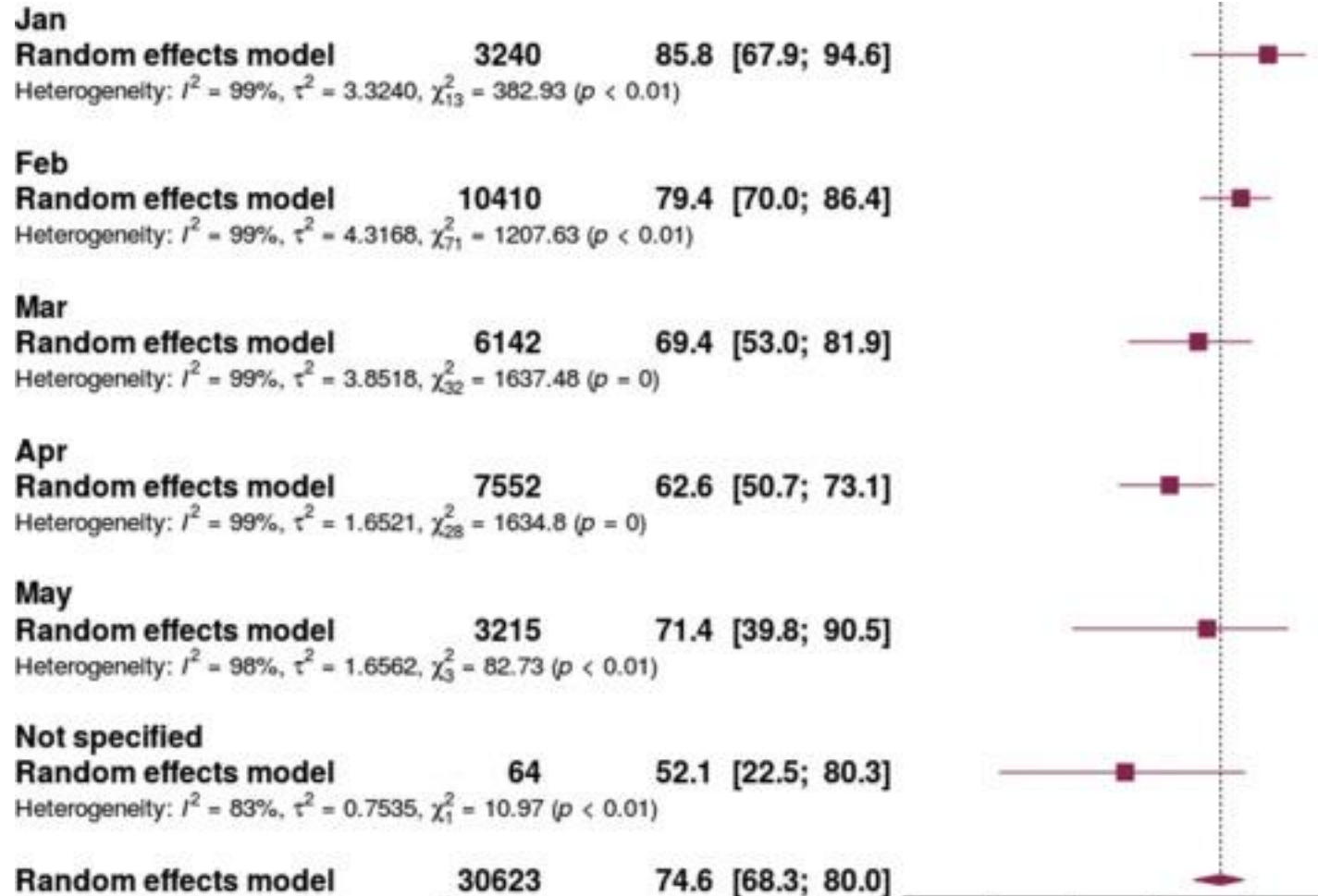
- A lot of reason for concern:
  - ~74% of COVID-19 patients received an antimicrobial prescription
  - Only 4% have a true bacterial infection
  - ~15% of hospitalized patients develop bacterial secondary infection
- Outside the US, huge emphasis on use of antibiotics (e.g., azithromycin) to prevent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

# 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%)

# Trends towards less antimicrobials in later months of pandemic



# 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

# Comparing viral pandemics

## COVID-19



8% secondary bacterial infections



75% receive antibiotics

## Influenza



23% secondary bacterial infection

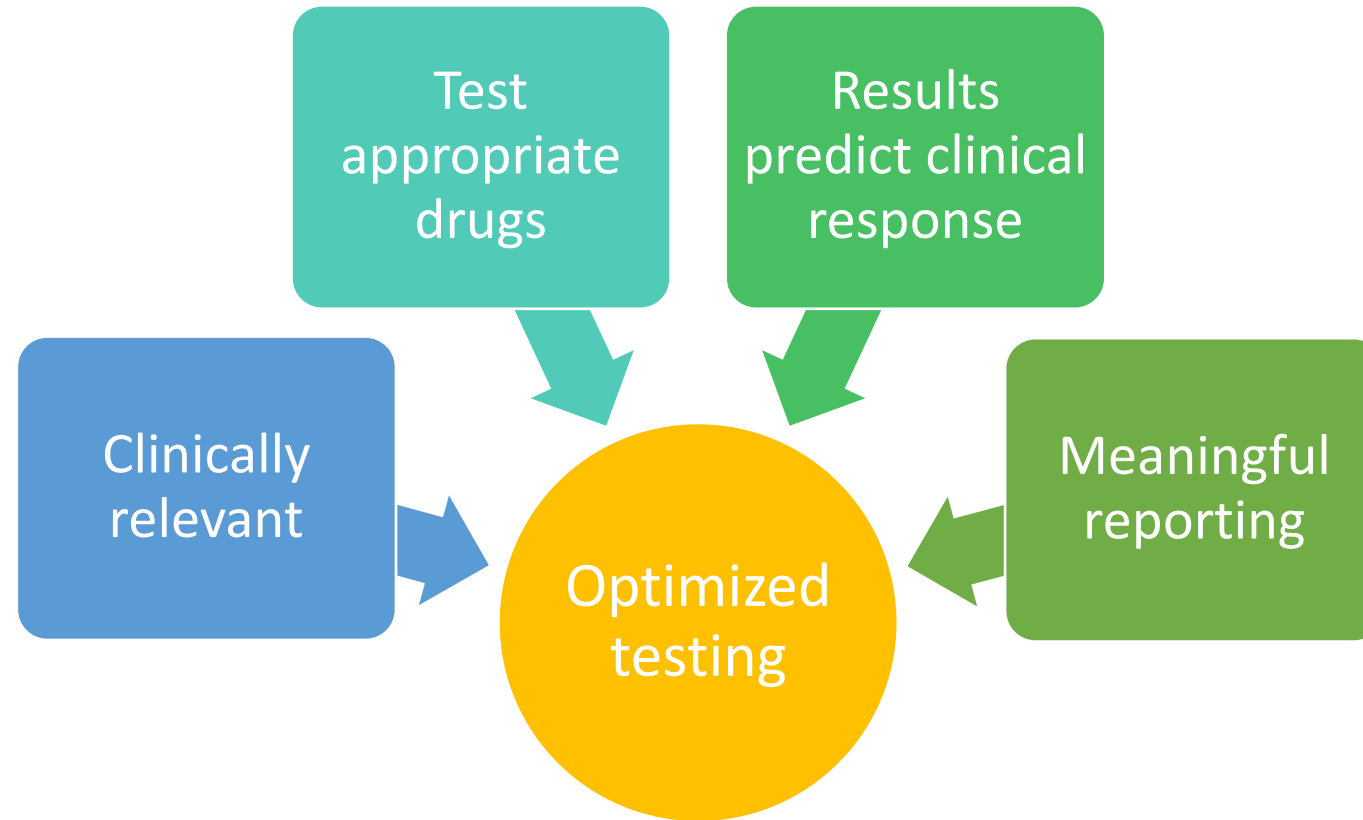


65% receive antibiotics

# 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  $\beta$ -lactamase Producing Enterobacterales Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with DTR-*P. aeruginosa*

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

\*Corresponding Author

**Not on the list? Colistin!!**

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

# Testing newer agents: GNRs

| Agent                   | Test  |                |                            | Manual MIC |
|-------------------------|-------|----------------|----------------------------|------------|
|                         | Disk  | Gradient strip | Automated Systems          |            |
| 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

# 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:

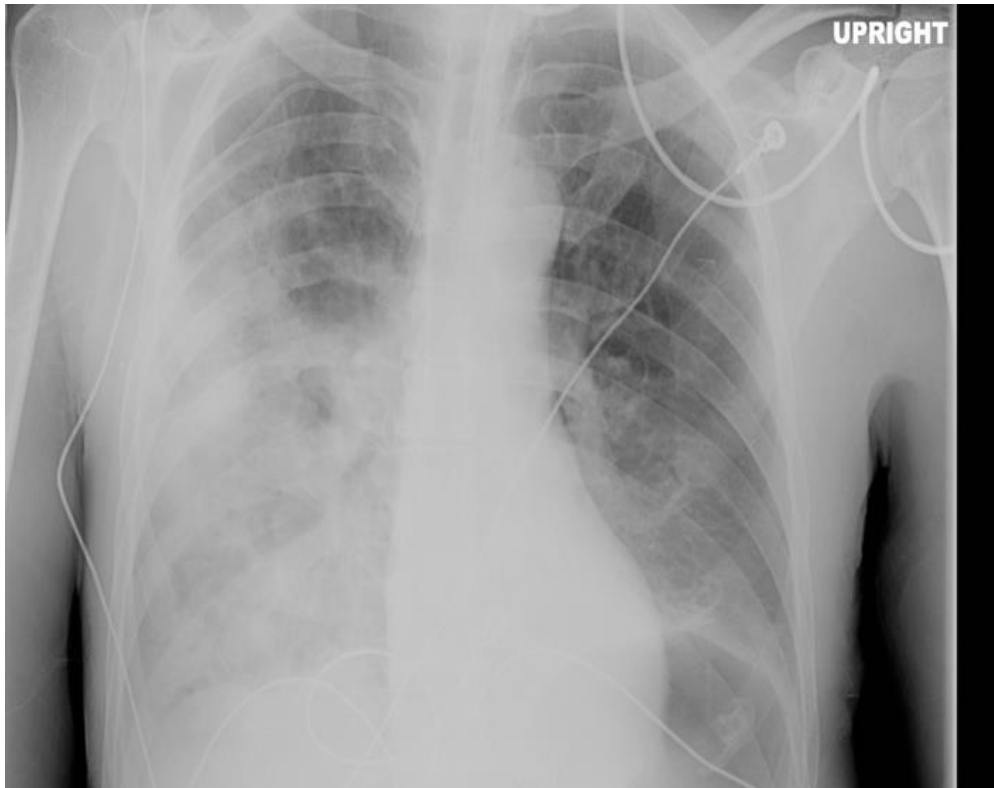


## ...includes

- 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

## 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*



Treated with meropenem + gentamicin

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

# 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.<sup>1,2,3</sup>
- Approximately 20% of CRE would be misclassified by use of outdated breakpoints.<sup>5,6</sup>
- Outdated breakpoints can direct treating physicians to inappropriate antimicrobial therapy, contributing to preventable patient morbidity and mortality.<sup>2,3</sup>
- Outdated breakpoints hinder the ability to identify CRE, impairing infection control initiatives and fueling the spread of CRE.<sup>5</sup>

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

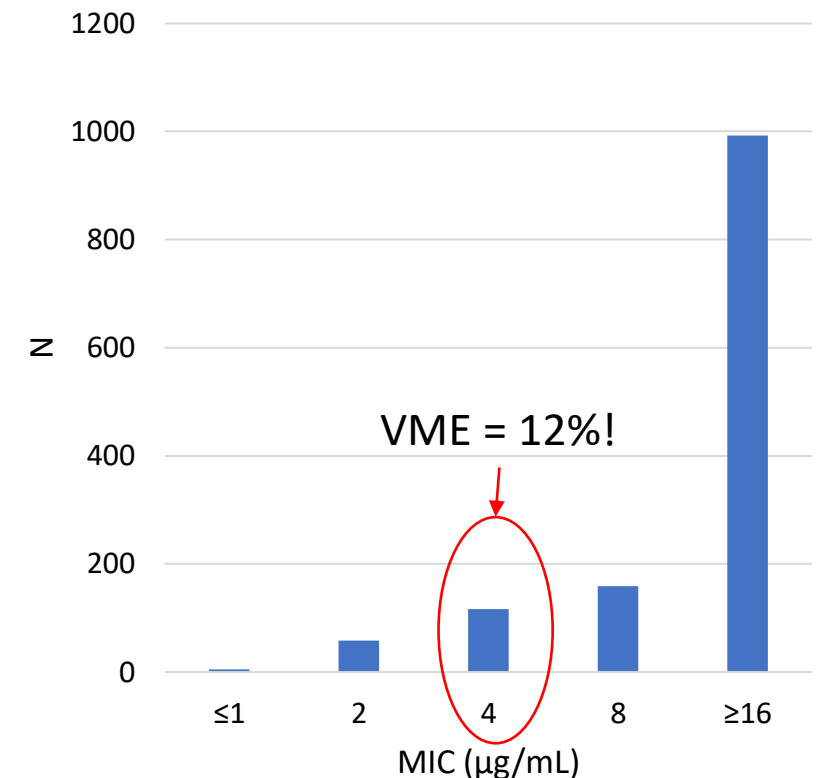
- To date, all CLSI BP updates involved “lowering” the BP
- If use obsolete BPs, there is a risk reporting “False “S” every time isolate is “R” by obsolete BPs and “S” with Updated BPs

## *Enterobacterales*

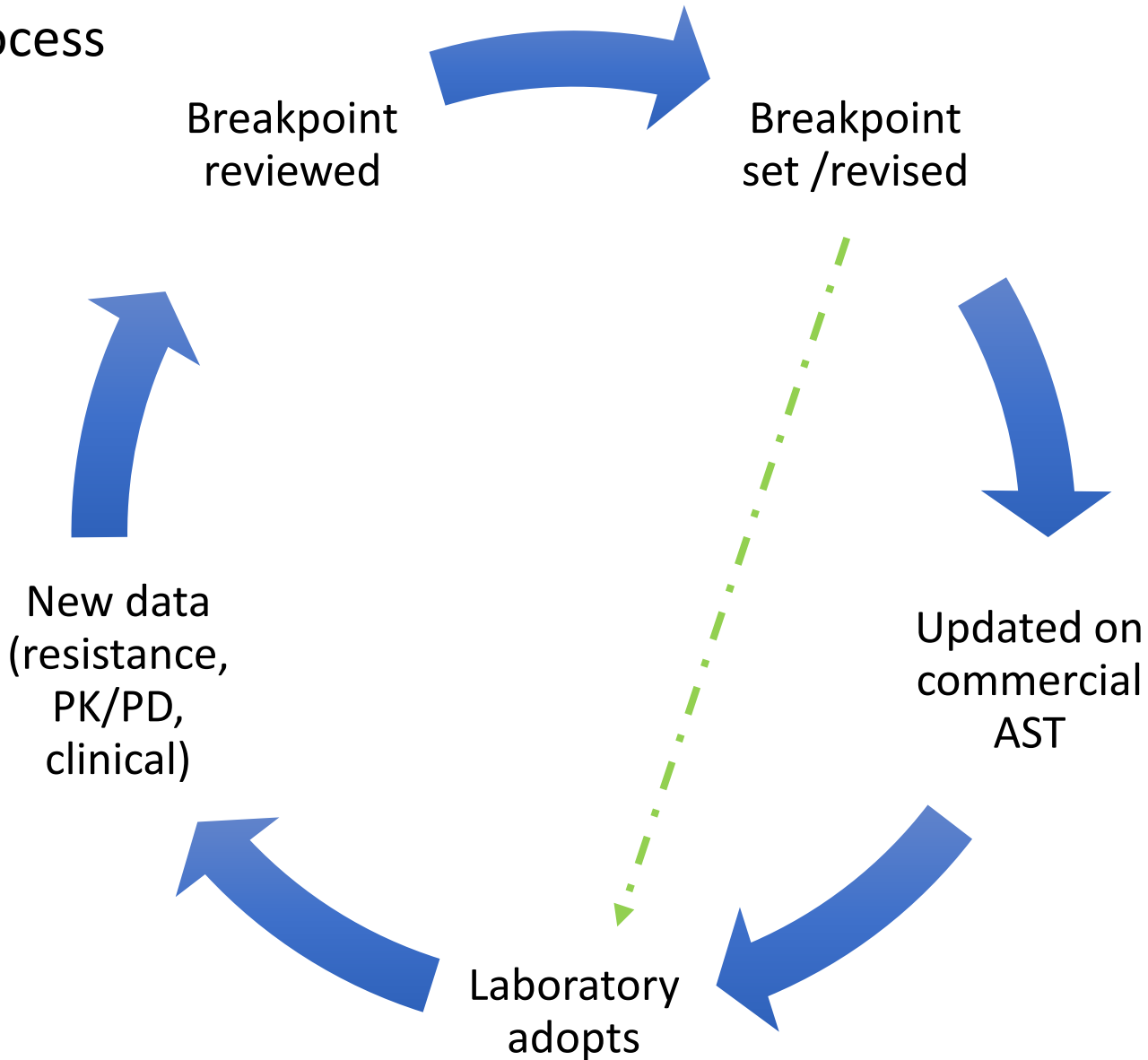
| Agent     | Obsolete Breakpoints (µg/ml) |   |     | Current Breakpoints (µg/ml) |   |    |
|-----------|------------------------------|---|-----|-----------------------------|---|----|
|           | S                            | I | R   | S                           | I | R  |
| Meropenem | ≤4  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

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

## Meropenem MIC, KPC producers



# 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: <ul style="list-style-type: none"> <li>• Serious patient care concerns</li> <li>• Serious public health concerns</li> </ul>   | Carbapenems – GNRs<br>Cephems – <i>Enterobacterales</i><br>Pip-tazo – <i>P. aeruginosa</i><br>Fluoroquinolones - <i>Salmonella</i>           |
| 2        | <ul style="list-style-type: none"> <li>• May not apply to your institution</li> <li>• May be handled with comments on report, alternative strategies</li> </ul> | Cefazolin – <i>Enterobacterales</i><br>Fluoroquinolones – <i>Enterobacterales</i> & <i>P. aeruginosa</i><br>Daptomycin - <i>Enterococcus</i> |
| 3        | Related to drugs infrequently used or to doses not used in USA                                                                                                  | Colistin – GNR<br>Piperacillin, ticarcillin, ticar-clav – <i>P. aeruginosa</i><br>Ceftaroline – <i>S. aureus</i>                             |

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



# Establishing Priorities for Updating BPs at Your Institution

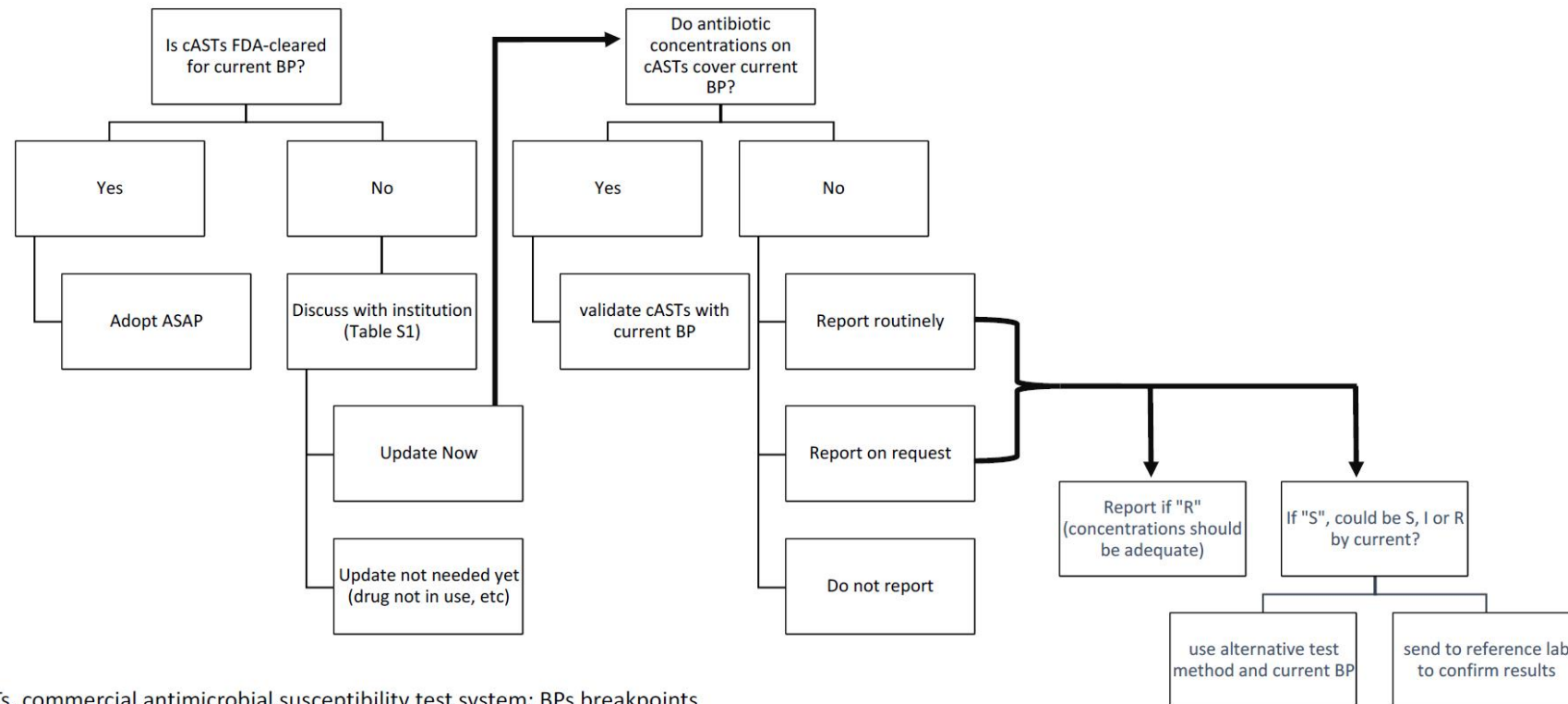
*Based on institutional-level practices, you should determine:*

- 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**

# 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

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 1<sup>st</sup>/2<sup>nd</sup> 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

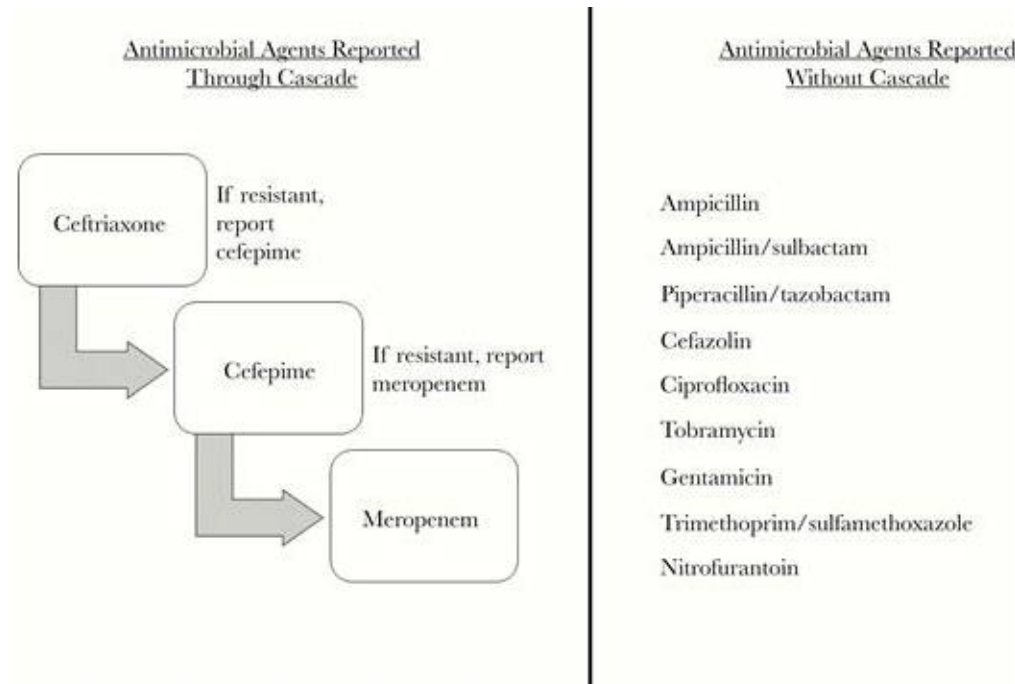
Often, AST device “expert rules” will suppress these for you

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  
PARTNERS FOR HEALTH

Santé  
publique  
Ontario  
PARTENAIRES POUR LA SANTÉ

## 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<sup>1,2</sup>, Nathalie Thilly<sup>3,4</sup>, Céline Pulcini<sup>3,5,\*</sup>

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

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

# 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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