Mass General Brigham

Bench to Bedside: Impact of microbiologic tests on clinical care and antimicrobial stewardship

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Disclosure

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Objectives

1. Implement rapid diagnostic tools in concert with antimicrobial stewardship interventions
2. Recognize specimen sources where susceptibility testing of commensal organisms may guide clinical care
3. Identify new and emerging antimicrobial agents against multi-drug-resistant organisms
4. Develop a reflex antimicrobial susceptibility testing algorithm for multi-drug-resistant organisms

Workshop Scenario #1

Your institution is evaluating cefepime-enmetazobactam for formulary consideration. The infectious diseases and antimicrobial stewardship groups reach out to discuss the process for susceptibility testing.

1. Which rapid diagnostics would prompt susceptibility testing consideration?
2. Would this be a reflex susceptibility test or restrict to request only?
    - If reflex, for all specimens or only specific sources?
    - If restricted, who would be authorized to request?
3. Any other considerations prior to performing susceptibility testing?

Workshop Scenario #2

Your institution has recently implemented a multiplex-PCR for blood cultures. How would you tailor your subsequent susceptibility testing based for the following results?

- Positive for KPC-producing *E. coli*
- Positive for NDM-producing *K. pneumoniae*
- Positive for OXA-48-producing *E. cloacae*
- Positive for vanA/B *E. faecium*

Obj. 1 Implement rapid diagnostic tools in concert with antimicrobial stewardship interventions

Why Rapid Diagnostic Testing?

Time to appropriate antimicrobial therapy has a significant effect on morbidity and mortality

- Increase in mortality of 7.6% for each hour delay in septic shock

Broad spectrum antibiotics may have collateral damage or may not be the most effective agent

- Vancomycin has been shown to be inferior to β-lactam antibiotics for methicillin-susceptible *Staphylococcus aureus* (MSSA)

Antibiotic use is unnecessary or inappropriate in as many as 30-50% of cases

Kumar A, et al. *Crit Care M*ed. 2006;34:1589-1596.
Kim SH, et al. *Antimicrob. Agents Chemother.* 2008;52(1):192-197.
Hecker MT, et al. *Arch Intern Med* 2003;163:972-978.

Antimicrobial Stewardship

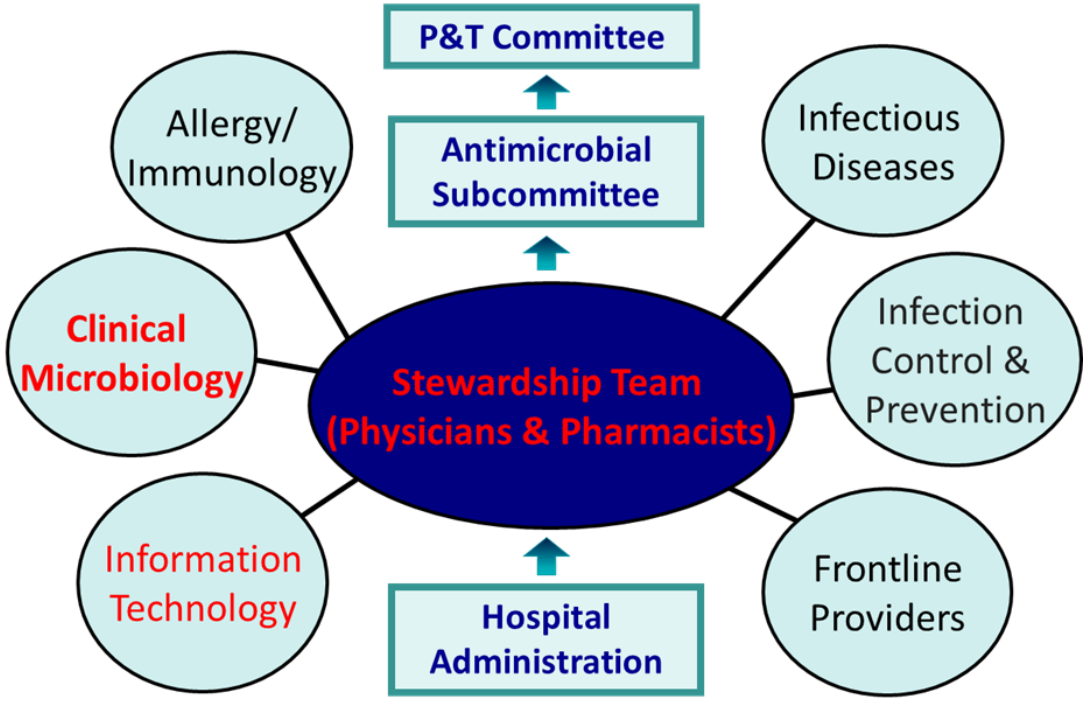
Antimicrobial stewardship programs are multidisciplinary

Goals are to improve outcomes and minimize collateral damage

- Secondary goal to lower costs

Prospective audit with feedback is a core strategy

Use of RDTs is suggested for respiratory and blood specimens



Dellit TH, et al. *Clin Infect Dis*. 2007;44(2):159-177.
Barlam TF, et al. *Clin Infect Dis*. 2016;62(10):e51-77

Key Roles for Microbiology Lab Staff in ASP

Promote education between the laboratory and clinicians about test characteristics and interpretation

Diagnostic Stewardship:
- Improved test ordering menus
- Report results in a way that encourages appropriate antibiotic therapy and de-escalation
- Multidisciplinary evaluations of new diagnostic tests

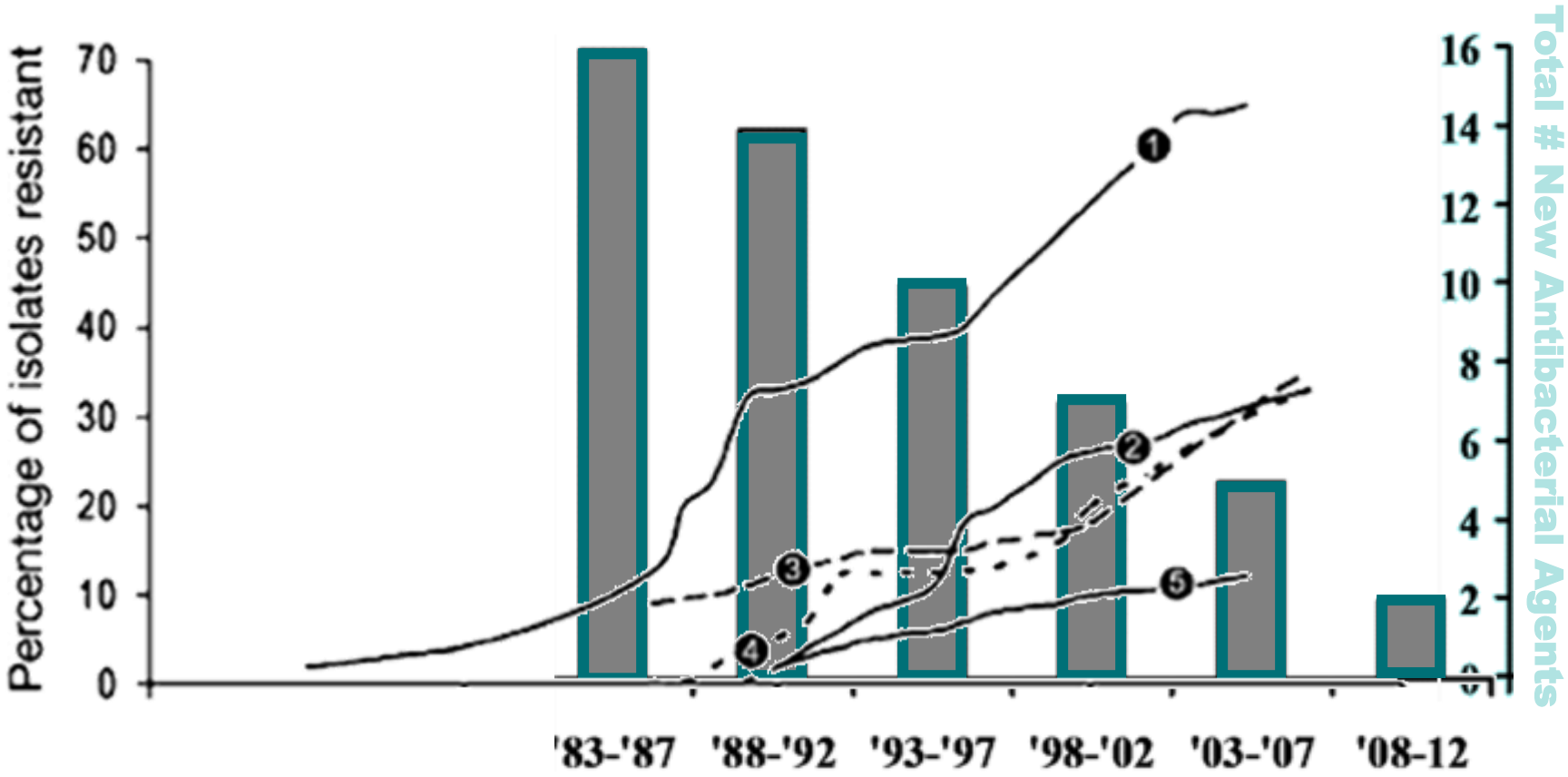
Action: Prospective Audit and Feedback
- Ensure ASP team has mechanisms to surveil positive cultures and susceptibility results
- Regular reviews of antimicrobial susceptibility testing panels and performance
- Review and implement changes in CLSI breakpoints

Publish annual antibiogram

Participation in Antimicrobial Resistance (AR) Option in CDC's National Healthcare Safety Network (NHSN)

www.cdc.gov/antibiotic-use/coreelements/implementation.html

Antimicrobial Development vs Resistance



1 = Methicillin-resistant *Staphylococcus aureus* (MRSA)

2 = Vancomycin-resistant *Enterococci* (VRE)

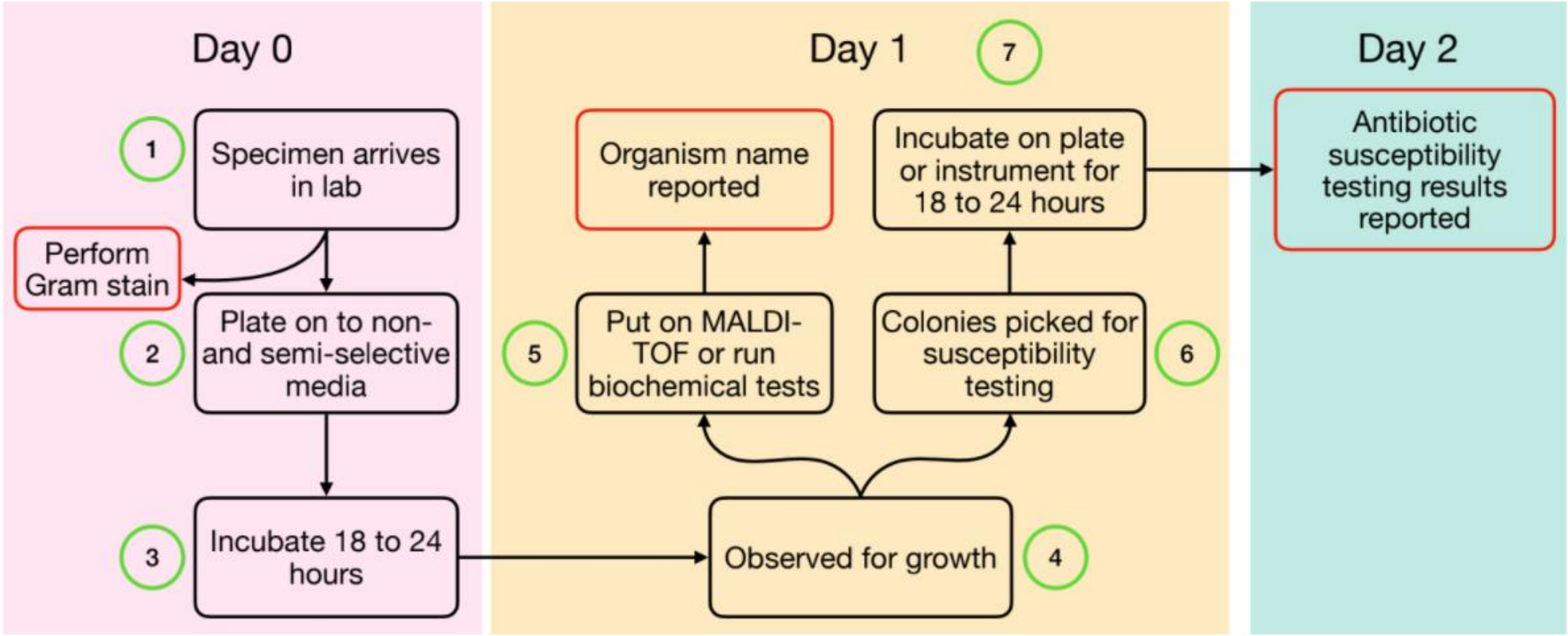
3 = Imipenem-resistant *Pseudomonas aeruginosa*

4 = Imipenem-resistant *Acinetobacter baumanii*

5 = Fluconazole-resistant *Candida* spp.

Adapted from Septimus EJ, Owens RC. *Clin Infect Dis* 2011;53:S8-S14.

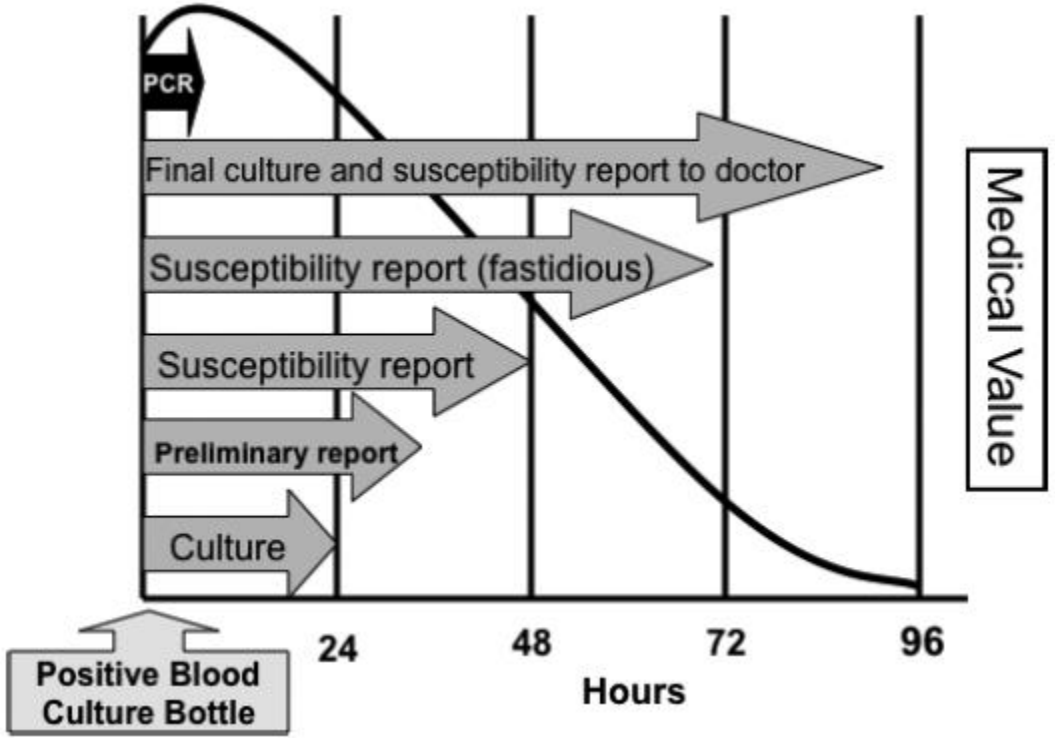
Typical Workup of Bacterial Specimens



Timeline of Standard Diagnostics

Basic microbiology

- Culture
- Gram stain
- Colony isolation
- Biochemical tests or MALDI-TOF
- Identification and susceptibility



Goff DA, et al. *Pharmacotherapy*. 2012;32(8):677–687

Current RDTs

Currently available RDTs use a variety of methods for detection

- Differing levels of complexity and turnaround times (TATs)

May be able to detect only a single organism or multiple organisms

- Some can detect antimicrobial resistance

May be helpful to guide targeted therapy and de-escalation

MALDI-TOF MS

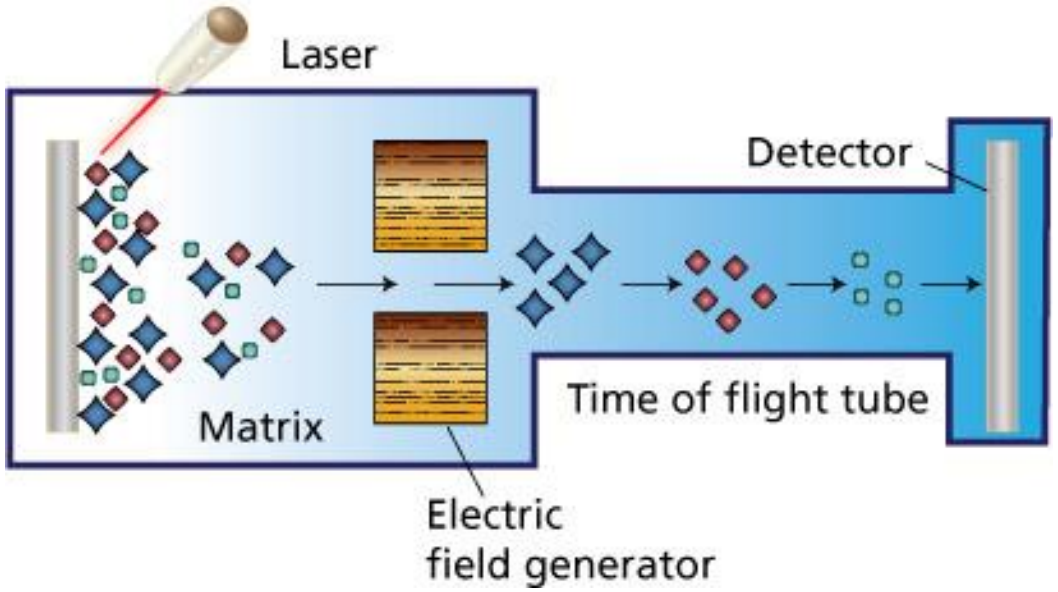
MALDI-TOF MS

Matrix-assisted laser desorption ionization – time of flight (MALDI-TOF) mass spectrometry (MS)

Can identify to either genus or species level

Very fast – 5 minutes to identification

Hardware is expensive but individual tests are inexpensive



MALDI-TOF vs Conventional Methods

Quasi-experimental study of patients with gram negative bacteremia

- 46-hour reduction in time to de-escalation ($p = 0.004$)
- 36.7-hour improvement in time to effective treatment in patients with inactive therapy ($p < 0.001$)
- Reduction in LOS by 2.6 days ($p = 0.01$) and cost by ~$20,000 ($p = 0.009$)

Quasi-experimental study of patients with bacteremia or candidemia

- Decrease in time to effective antibiotic therapy (20.4 vs 30.1 hours; $p = 0.021$)
- 2.8-day decrease in mean LOS ($p = 0.07$)
- Reduction in mortality from 20.3% to 14.5% ($p = 0.02$)

Perez KK, et al. *Arch Pathol Lab Med*. 2013;137:1247-1254.
Huang AM, et al. *Clin Infect Dis*. 2013;57:1237-1245.

MALDI-TOF MS Pros and Cons

Advantages

- Can identify many different bacteria and fungi
- Not specific to a certain specimen
- Very easy to set up and quick to run

Disadvantages

- High upfront cost
- Requires pure colony
  - Lysing kits may allow detection directly from positive blood culture
- No susceptibility or resistance information

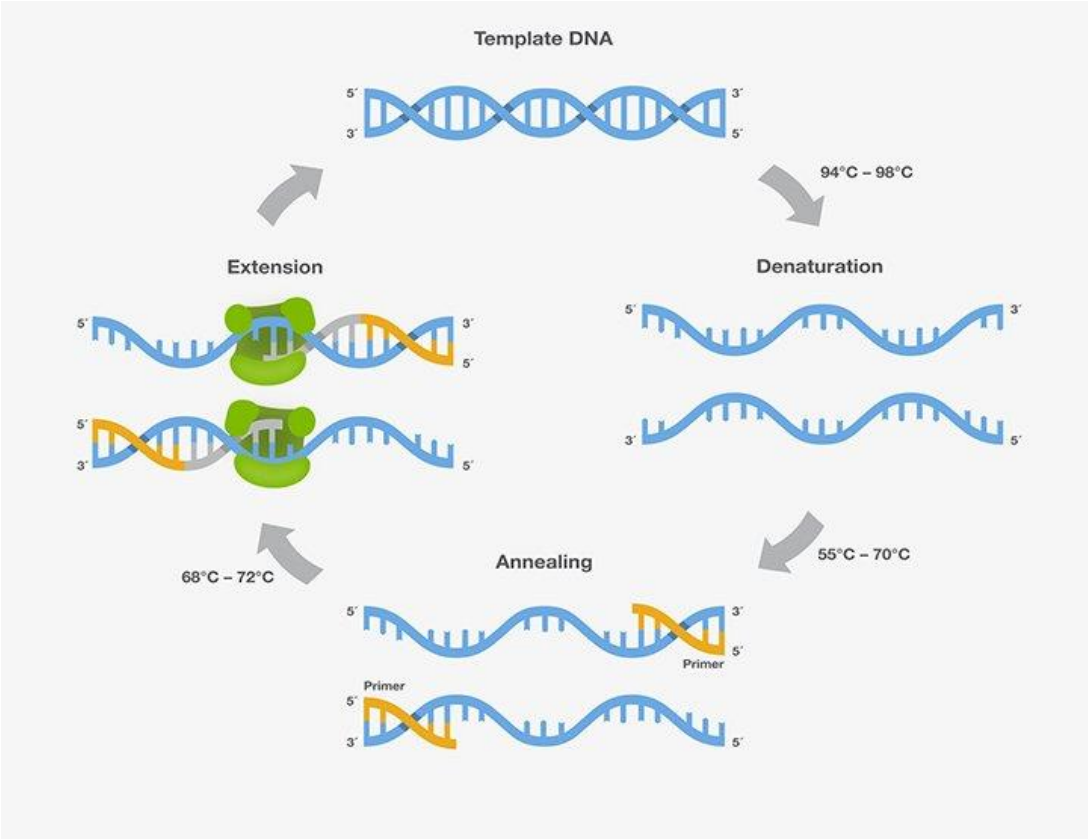
PCR

PCR

Polymerase chain reaction (PCR) is a type of nucleic acid amplification test (NAAT)

Detects genetic material of pathogen

Multiplex PCR (mPCR) can detect multiple organisms and/or resistance mechanisms



https://www.thermofisher.com/ng/en/home/life-science/cloning/cloning-learning-center/invitrogen-school-of-molecular-biology/pcr-education/pcr-reagents-enzymes/pcr-cycling-considerations.html

PCR-Based RDTs for Detecting *Staphylococcus* spp.

Organism	Time (h)	Technology	Batch	Pure colony	Auto-mated	CLIA Complexity	Trade Name
MRSA	2	PCR	Yes	No	Yes	High	Roche LightCycler MRSA
MSSA, MRSA, CoNS	2	Multiplex PCR	Yes	No	Yes	High	BD GeneOhm Staph SR
MSSA, MRSA, CoNS	1	Multiplex PCR	No	No	Yes	Moderate	Cepheid Xpert MRSA/SA BC
MSSA, MRSA	1	Multiplex PCR	No	No	Yes	Moderate	Cepheid Xpert MRSA/SA SSTI

Adapted from Bauer KA, et al. *Clin Infect Dis*. 2014;59(S3):S134-5145

Xpert vs Conventional Methods

Quasi-experimental study of patients with blood cultures positive for GPCC

- 55% vs 76% ($p < 0.01$) of patients without *S. aureus* bacteremia treated for *S. aureus* infection
- 5.2 vs 49.8 hours ($p = 0.007$) until MRSA treatment switched to MSSA treatment

Quasi-experimental study of patients with *S. aureus* bacteremia

- Mean reduction in time to MSSA treatment of 1.6 d ($p = 0.02$)
- Length of stay reduced by 6.2 days ($p = 0.07$)
- Hospital costs reduced by $21,387 ($p = 0.02$)

Parta M, et al. *Infect Control Hosp Epidemiol.* 2010;31(10):1043-1048.
Bauer KA, et al. *Clin Infect Dis.* 2010;51(9):1074-1080.

Multiplex PCR

Hands-on time of 2 minutes and turnaround time of 1-2 hours

Three major mPCR platforms available for positive blood cultures

- Biofire BCID2
- Diasorin Verigene BC-GP and BC-GN
- Cobas eplex BCID-GP, BCID-GN, and BCID-FP

mPCR for Gram-Positive Cocci

Pathogen	BioFire	Verigene	eplex
Enterococcus spp.			✓
E. faecalis	✓		✓
E. faecium	✓	✓	✓
Staphylococcus spp.	✓	✓	✓
S. aureus	✓	✓	✓
S. epidermidis	✓	✓	✓
S. lugdunensis	✓	✓	✓
Streptococcus spp.	✓	✓	✓
S. agalactiae		✓	✓
S. anginosus (group)	✓	✓	✓
S. pneumoniae	✓	✓	✓
S. pyogenes	✓	✓	✓
Micrococcus spp.			✓

mPCR for Gram-Positive Bacilli

Pathogen	BioFire	Verigene	eplex
Bacillus cereus group			✓
Bacillus subtilis group			✓
Corynebacterium spp.			✓
Cutibacterium acnes			✓
Lactobacillus spp.			✓
Listeria spp.		✓	✓
L. monocytogenes	✓		✓

mPCR for Enterobacterales

Pathogen	BioFire	Verigene	eplex
Enterobacterales	✓		
Citrobacter spp.		✓	✓
Cronobacter sakazakii			✓
Enterobacter spp.	✓ (only *E. cloacae* complex)	✓	✓ (also *E. cloacae* complex)
Escherichia coli	✓	✓	✓
Klebsiella aerogenes	✓		
Klebsiella oxytoca	✓	✓	✓
Klebsiella pneumoniae	✓	✓	✓
Morganella morganii			✓
Proteus spp.	✓	✓	✓ (also *P. mirabilis)*
Salmonella spp.	✓		✓
Serratia marcescens	✓		✓ (also *Serratia* spp.)

mPCR for Other Gram Negatives

Pathogen	BioFire	Verigene	eplex
Acinetobacter spp.		✓	
A. calcoaceticus-baumannii complex	✓		✓
Bacteroides fragilis	✓		✓
Fusobacterium nucleatum			✓
Fusobacterium necrophorum			✓
Haemophilus influenzae	✓		✓
Neisseria meningitidis	✓		✓
Pseudomonas aeruginosa	✓	✓	✓
Stenotrophomonas maltophilia	✓		✓

mPCR for Yeasts

Pathogen	BioFire	eplex
Candida albicans	✓	✓
Candida auris	✓	✓
Candida dubliniensis		✓
Candida glabrata	✓	✓
Candida guillermondii		✓
Candida kefyr		✓
Candida krusei	✓	✓
Candida lusitaniae		✓
Candida parapsilosis	✓	✓
Candida tropicalis	✓	✓
Cryptococcus neoformans/gatii	✓	✓ (individually)
Fusarium spp.		✓
Rhodotorula spp.		✓

mPCR for Genotypic Resistance

Resistance Gene	BioFire	Verigene	eplex
mecA		✓	✓
mecC			✓
mecA/C	✓		
mecA/C and MREJ	✓		
vanA/B	✓	✓	✓ (individual)
CTX-M	✓	✓	✓
IMP	✓	✓	✓
KPC	✓	✓	✓
NDM	✓	✓	✓
OXA	✓ (OXA-48-like)	✓	✓ (OXA-23 and OXA-48)
VIM	✓	✓	✓
mcr-1	✓		

mPCR vs Conventional Methods

Quasi-experimental study of patients with GNR bacteremia

- Pathogen identification 10.9 h vs 37.9 h ($p < 0.001$)
- Reductions in LOS, 30-day mortality, and mortality associated with multidrug-resistant organisms
- Reduction in time to effective therapy for ESBL-producing organisms

Quasi-experimental study of pediatric patients with positive blood cultures

- Time to optimal therapy of 26.7 vs 60.2 hours ($p = 0.001$)
- Time to effective antibiotics reduced from 6.9 to 3.4 hours ($p = 0.03$)
- Unnecessary antibiotics for contaminants decreased from 76% to 26% ($p < 0.001$)

Walker T, et al. *J Clin Microbiol*. 2016;54(7):1789-96.
Messacar K, et al. *J Pediatric Infect Dis Soc*. 2017;6(3):267-274.

Verigene vs BioFire

80 positive blood cultures with gram positive isolates were evaluated by conventional identification and susceptibility testing and compared to:

- Verigene BC-GP – 100% agreement
- BioFire BCID – 85% agreement
  - Missed 2 CoNS and 1 Viridans group *Streptococcus*
  - Identified 1 MSSA as MRSA and 8 CoNS as CoNS+*Enterococcus*

BioFire reported 8 mecA that Verigene did not

TAT for BioFire was half as long as Verigene

Sailey CJ, et al. Abstract #D-106 at the 54th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, District of Columbia, United States; September 2014.

BioFire for Polymicrobial Infections

BioFire BCID2 panel detects gram positive, gram negative, and yeast pathogens

- Other RDTs may require multiple panels/reagents for each of these types of organisms

BioFire may be able to detect pathogens which were not evident on preliminary gram stain

- Case report of a patient found to have GPCCs on gram stain
  - BioFire uncovered a polymicrobial infection, including gram positive, gram negative, and fungal pathogens
  - Verigene BC-GN and eplex BCID-GN and -FP likely would not have been run based on gram stain

Timbrook T, et al. *J Clin Microbiol*. 2015;53(7):2371-3.

Syndromic mPCR Panels

Panels	BioFire	Magpix	Verigene	eplex
Respiratory	18 viruses 4 atypical bacteria	17 viruses 2 atypical bacteria	13 viruses 3 atypical bacteria	16 viruses 2 atypical bacteria
Pneumonia	8 viruses 15 typical bacteria 3 atypical bacteria 8 resistance genes			
Gastrointestinal	5 viruses 7 bacteria 4 parasites	3 viruses 7 bacteria 3 parasites	2 viruses 5 bacteria 2 toxins	
Joint infection	30 bacteria 1 fungus 8 resistance genes			
Meningitis/ encephalitis	7 viruses 6 bacteria 1 fungus			

Syndromic mPCR vs Conventional Methods

Quasi-experimental study of 1,136 patients with respiratory infections

- No difference in rates of antibiotic prescriptions
- Decreased mean duration of antibiotics from 3.2 to 2.8 days (p=0.003)
- Positive results decreased time in isolation precautions and length of stay

Prospective multicenter study of 1,887 patients with gastroenteritis

- Increase in detection of pathogen vs culture (35.3% vs 6.0%)
- Reduction in time to result (18 vs 47 hours, p<0.001) and antibiotic initiation (26 vs 72 hours, p<0.001)

Rogers BB, et al. *Arch Pathol Lab Med.* 2015;139(5):636-41.
Cybulski Jr. RJ, et al. *Clin Infect Dis*. 2018 ;67(11):1688-1696.

mPCR Pros and Cons

Advantages

- Rapid turnaround with very little hands-on time
- Detects most common pathogens
- Provides some resistance information
- Multiple syndromic panels available

Disadvantages

- Cost of hardware and panels is higher than many other RDTs
- Difficult to distinguish active infection from colonization/previous infection
- Some pathogens/resistance not included on panel

Automated FISH/Morphokinetic Cellular Analysis

Automated FISH/MCA

Accelerate Pheno
- PhenoTest BC – detects 14 bacterial genera and 2 yeast species

Combination of automated FISH and “morphokinetic cellular analysis”
- Uses fluorescence imaging and growth curve algorithm to predict susceptibility of 6 gram-positive and 8 gram-negative organisms

Hands-on time of 2 minutes

Turnaround time of 1.33 hours to identification and 6.6 hours to susceptibility

97.4% sensitivity and 99.3% specificity for pathogen identification

95.1% essential agreement and 96.0% categorical agreement for susceptibility

Willey BM, et al. *Open Forum Infect Dis*. 2017; 4(Suppl 1): S594–S595.
http://acceleratediagnostics.com/news/accelerate-diagnostics-submits-de-novo-request-fda-accelerate-pheno-system-accelerate-phenotest-bc-kit/

Automated FISH/MCA vs Conventional Methods

Quasi-experimental study of 204 patients with positive blood cultures

- Reduction in median time to optimal therapy (7 vs 11 vs 23 hours, p=0.024)
- Reduction in median time to antibiotic de-escalation (12 vs 27.8 vs 27.5 hours, p=0.019)
- No differences in:
  - Length of therapy
  - Length of stay
  - Mortality

RCT of 448 patients with gram-negative bacilli bacteremia

- Reduction in median time to gram-negative antibiotic de-escalation of 24.8 hours (p<0.001)
- Reduction in median time to escalation of antibiotics of 43.3 hours (p=0.01)
- No differences in mortality or length of stay

Ehren K, et al. *Clin Infect Dis*. 2020;70(7):1285-1293.
Banerjee R, et al. *Clin Infect Dis*. 2021;73(1):e39-e46.

Automated FISH/MCA Pros and Cons

Advantages

- Identifies similar number of pathogens to mPCR
- Not limited to specific resistance genes
- Rapid susceptibility with MICs

Disadvantages

- Less real-world clinical data
- Sensitivity and specificity may change with increased use
- Increased cost of instrument and panels vs traditional AST

Volatile Organic Compound Sensing

VOC Sensor

Vitek Reveal – rapid susceptibility testing of 10 gram-negative organisms

Uses VOC emissions and growth curve algorithm to predict susceptibility

Hands-on time of ~3 minutes

Turnaround time of 5.5-6 hours

97.0% essential agreement and 96.2% categorical agreement for susceptibility vs Vitek 2

Tibbetts R, et al. *J Clin Microbiol*. 2022;60(6):e0009822.

VOC Sensors

Advantages

- Not limited to specific resistance genes
- Most rapid susceptibility with MICs

Disadvantages

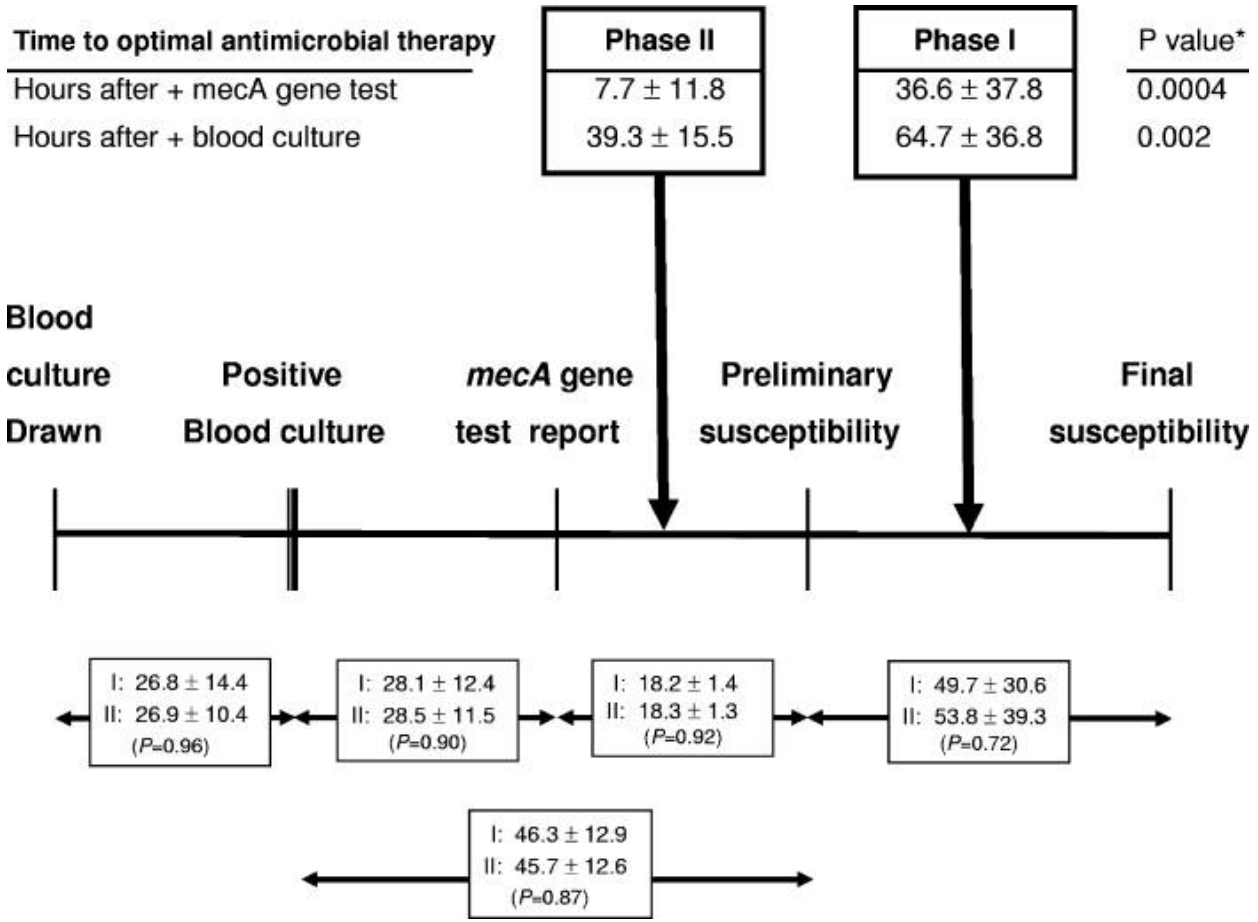
- No identification of pathogen
- Requires sealer and sensor instrument
- No clinical experience

RDTs and Antimicrobial Stewardship

mecA without ASP Intervention

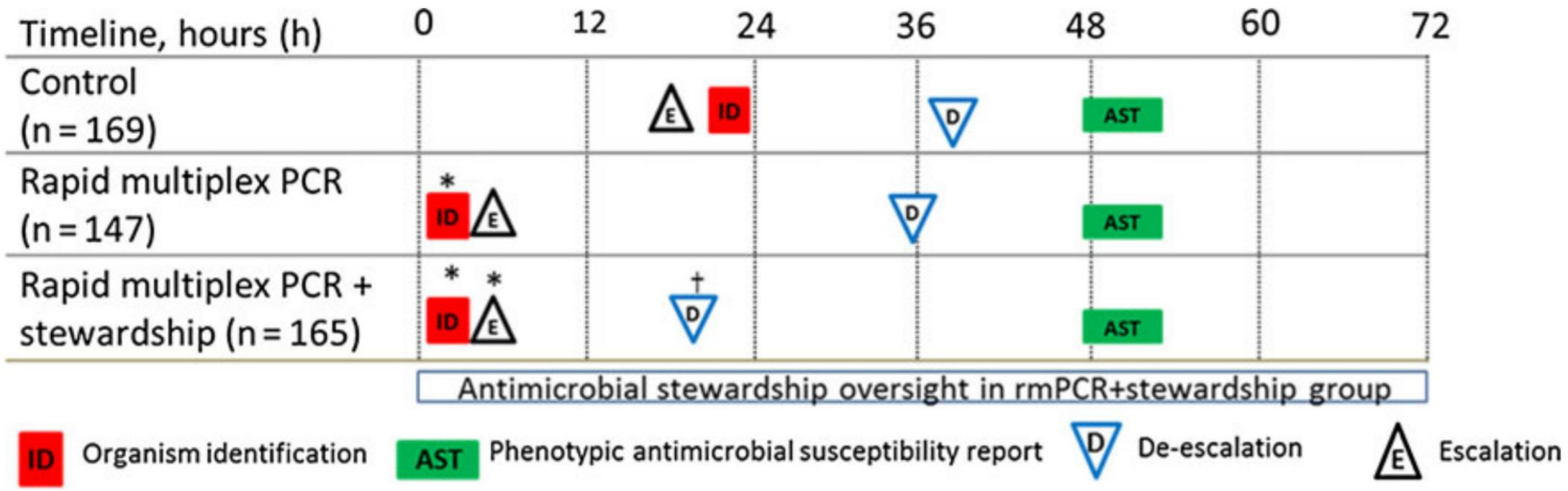
Phase I – Without pharmacist intervention

Phase II – With pharmacist intervention



Carver PL, et al. *J Clin Microbiol.* 2008;46:2381-2383.

mPCR without ASP Intervention

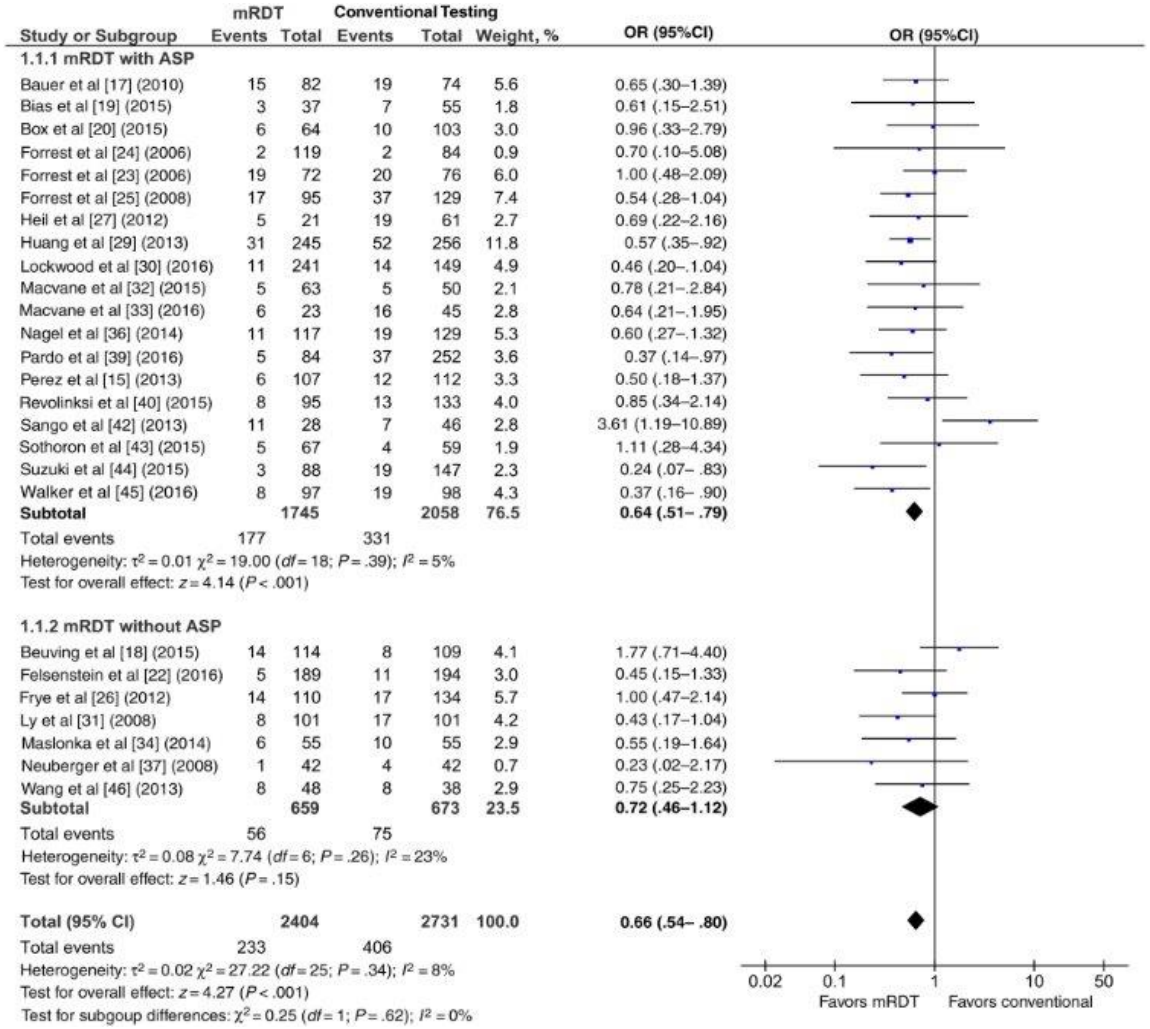


RDTs without ASP Intervention

Meta-analysis of 31 trials of molecular RDT on clinical outcomes

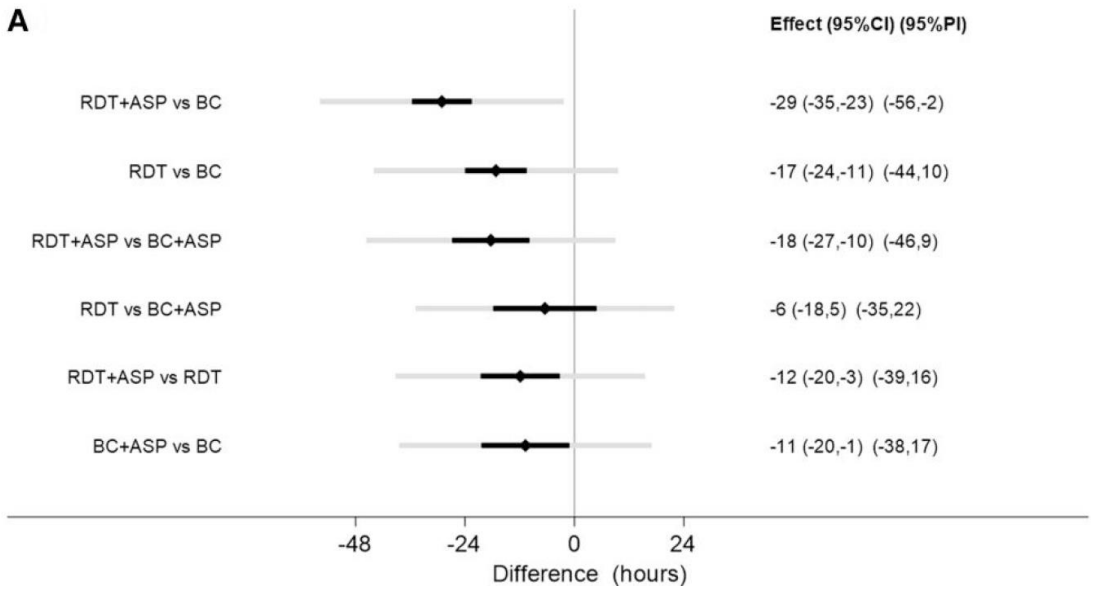
RDTs associated with decreased mortality

Difference was non-significant when implemented without ASP intervention

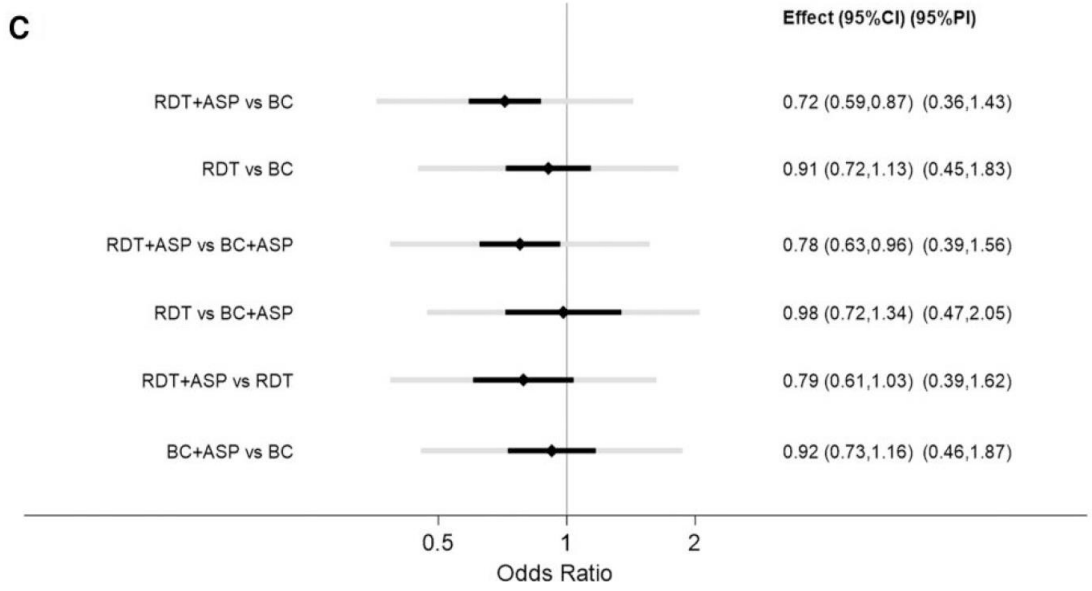


Impact of ASP on Time to Appropriate Therapy and Mortality

Time to Appropriate Therapy



Mortality



Choosing and Implementing an RDT

Prevalence and/or burden of pathogen

Cost of device and test

- May need to work with clinicians to justify costs through other savings to health system

Workflow of lab

Need to have a plan for notification/intervention!

Take Home Points

There are a variety of RDTs available with different pros and cons

RDTs provide results more quickly than conventional methods

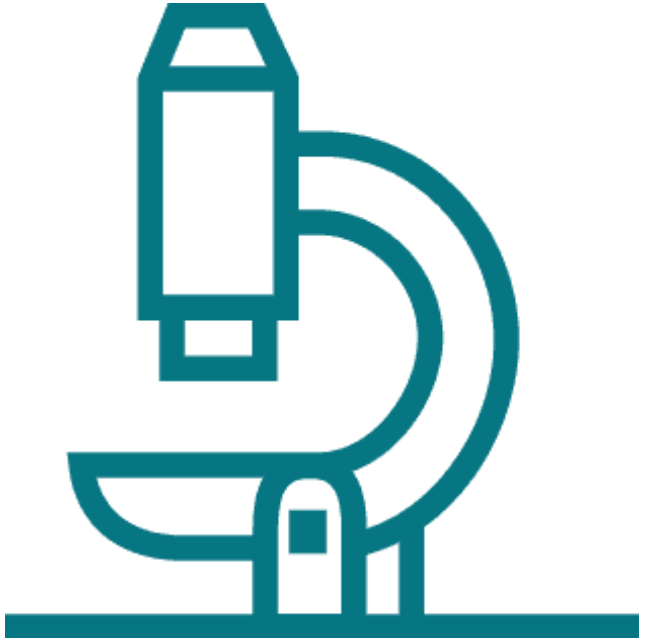
- Often no difference is seen without active notification and follow-up

RDTs may have an even bigger impact as they become more rapid

- Potential for use in targeted therapy for multidrug-resistant organisms

Obj. 2 Recognize specimen sources where susceptibility testing of commensal organisms may guide clinical care

To test or not to test? When susceptibility testing of commensal organisms is and **is not** needed for clinical care



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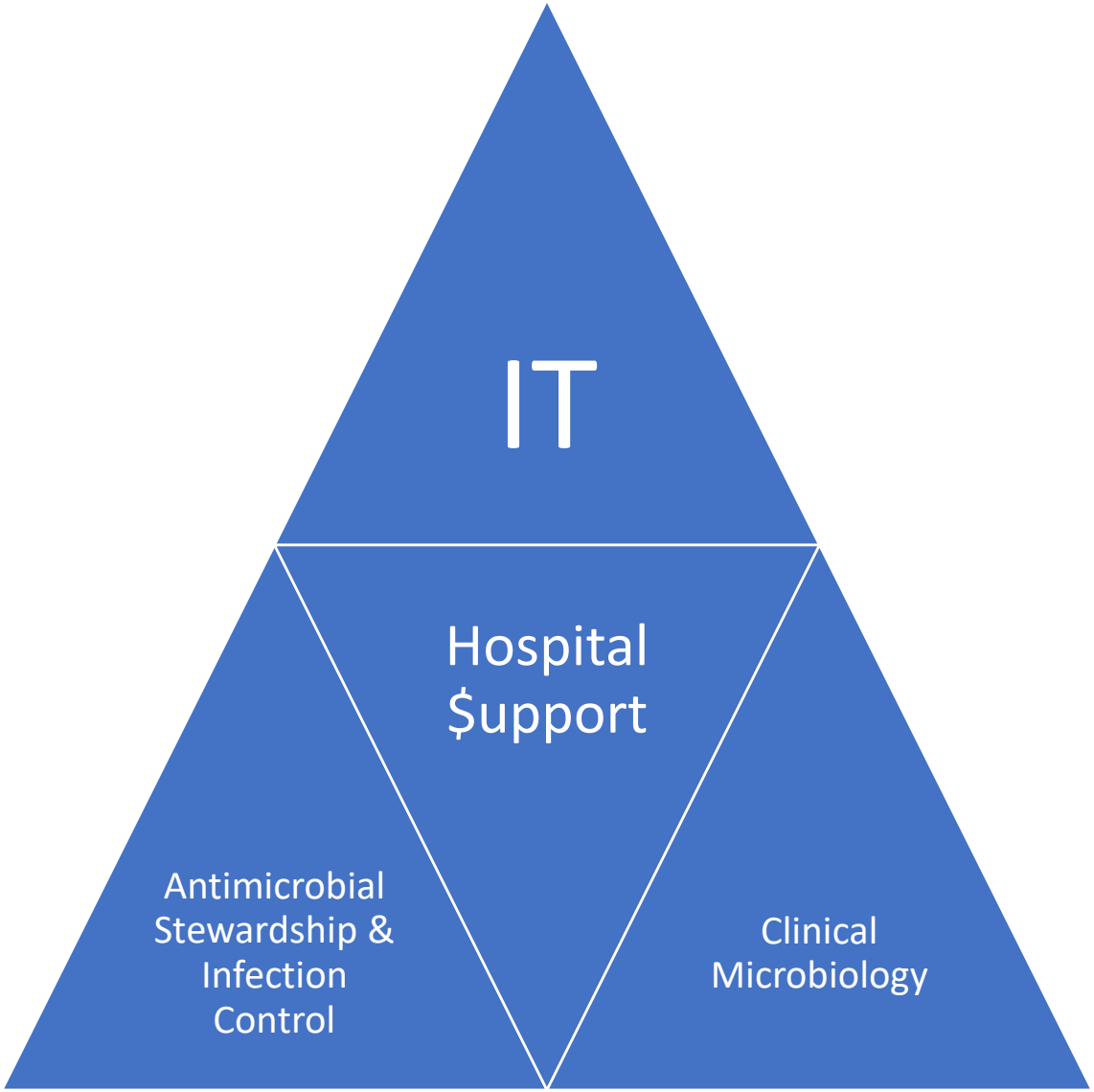
Disclosures

- none

Objective:

- Recognize specimen sources where susceptibility testing of commensal organisms may be necessary guide clinical care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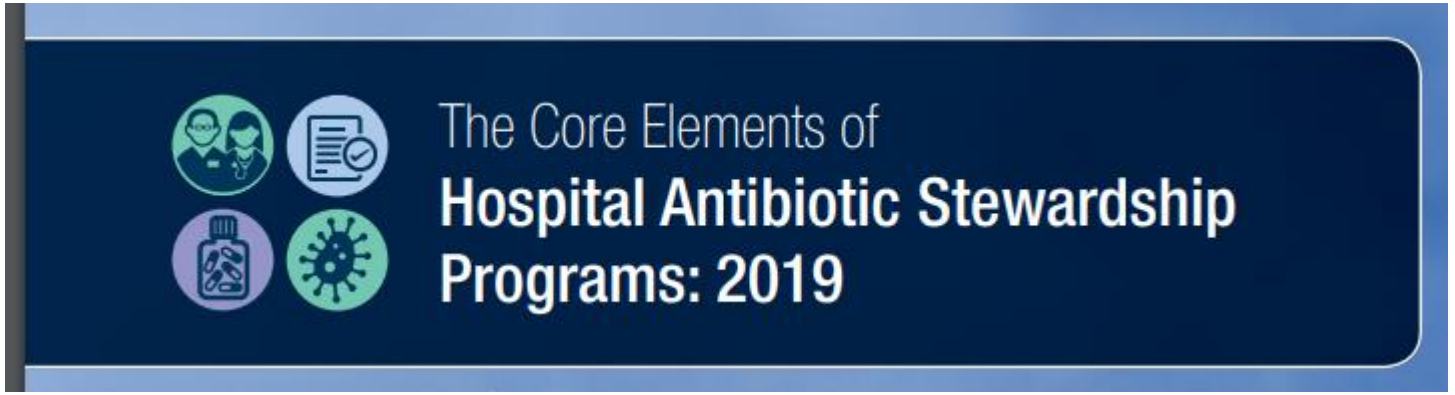


Microbiology-based Interventions

The microbiology lab in consultation with the stewardship program often implement the following interventions:

- **Selective reporting of antimicrobial susceptibility testing results:** tailoring hospital susceptibility reports to show antibiotics that are consistent with hospital treatment guidelines or recommended by the stewardship program (75) (76).
- **Comments in microbiology reports:** for example, to help providers know which pathogens might represent colonization or contamination (77).

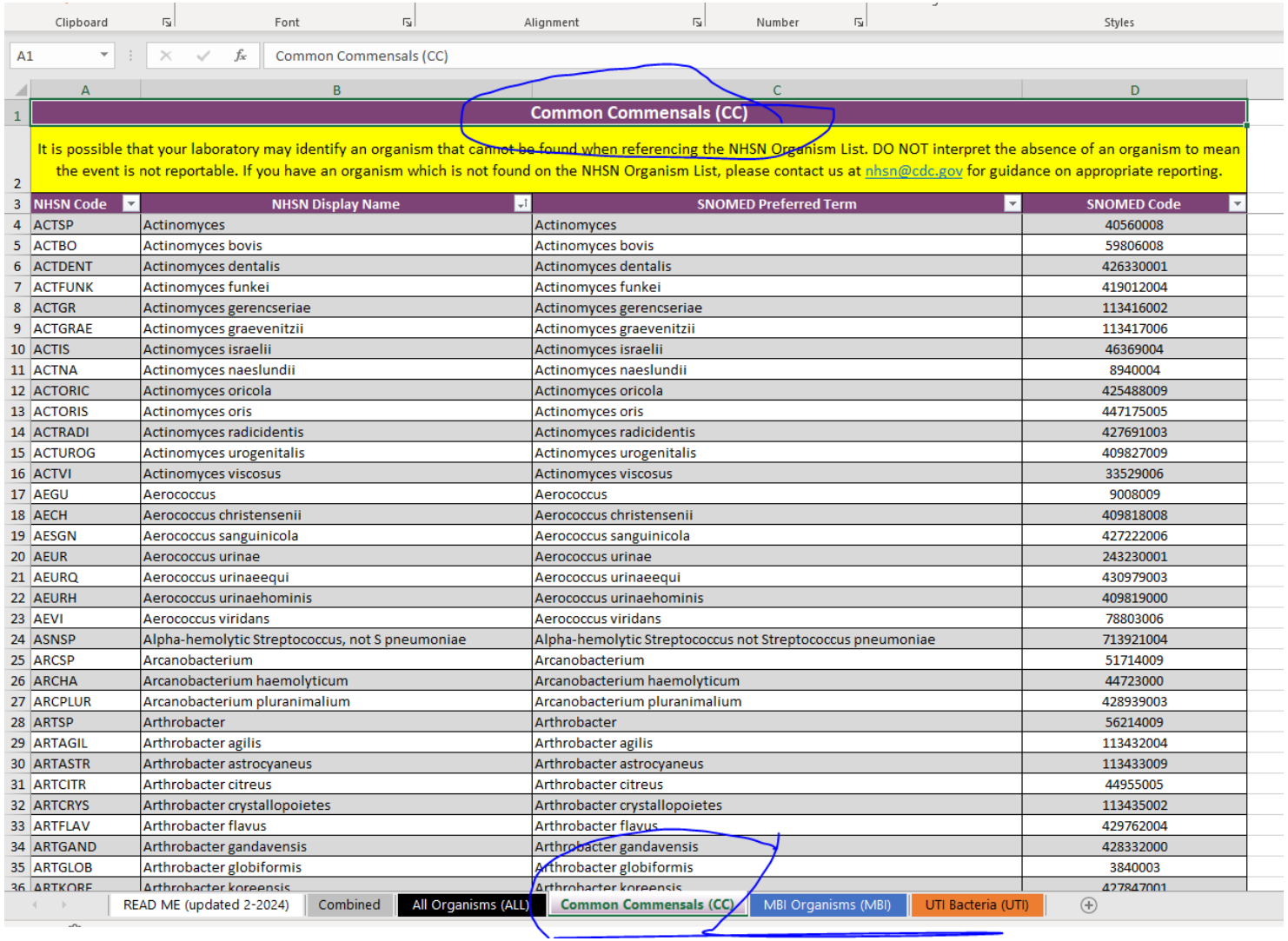
https://www.cdc.gov/antibiotic-use/hcp/core-elements/hospital.html

What are commensals?

- Commensal bacteria – aka Human Microbiome
  - Microorganisms that live on the body's epithelial surfaces w/o causing infections or harm
    - Epidermis/skin, respiratory tract, gastrointestinal tract, and genitourinary tract
  - Bacteria in an average human body number 10X times > human cells
  - Microorganisms comprise 1 -3% percent of body mass
    - e.g., 2 to 6 lbs of bacteria ~ 200-pound adult
- Commensal bacteria effect in human health
  - Protection from pathogenic bacteria
  - Digestions and metabolism
  - Prevent colonization of pathogenic microbes (e.g., *Clostridioides difficile)*
  - Synthesize growth factors and vitamins (e.g., vitamin K)

Khan R et al. Front Immunol. 2019 May 31;10:1203
https://www.hmpdacc.org/overview/

CDC/NHSN Common Commensal Organisms



Common Commensals (CC)

It is possible that your laboratory may identify an organism that cannot be found when referencing the NHSN Organism List. DO NOT interpret the absence of an organism to mean the event is not reportable. If you have an organism which is not found on the NHSN Organism List, please contact us at nhsn@cdc.gov for guidance on appropriate reporting.

NHSN Code	NHSN Display Name	SNOMED Preferred Term	SNOMED Code
ACTSP	Actinomyces	Actinomyces	40560008
ACTBO	Actinomyces bovis	Actinomyces bovis	59806008
ACTDENT	Actinomyces dentalis	Actinomyces dentalis	426330001
ACTFUNK	Actinomyces funkei	Actinomyces funkei	419012004
ACTGR	Actinomyces gerencseriae	Actinomyces gerencseriae	113416002
ACTGRAE	Actinomyces graevenitzii	Actinomyces graevenitzii	113417006
ACTIS	Actinomyces israelii	Actinomyces israelii	46369004
ACTNA	Actinomyces naeslundii	Actinomyces naeslundii	8940004
ACTORIC	Actinomyces oricola	Actinomyces oricola	425488009
ACTORIS	Actinomyces oris	Actinomyces oris	447175005
ACTRADI	Actinomyces radicidentis	Actinomyces radicidentis	427691003
ACTUROG	Actinomyces urogenitalis	Actinomyces urogenitalis	409827009
ACTVI	Actinomyces viscosus	Actinomyces viscosus	33529006
AEGU	Aerococcus	Aerococcus	9008009
AECH	Aerococcus christensenii	Aerococcus christensenii	409818008
AESGN	Aerococcus sanguinicola	Aerococcus sanguinicola	427222006
AEUR	Aerococcus urinae	Aerococcus urinae	243230001
AEURQ	Aerococcus urinaeequi	Aerococcus urinaeequi	430979003
AEURH	Aerococcus urinaehominis	Aerococcus urinaehominis	409819000
AEVI	Aerococcus viridans	Aerococcus viridans	78803006
ASNSP	Alpha-hemolytic Streptococcus, not S pneumoniae	Alpha-hemolytic Streptococcus not Streptococcus pneumoniae	713921004
ARCSP	Arcanobacterium	Arcanobacterium	51714009
ARCHA	Arcanobacterium haemolyticum	Arcanobacterium haemolyticum	44723000
ARCPLUR	Arcanobacterium pluranimalium	Arcanobacterium pluranimalium	428939003
ARTSP	Arthrobacter	Arthrobacter	56214009
ARTAGIL	Arthrobacter agilis	Arthrobacter agilis	113432004
ARTASTR	Arthrobacter astrocyaneus	Arthrobacter astrocyaneus	113433009
ARTCITR	Arthrobacter citreus	Arthrobacter citreus	44955005
ARTCRYS	Arthrobacter crystallopoietes	Arthrobacter crystallopoietes	113435002
ARTFLAV	Arthrobacter flavus	Arthrobacter flavus	429762004
ARTGAND	Arthrobacter gandavensis	Arthrobacter gandavensis	428332000
ARTGLOB	Arthrobacter globiformis	Arthrobacter globiformis	3840003
ARTKORE	Arthrobacter koreensis	Arthrobacter koreensis	427847001

READ ME (updated 2-2024) | Combined | All Organisms (ALL) | Common Commensals (CC) | MBI Organisms (MBI) | UTI Bacteria (UTI)

https://www.cdc.gov/nhsn/xls/master-organism-com-commensals-lists.xlsx

Conditions when commensal bacteria can become pathogenic

- Compromised hosts
  - Rheumatic heart disease
  - Immunosuppression/neutropenia/transplantation
  - Radiation therapy
  - Chemotherapy
  - Perforated mucous membranes/burns/trauma
  - Severe respiratory viral infections (e.g., Influenza, COVID-19, RSV)

Specimen types that may contain commensal organisms

- Blood cultures
- Respiratory specimens
- Urine specimens
- Stool samples
- Wound swabs
- Intra-abdominal specimens

Blood cultures

Blood Culture Contamination: An Overview for Infection Control and Antibiotic Stewardship Programs Working with the Clinical Laboratory

- Three Rs for obtaining blood cultures:
  - **Right** patients, in the **Right** settings, and at the **right** time
- Patients' w/ a low pretest probability of bacteremia**, a positive culture is more likely to represent contamination than infection**

https://www.cdc.gov/antibiotic-use/core-elements/pdfs/fs-bloodculture-508.pdf

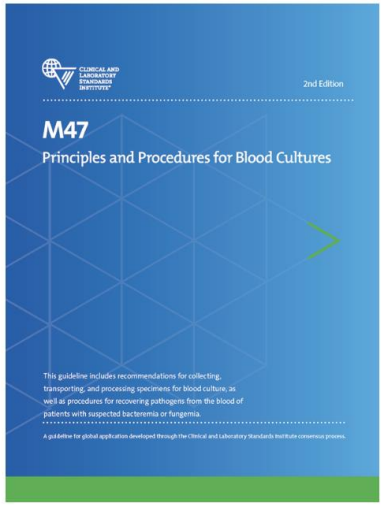
Table 2. Indications for Obtaining Initial Blood Cultures[31,32,34-44]

Conditions	Notes
Febrile neutropenia	
Fever without a source	
Suspected endovascular infections, including CLABSIs	
Suspected infective endocarditis	
Suspected sepsis	
• Cholangitis • Complicated pneumonia • Complicated SSTIs • Meningitis • Osteomyelitis • Pyelonephritis • Septic arthritis	• These syndromes are frequently associated with bacteremia. • Examples of complicated SSTIs include burn wounds, immersion injuries, puncture wounds from animal bites, infections in patients with neutropenia or other immunocompromising conditions, pyomyositis, gangrene, necrotizing fasciitis, and myonecrosis.
Unexplained leukocytosis	

Abbreviations: CLABSI, central line–associated bloodstream infection; SSTI, skin and soft tissue infection.

CLSI. *Principles and Procedures for Blood Cultures*. 2nd ed. CLSI guideline M47. Clinical and Laboratory Standards Institute; 2022

Antimicrobial Susceptibility Testing (AST)



- CLSI recommends AST be performed only on clinically relevant isolates recovered from blood cultures
  - AST should not be performed on contaminants (*with exceptions)
- Select antibiotics to test based on patient population, formulary, and antimicrobial Stewardship Considerations
- Suppress results for antimicrobial agents with no activity in systemic infections (e.g., nitrofurantoin, Fosfomycin)
- Suppress results for antimicrobials that are inactive against ID'd organism
  - e.g., cephalosporins vs *listeria monoctyogenes*, ampicillin vs *Klebsiella* spp.
- Consider measures that support antimicrobial stewardship
  - e.g., cascade antimicrobial reporting

CLSI. *Principles and Procedures for Blood Cultures*. 2nd ed. CLSI guideline M47. Clinical and Laboratory Standards Institute; 2022

Positive Blood culture: Interpretations

Always clinically significant

- *Staphylococcus aureus*
- *Streptococcus pneumoniae*
- Group A Streptococcus
- Enterobacterales
- *Haemophilus influenzae*
- *Pseudomonas aeruginosa*
- *Candida* spp.

May be clinically significant

- *Enterococci* spp.
- (e.g., *E. faecium, E. faecalis)*
- Viridans *Streptococci*

  (e.g., *S. mutans, S. salivarius, S. anginosus, S. mitis, S. sanguinis, S. bovis*)

Often contaminants

- Coagulase-negative *staphylococci* (except - *Staphylococcus lugdunensis*)
- Corynebacterium spp. (except *C. jeikeium and C. diphtheriae*)
- *Cutibacterium acnes*
- *Bacillus* species (except *B. anthracis*)
- *Micrococcus* spp.
- *Aerococcus* spp.

- Aerobic organisms isolated > 72 hours are often considered a contaminant
- (+) Blood cultures that are not compatible with a clinical syndrome are usually a contaminant
- A single (1/4) blood culture with Coagulase negative Staphylococcus (e.g., Staph epi, Staph hominis) is often a contaminant

Doern GV, et al. Clin Microbiol Rev. 2019 Oct 30;33(1):e00009-19.

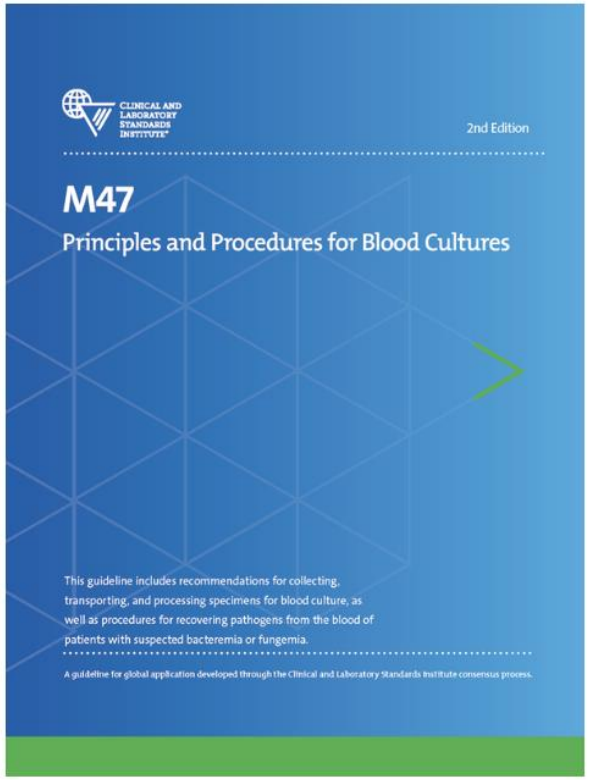
Clinical scenarios/patient populations for susceptibility testing of commensals in blood cultures

- Neonatal and newborns
- Infective endocarditis
- Infected endovascular devices (e.g., pacemakers or vascular grafts)
- Central line-associated bloodstream infections (CLABSIs)
- Prosthetic joints or other prosthetic hardware
- Severe immunocompromise (e.g., BMT, SOT, high-dose corticosteroids, or other immunosuppressive medications)

Doern GV, et al. Clin Microbiol Rev. 2019 Oct 30;33(1):e00009-19.

Blood Culture contamination rates

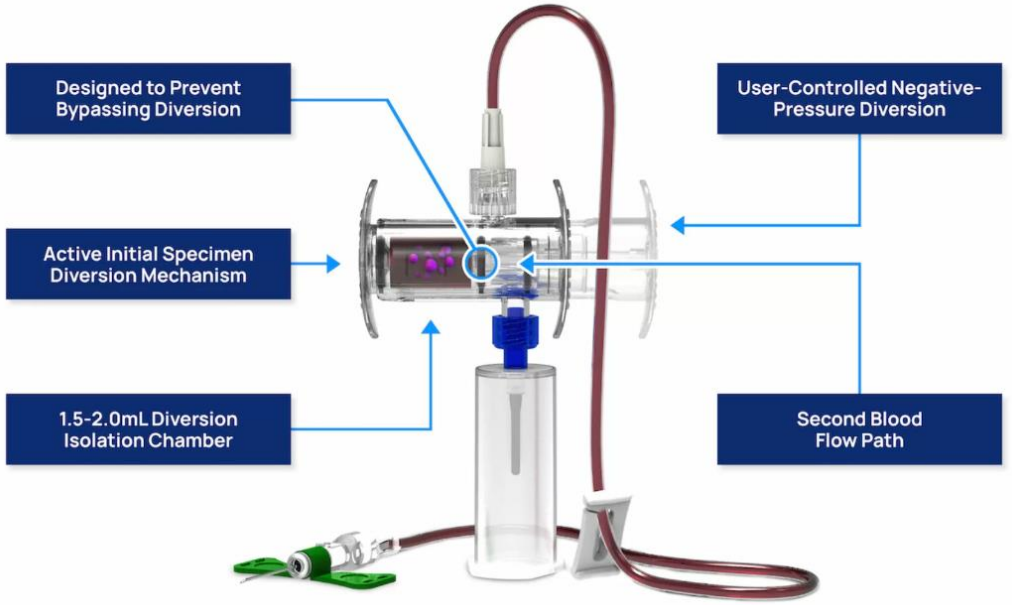
- CLSI recommends an overall blood culture contamination rate < 3%
- Many institutions fail to meet this threshold
  - Contamination rates routinely range from 0.6% to 6%
- False-positive blood cultures increase laboratory costs by ~ 20%
- Associated with a ~ 40% increase in antibiotic usage
- Prolonged hospital LOS and ↑ toxicities from antibiotic exposure



CLSI. *Principles and Procedures for Blood Cultures*. 2nd ed. CLSI guideline M47. Clinical and Laboratory Standards Institute; 2022

Can a blood culture initial specimen diversion device reduce contamination?

- Single center, prospective, controlled, open label study
- 904 subjects with 1808 blood cultures
- Sterile blood culture device designed to divert and sequester the initial 1.5 to 2.0 mL of blood prior to culture bottle inoculation
- 152/1808 (8.4%) of blood cultures yielded microbial growth
  - 134/1808 (7.4%) true pathogens
  - 18/1808 (1%) contaminants
- ISDD was associated with less blood culture contamination vs SOC: 2/904 [0.22%] vs 16/904 [1.78%], *P* = .001).



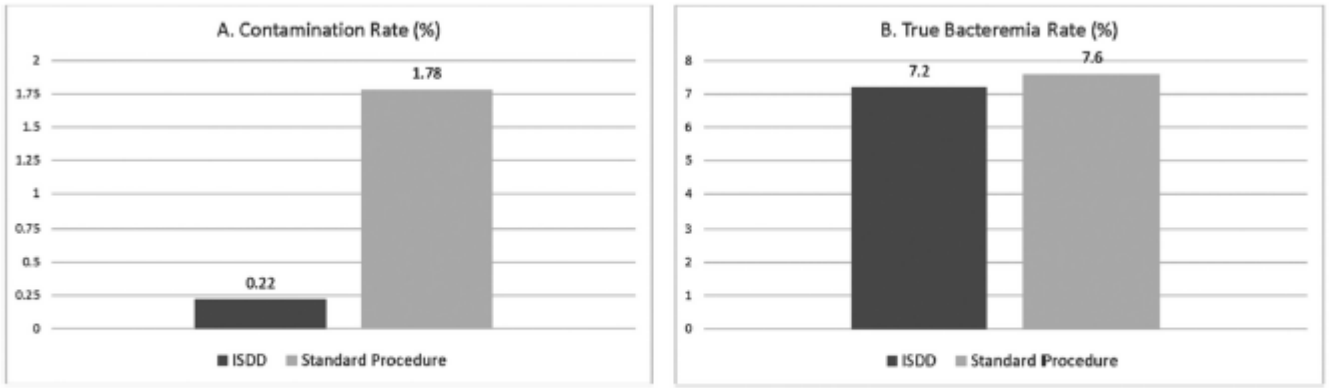


Figure 1. Performance of ISDD vs standard procedure. *A*, Contamination rate. *B*, Detection of true bacteremia. Abbreviation: ISDD, initial specimen diversion device.

Rupp ME, et al. Clin Infect Dis. 2017 Jul 15;65(2):201-205.

Blood culture contamination results in increased hospital costs & exposure to antimicrobials

TABLE 2 Distribution of component downstream costs stratified by result of initial blood culture collected in the ED

	Cost ($/culture)									
	Microbiology			Hospital, indirect[a]					Total	
Category	With RDT[b]	Without RDT	Pharmacy	LOS	ADRs	HAIs	Additional procedures	Total	With RDT	Without RDT
Contaminated blood culture	477	275	423	10,500	47	480	1,100	12,126	13,026	12,824
Negative blood culture	119	118	295	7,500	30	343	0	7,873	8,287	8,286
Attributable to blood culture contamination	358	158	127	3,000	16	137	1,100	4,253	4,739	4,538

[a]LOS, length of stay; ADR, adverse drug reaction; HAI, hospital acquired infection.
[b]RDT, rapid diagnostic testing.

- ✓ Median LOS 2 days longer for patients w/ contaminated blood Cx
- ✓ Direct & indirect hospital costs >$4,500 for contaminated blood Cx

Skoglund E, et al. J Clin Microbiol. 2019 Jan 2;57(1):e01015-18.

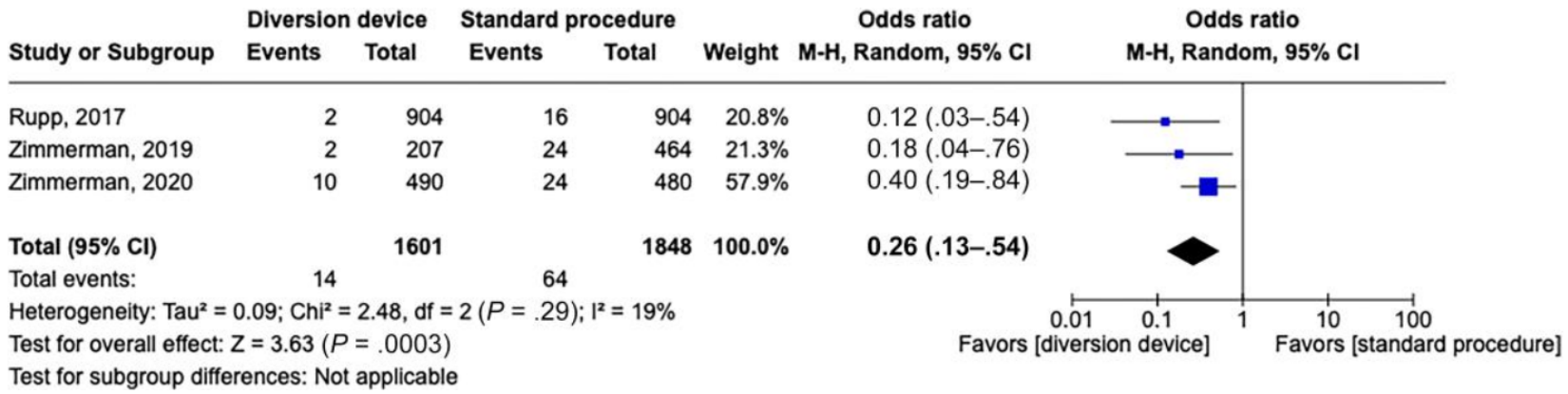


Figure 2. Forest plot of blood culture contamination with a diversion device or a standard procedure of blood collection, in high-quality (Downs and Black ≥18) studies. Odds ratios were determined with the Mantel-Haenszel random-effects method. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

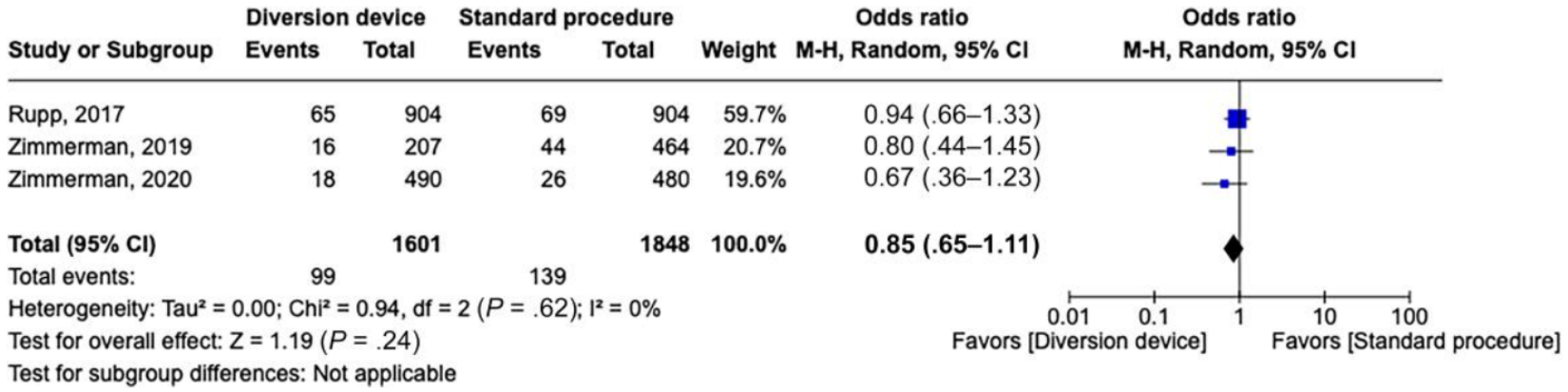
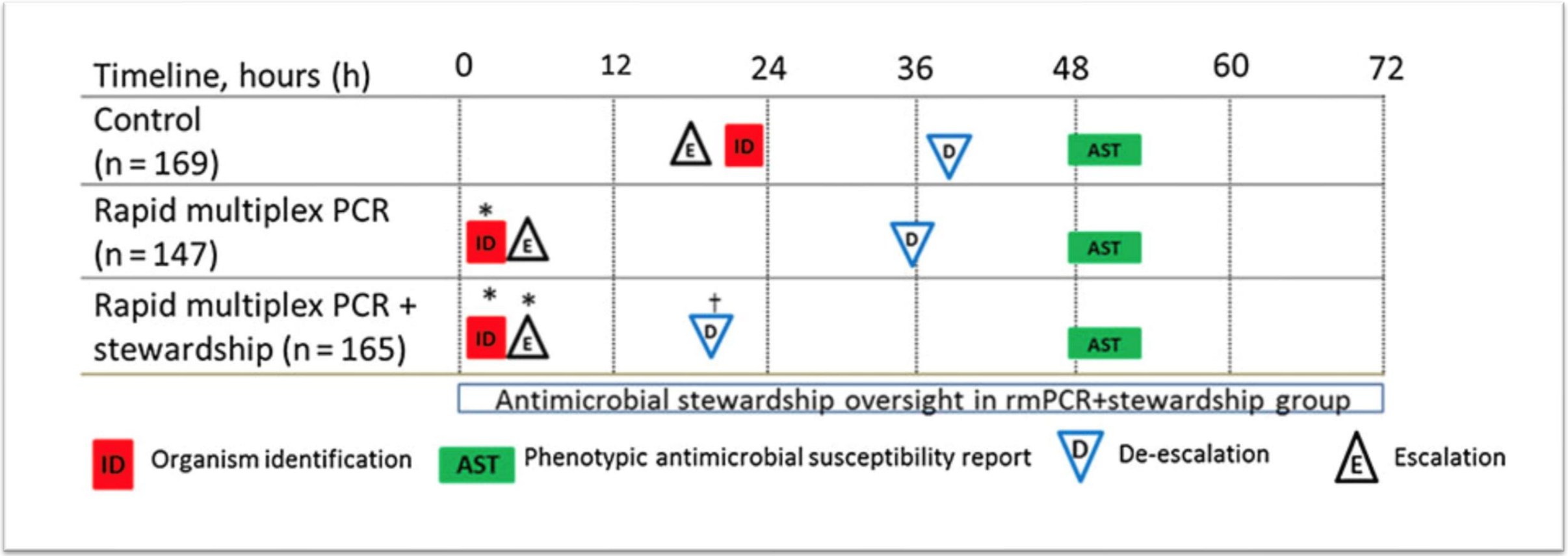


Figure 3. Forest plot of true infection detection with a diversion device or a standard procedure of blood collection. Odds ratios were determined with the Mantel-Haenszel random-effects method. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

Antimicrobial Stewardship Activities around Blood Culture Reporting and Interoperating

Importance of coupling Rapid Diagnostic Tests w/ASP Team



Banerjee R, et al. Clin Infect Dis. 2015 Oct 1;61(7):1071-80.

Biofire BCID2 Panel: Species & Antimicrobial Resistance Genes

GRAM-NEGATIVE BACTERIA

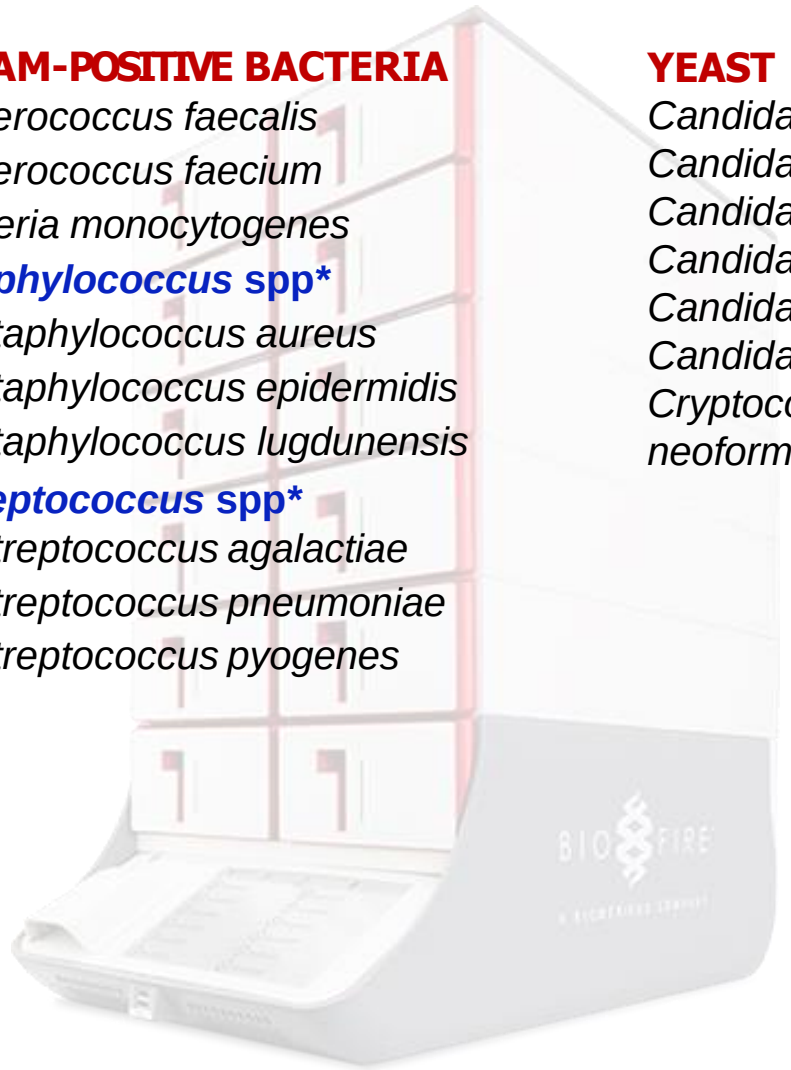
Acinetobacter calcoaceticus-baumannii complex
Bacteriodes fragilis
Enterobacterales* spp
- *Enterobacter cloacae* complex
- *Escherichia coli*
- *Klebsiella aerogenes*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae* group
- *Proteus*
- *Salmonella*
- *Serratia marcescens*

Haemophilus influenzae
Neisseria meningitidis
Pseudomonas aeruginosa
Stenotrophomonas maltophilia

GRAM-POSITIVE BACTERIA

Enterococcus faecalis
Enterococcus faecium
Listeria monocytogenes
Staphylococcus* spp
- *Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *Staphylococcus lugdunensis*

Streptococcus* spp
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*



YEAST

Candida albicans
Candida auris
Candida glabrata
Candida krusei
Candida parapsilosis
Candida tropicalis
Cryptococcus neoformans/gattii

ANTIMICROBIAL RESISTANCE GENES

Carbapenemases
- IMP
- KPC
- Oxa-48-like
- NDM
- VIM

Colistin Resistance
- *mcr-1*

ESBL
- CTX-M

Methicillin Resistance
- *mecA/C*
- *mecA/C* and MREJ

Vancomycin Resistance
- *vanA/B*

*** *Enterobacterales, Staphylococcus,* and *Streptococcus* are family (genus) level targets. They may also be accompanied by a species level target (i.e. *Enterobacterales* and *E. coli*).**

Antimicrobial Stewardship Guideline for RDT

Brigham ar
Founding Membe

Title:	
Guideline Section:	
Guideline Type:	
Sponsor:	
Last effective date:	

Background

- The BioFire Film
  pathogens and 1
  uses a Multiplex
  99% sensitivity a
  performed by th
  hours, compare

Interpretation

- Tables 2a, 2b, ar
  based on analys
  recommendatio
  susceptibilities.
  guide antimicrol
  other patient-sp
  instance, when

Table 2a: Treatment Recommendations for Gram-Positive Bacteria *(while awaiting final susceptibilities)*

Pathogen Result	Resistance Result	Preferred Initial Therapy	Comments
Enterococcus faecalis	N/A	Ampicillin	Regardless of VanA/B result
Enterococcus faecium	VanA/B negative	Vancomycin	
	VanA/B positive	Daptomycin[1] or Linezolid[1]	VRE if VanA/B positive
Listeria monocytogenes	N/A	Ampicillin	TMP-SMX can be used if patient has a severe penicillin allergy
***Staphylococcus* spp. (only)[2]**	N/A	Vancomycin only if more than 1 of 4 blood cultures are positive and invasive infection is suspected	Presumed to be coagulase-negative *Staphylococcus* spp., possible contamination
Staphylococcus aureus	MecA/MREJ negative	Cefazolin or Oxacillin	Likely MSSA – consult ID
	MecA/MREJ positive	Vancomycin	MRSA – consult ID
Staphylococcus epidermidis	MecA/C negative	Cefazolin only if more than 1 of 4 blood cultures are positive and invasive infection is suspected	
	MecA/C positive	Vancomycin only if more than 1 of 4 blood cultures are positive and invasive infection is suspected	
Staphylococcus lugdunensis	MecA/C negative	Cefazolin or Oxacillin	
	MecA/C positive	Vancomycin	
***Streptococcus* spp. (only)[3]**	N/A	Ceftriaxone – consider withholding if patient does not have signs of invasive infection	Likely Viridans group strep or other non-group A/B/pneumoniae strep, possible contamination

BWH BioFire Blood Culture Identification Panel 2 (BCID2) Guidelines

08/04/2024 1304	08/05/2024 2353	BLOOD CULTURE ORGANISM ID PCR [1431862230] (Abnormal)	Final result

Component	Value
Staphylococcus Species	DETECTED ! Staphylococcus detected at a Genus level. If detected alone, this suggests the presence of a non-aureus, non-lugdunensis, or non-epidermidis staphylococcal species. This may represent a contaminant, particularly if detected in 1 out of 4 bottles.
--Staphylococcus aureus	Not Detected
--Staphylococcus epidermidis	Not Detected
--Staphylococcus lugdunesis	Not Detected
Enterococcus faecalis	Not Detected
Enterococcus faecium	Not Detected
Streptococcus Species	Not Detected
--Streptococcus pyogenes (Group A)	Not Detected
--Streptococcus agalactiae (Group B)	Not Detected
--Streptococcus pneumoniae	Not Detected
Enterobacterales Family	Not Detected
--Enterobacter cloacae complex	Not Detected
--Escherichia coli	Not Detected
--Klebsiella aerogenes	Not Detected
--Klebsiella oxytoca	Not Detected
--Klebsiella pneumoniae	Not Detected
--Proteus species	Not Detected
--Salmonella Species	Not Detected
--Serratia marcescens	Not Detected
Pseudomonas aeruginosa	Not Detected
Acinetobacter baumanii	Not Detected
Stenotrophomonas maltophilia	Not Detected
Listeria monocytogenes	Not Detected
Bacteroides fragilis	Not Detected
Haemophilus influenzae	Not Detected
Neisseria meningitidis	Not Detected
Candida albicans	Not Detected
Candida auris	Not Detected
Candida glabrata	Not Detected
Candida krusei	Not Detected
Candida parapsilosis	Not Detected
Candida tropicalis	Not Detected
Cryptococcus neoformans/gattii	Not Detected
Additional Information	For additional information, see the BWH BCID2 Guidelines located at the following URL https://hospitalpolicies.ellucid.com/documents/view/26084
Bottle Type	BFA

EHR embedded messages in Blood Culture PCR results

Blood Culture, Routine [1430952395] (Abnormal) Blood PORT CENTRAL	Final result	Component	Value
		Special Requests	None
		GRAM STAIN	GRAM POSITIVE COCCI in CLUSTERS from AEROBIC 'FAN' (BACT/ALERT) MEDIUM Critical Result. Results called to and read back by: Dr Daria Ade 38646 8/5 @1928 ! GRAM POSITIVE COCCI in CLUSTERS from ANAEROBIC 'FAN' (BACT/ALERT) MEDIUM A BioFire Blood Culture Identification Panel (BCID2), molecular blood panel will be run unless it has previously been reported on a specimen with the same Gram stain morphology in the past 7 days. Please see Blood culture organism ID PCR
		BLOOD CULTURE	STAPHYLOCOCCUS CAPITIS from AEROBIC and ANAEROBIC 'FAN' (BACT/ALERT) MEDIUM NEGATIVE FOR BETA LACTAMASE PRODUCTION !

Susceptibility

	Staphylococcus capitis MIC METHOD	
Beta Lactamase		Positive **
Ciprofloxacin	<=0.5	Susceptible
Clindamycin	0.25	Susceptible
Daptomycin	0.25	Susceptible
Erythromycin	<=0.25	Susceptible
Gentamicin	<=0.5	Susceptible
inducible clindamycin		Negative **
Levofloxacin	0.5	Susceptible
Linezolid	2	Susceptible
Minocycline	<=0.5	Susceptible
Moxifloxacin	<=0.25	Susceptible
Oxacillin/cephalosporins	<=0.25	Susceptible
Penicillin G	<=0.03	Susceptible [1]
Rifampin	<=0.5	Susceptible
Tetracycline	2	Susceptible
Trimethoprim/sulfamethoxazole	<=10	Susceptible
Vancomycin	<=0.5	Susceptible

** Suppressed Antibiotic

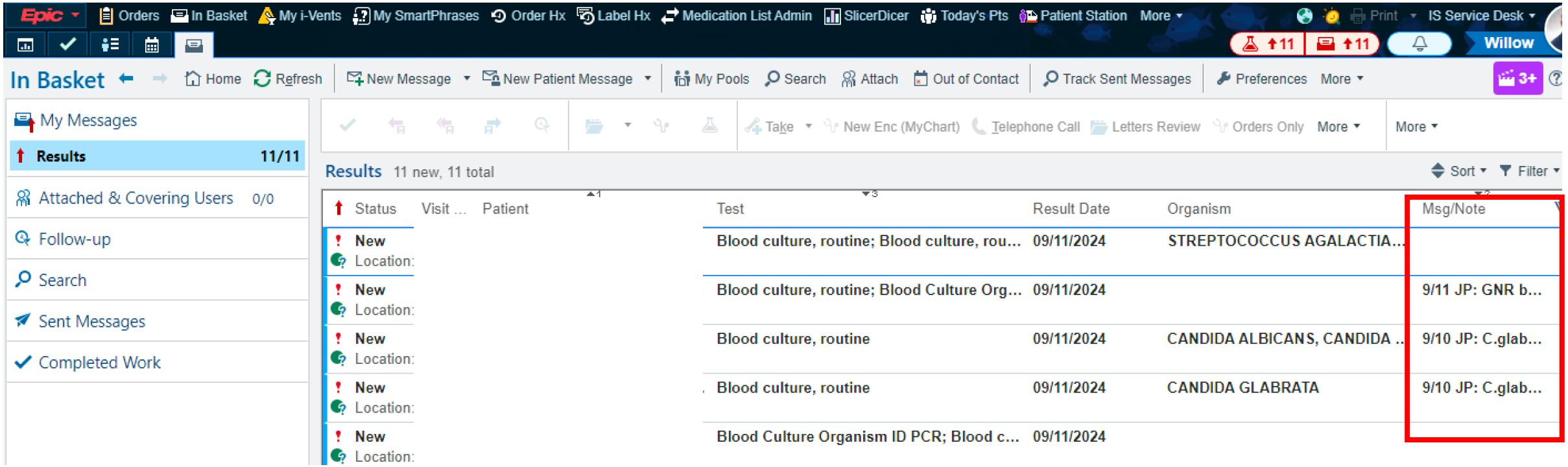
1 Corrected On: 08/09/2024 at 1332: Previously Reported as: Pending

Linear View

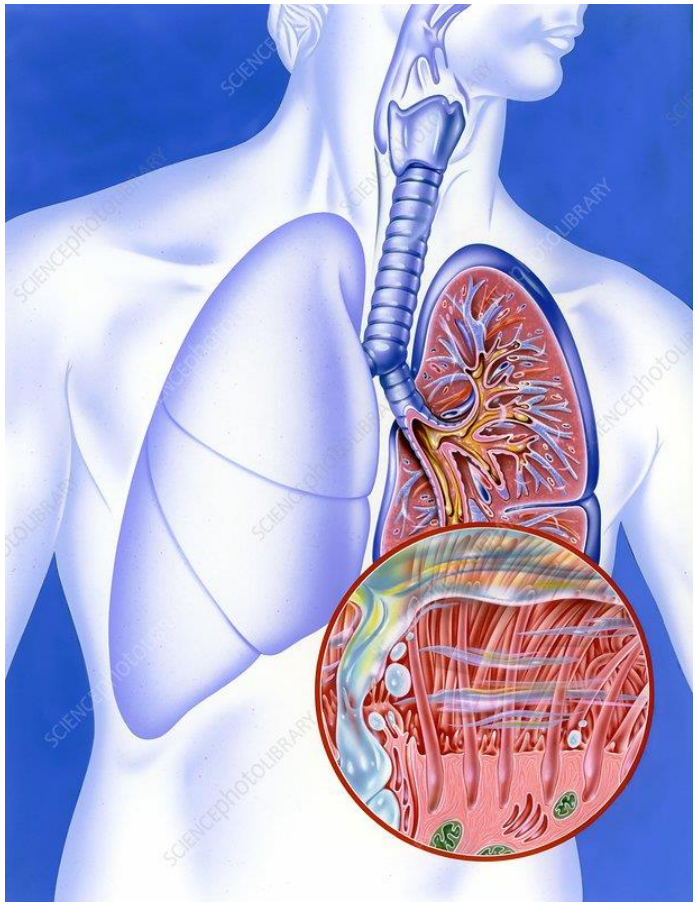
Susceptibility Comments

Staphylococcus capitis

Antimicrobial Stewardship Team Reviews of Positive Blood Cultures

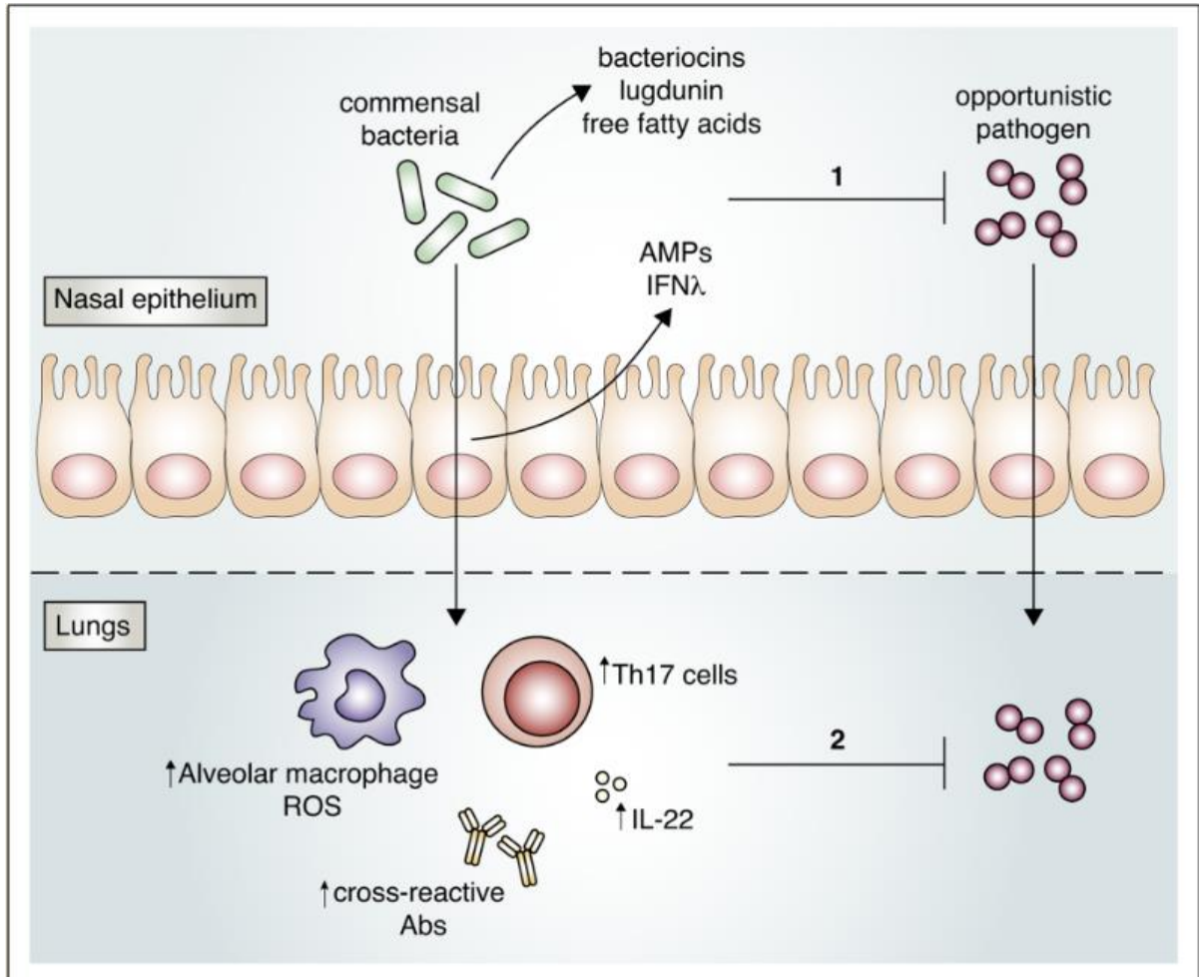


Respiratory cultures



Common respiratory commensals

- Many bacteria inhabiting the upper respiratory tract (URT) are rarely associated with disease
- Several ‘core’ genera present in most healthy individuals, include:
  - *Staphylococcus* spp.
  - *Streptococcus* spp.
  - *Corynebacterium*
  - *Prevotella*
  - *Veillonella*
  - *Propionibacterium*
  - *Fusobacterium* (adults)
  - *Moraxella* (children)
  - *Candida* spp.
- URT commensal bacteria protect against respiratory tract infection from opportunism pathogens
  - e.g., *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis and Staphylococcus aureus*



Clark SE. Curr Opin Immunol. 2020 Oct;66:42-49.

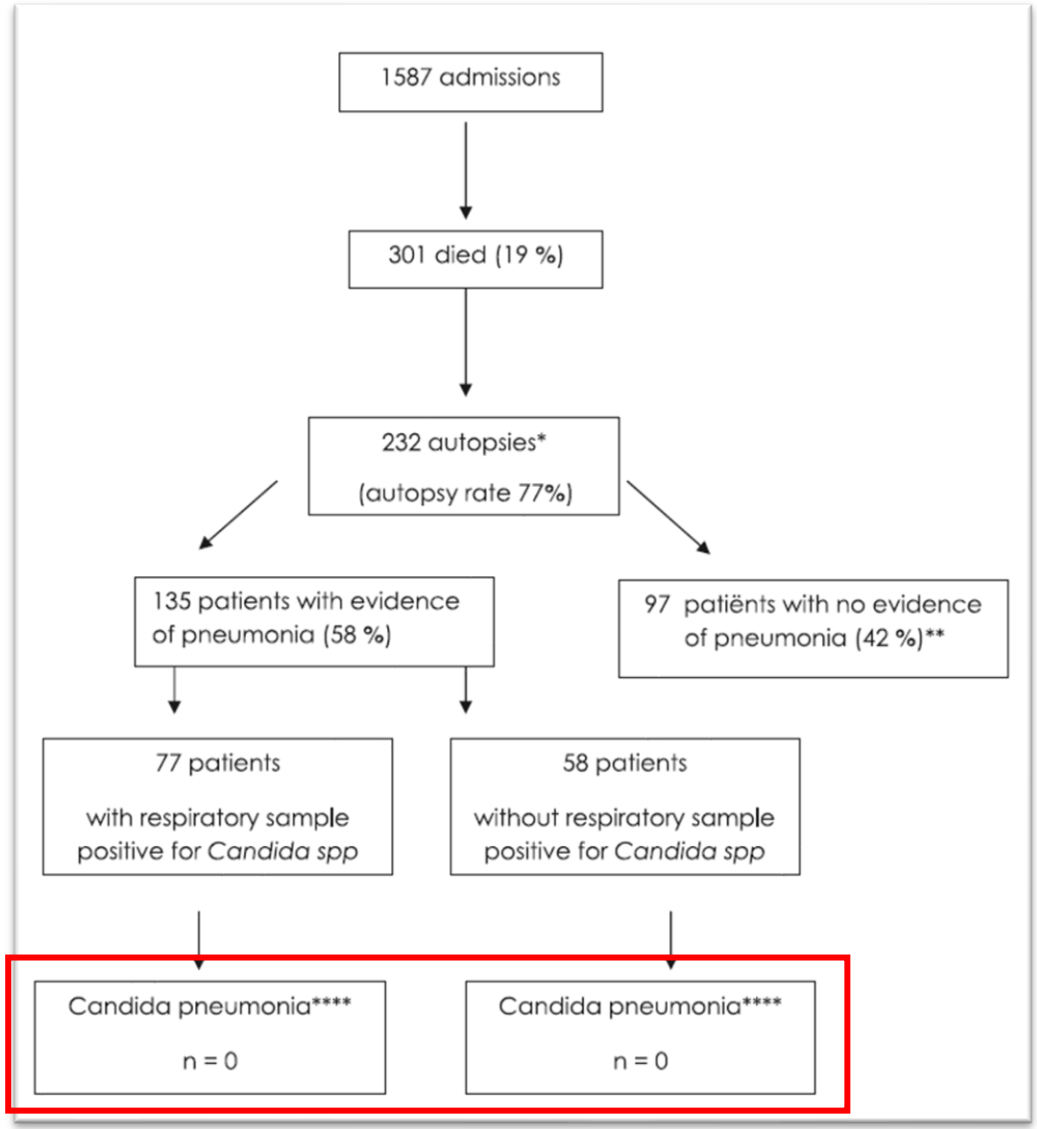
When commensals should be worked-up

- Clinical evidence of Lower respiratory tract infection
- specimens isolated from bronchoalveolar lavage sampling
- Significant aspiration events
- Ventilator-associated pneumonia
- Some organisms are virtually never pulmonary pathogens
  - *Candida* spp*,* coagulase-negative *staphylococci,* and *enterococci*

Clinical Significance of *Candida* spp. Isolated in Respiratory Cultures

- N = 1,587 ICU patients
- APACHE II score was 20.4
- 301 (19%) died during ICU stay
- 77 patients w/ pneumonia upon autopsy and positive cultures (tracheal aspirates or BAL) for *Candida* spp

0/77 patients had e/o Candida pneumonia



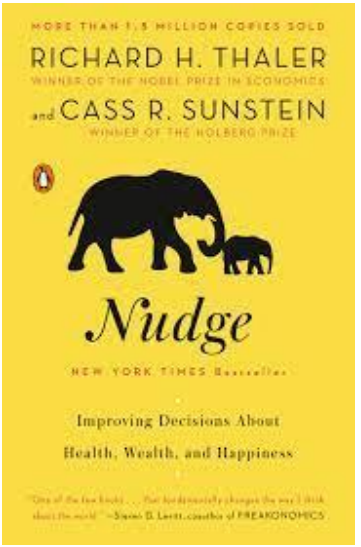
Meersseman W, et al. Intensive Care Med. 2009 Sep;35(9):1526-31.

Open Forum Infectious Diseases

MAJOR ARTICLE

Microbiology Comment Nudge Improves Pneumonia Prescribing

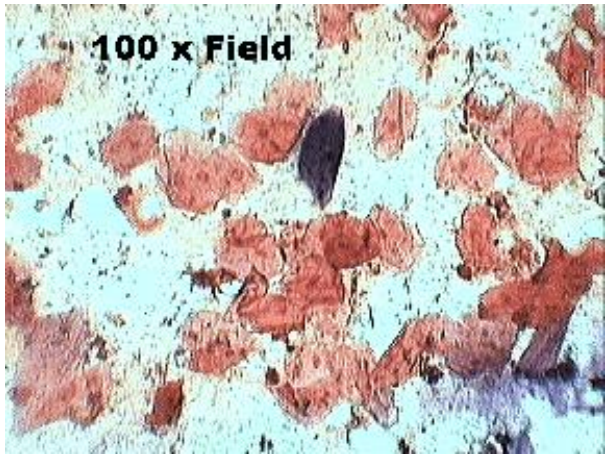
Mary A. Musgrove,[1] Rachel M. Kenney,[1] Ronald E. Kendall,[2] Michael Peters,[1] Robert Tibbetts,[3] Linoj Samuel,[3] and Susan L. Davis[1,4]



- A change in microbiology messaging on respiratory cultures growing commensal flora only
  - **Prior message: "commensal respiratory flora"**
  - **New message: "commensal respiratory flora only: No S. aureus/MRSA or *P. aeruginosa*."**
- Primary outcome was de-escalation of anti-MRSA or antipseudomonal antibiotics
- n=105 in pre-intervention group; n=105 postintervention group
- Overall Abx de-escalations 39% vs 73% in pre- and post- groups (P < .001)
  - MRSA abx de-escalated in 37% vs 71% in pre- and post- groups (P < .001)
  - Antipseudomonal abx de-escalated in 32% vs 70% in pre- and post- groups (P < .001)

Musgrove MA, et al. Open Forum Infect Dis. 2018 Jul 10;5(7):ofy162.

Greater than 10 Squamous Epithelial cells/LPF: Cut-off for working up sputum cultures



- Serious contamination of the sputum with saliva
- Includes a clarifying message
- Reduces unnecessary work-up and antibiotic Rx

Respiratory Culture/Gram Stain [1455852817]	Final result	Component	Value
Other from Sputum		**Special Requests**	None
		GRAM STAIN	NO POLYS
			>10 EPITHELIAL CELLS/LPF
			2+ GRAM NEGATIVE RODS
		Respiratory Cult/Smear	Gram stain evaluation indicated >10 squamous epithelial cells per low power field. Specimen is contaminated with oral flora and may not represent the lower respiratory tract. Please submit a new specimen if clinically indicated.

Urine cultures

Which patients need urine cultures?

Patients without Urinary Catheters		
Appropriate Dysuria, suprapubic pain, flank pain, Costovertebral angle (CVA) tenderness, or septic shock	**Uncertain** Fever or systemic leukocytosis with no other known cause	**Inappropriate** Altered mental status, or change in urine characteristics (color, sediment, smell)

Patients with Urinary Catheters		
Appropriate Dysuria, suprapubic pain flank pain, Costovertebral angle (CVA) tenderness, or septic shock	**Uncertain** Fever, systemic leukocytosis with no other known cause, or delirium*	**Inappropriate** Change in urine characteristics (color, sediment, smell)

* Exceptions: pregnancy; patients undergoing urological procedures, renal transplant recipients

Claeys KC, et al. Clin Infect Dis. 2022 Aug 31;75(3):382-389.

Optimal Urine Culture Diagnostic Stewardship

Table 1. Ordering Urine Cultures: Best Practices for Diagnostic Stewardship of Urine Culture Ordering Included These Recommendations

Appropriate practices
• Require documentation of signs or symptoms of UTI to obtain a urine culture, which includes dysuria or flank pain
• Replace stand-alone urine culture orders with conditional reflex urine cultures[a,b]
• Implement best practice alerts to discourage ordering urine cultures in the absence of signs or symptoms of UTI[a]
• Automatically cancel repeat urine cultures within 5 days of a positive culture (during the same hospital admission and 7 days for long-term care residents)
Inappropriate practices
• Include urine cultures in standard order sets for:
○ Emergency department evaluation
○ Hospital admission
○ Inpatient pre-op
○ Assessment of altered mental status
○ Assessment of falls in long-term care
• Order urine cultures in response to change in urine characteristics

Guidance is for all healthcare settings unless noted specifically. Conditional reflex urine cultures are defined as cultures, although ordered by the clinician, that are only performed after specific criteria are met on urinalysis (ie, white blood cells >10 per high-power field).

Abbreviation: UTI, urinary tract infection.

[a]Except for patients undergoing urological procedures.

[b]Disagreement around use of urinary catheters and the emergency room setting.

Claeys KC, et al. Clin Infect Dis. 2022 Aug 31;75(3):382-389.

When to test and not to test

- Bacterial or fungal isolates of uncertain clinical importance should not be tested for antimicrobial susceptibility (e.g., Candida spp., Streptococcus spp.)
- “mixed bacterial flora” (≥3 bacteria grow, and none is present at >100,000 CFU/mL

Table 4. Interpreting culture results for urine specimens yielding common urinary tract pathogens.

Probability of contamination, no. of microorganisms isolated	Quantitation, cfu/mL	Interpretation
Low probability[a]		
1	$<10^2$	Probable contaminant
1	$\geq 10^2$	Significant isolate
2	$<10^2$ for each	Probable contaminants
2	$\geq 10^2$ for each	Significant isolates
2	$\geq 10^2$ for 1	Significant isolate and contaminant
≥3	$\geq 10^5$ for 1	Significant isolate and contaminants
≥3	$\geq 10^5$ for each	Probable contaminants
High probability[b]		
1	$<10^2$	Probable contaminant
1	$\geq 10^2$	Significant isolate
2	$\geq 10^5$ for each	Significant isolates
2	$\geq 10^5$ for 1	Significant isolate and contaminant
2	$<10^5$ for each	Probable contaminants
≥3	$\geq 10^5$ for 1	Significant isolate and contaminants
≥3	$\geq 10^5$ for each	Probable contaminants

Wilson ML, et al. Clin Infect Dis. 2004 Apr 15;38(8):1150-8.

Common pathogens isolated in urine cultures

Frequently Uropathogens (>100,000 CFUs/mL)

- *Escherichia coli*
- Enterobacterales (e.g., *Klebsiella* spp. and *Proteus* spp.)
- *Pseudomonas*
- Enterococci
- *Staphylococcus aureus*
- *Staphylococcus saprophyticus*

Susceptibility testing generally performed

Rarely Uropathogens

- Yeast or Candida spp
- Aerococcus spp
- *Coynebacterium ureolyticum*
- *Gardnerella vaginalis*

Susceptibility testing is not routinely performed

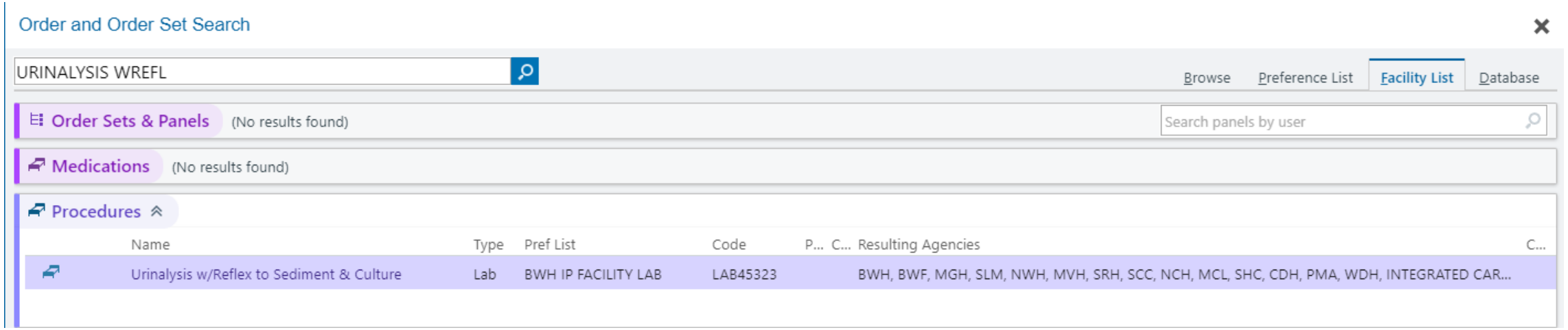
Not usually Considered Uropathogens

- Lactobacillus spp.
- Diphtheroids (exp. *Corynebacterium ureolyticum*)
- *Streptococcus viridians*
- Micrococcus spp
- Bacillus spp, not anthracis
- Staphylococcus spp. in mixed cultures (exp. *S. aureus and S. saprophyticus*)
- *Mixed growth consistent with normal urethral flora and/or colonizing bacteria*

Susceptibility testing is not routinely performed

BWH Policy for urinalysis with reflex urine culture

- Orders placed using “urinalysis with reflex urine culture” order set
  - Specimens for urinalysis and urine culture will be collected simultaneously
  - Urine culture will be run only when urinalysis shows ≥10 WBC/hpf



BWH Unnecessary Urine Culture Cancellation MSEC Policy accessed September 18, 2024

BWH urinalysis with reflex urine culture exceptions

- Standalone urine culture may be ordered for specific indications:
  1. Documented pyuria (≥10 WBC/hpf) within the past 3 days
  2. Pregnancy
  3. Impending urological procedure
  4. Neutropenia (ANC < 1000)
  5. Infant (Age < 3 years)
  6. Renal transplant within the preceding 6 months
  7. Infectious disease physician request
  8. Research Protocol

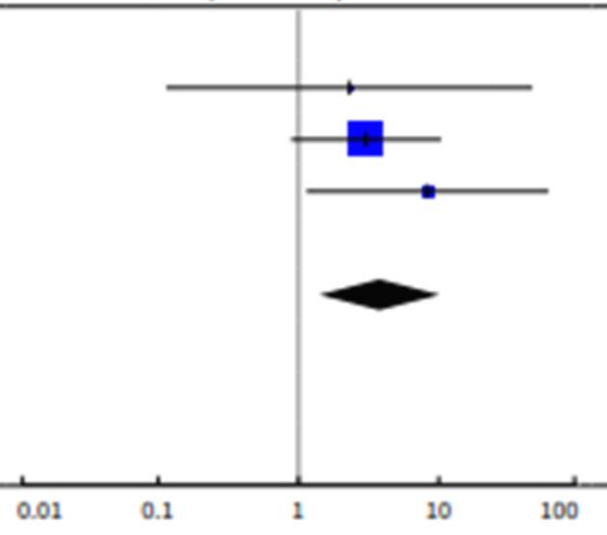
BWH Unnecessary Urine Culture Cancellation MSEC Policy accessed September 18, 2024

Should asymptomatic bacteriuria be treated?

Analysis 1.1. Comparison 1 Antibiotics versus placebo or no treatment, Outcome 1 Symptomatic UTI.

Analysis 1.4. Comparison 1 Antibiotics versus placebo or no treatment, Outcome 4 Any adverse event.

Study or subgroup	Antibiotics n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Cai 2012	0/361	0/312			Not estimable
Giamarellou 1998	2/64	0/29		10.83%	2.31[0.11,46.6]
Harding 2002	10/55	3/50		64.46%	3.03[0.88,10.39]
Nicolle 1987	9/26	1/24		24.71%	8.31[1.14,60.78]
Total (95% CI)	**506**	**415**		**100%**	**3.77[1.4,10.15]**
Total events: 21 (Antibiotics), 4 (Placebo/no treatment)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.85$, df=2(P=0.65); $I^2=0\%$					
Test for overall effect: Z=2.63(P=0.01)					



Zalmanovici Trestioreanu A, et al. Cochrane Database Syst Rev. 2015 Apr 8;4(4):CD009534.

Clinical Infectious Diseases

IDSA FEATURES

Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America[a]

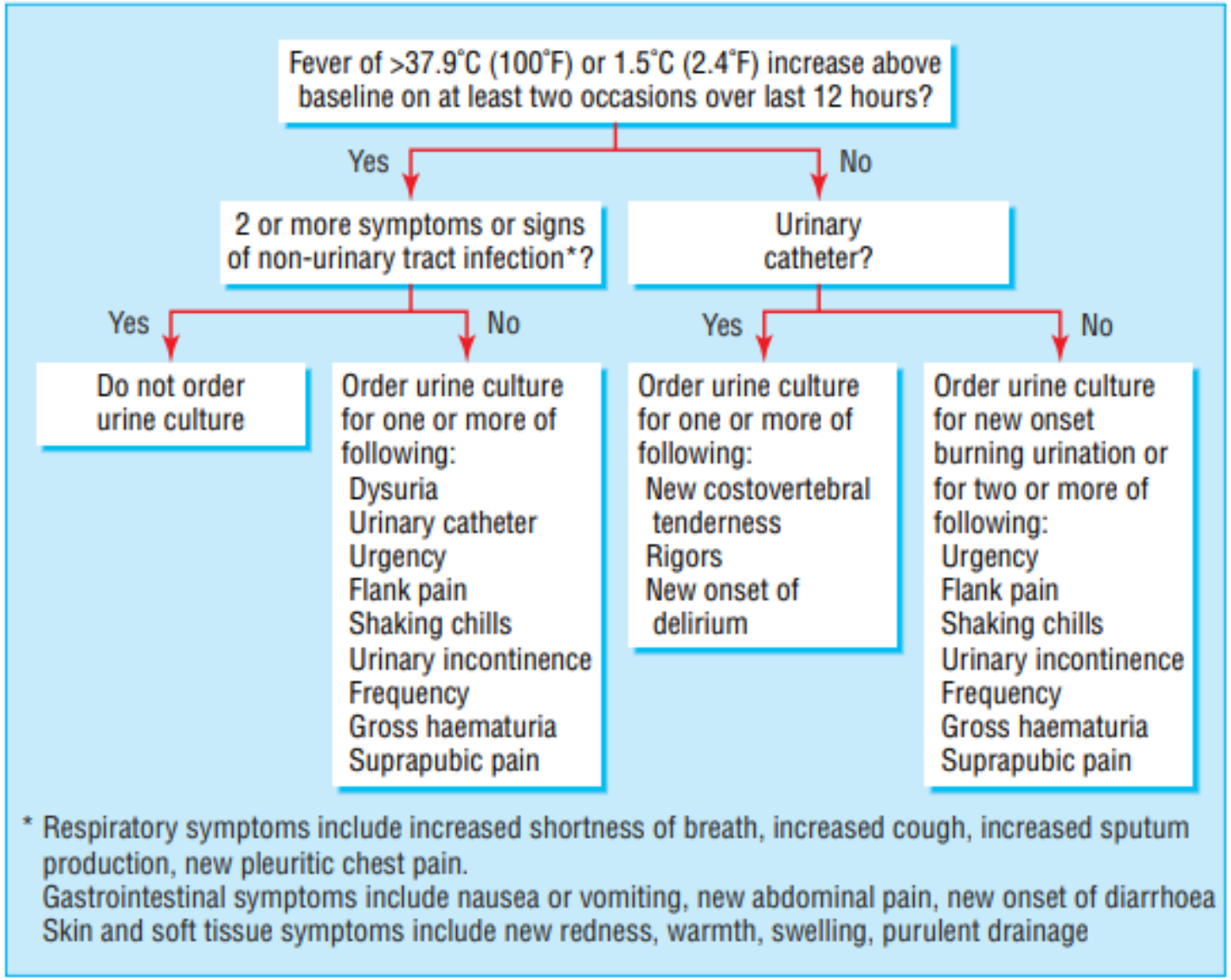
Lindsay E. Nicolle,[1] Kalpana Gupta,[2] Suzanne F. Bradley,[3] Richard Colgan,[4] Gregory P. DeMuri,[5] Dimitri Drekonja,[6] Linda O. Eckert,[7] Suzanne E. Geerlings,[8] Béla Köves,[9] Thomas M. Hooton,[10] Manisha Juthani-Mehta,[11] Shandra L. Knight,[12] Sanjay Saint,[13] Anthony J. Schaeffer,[14] Barbara Trautner,[15] Bjorn Wullt,[16] and Reed Siemieniuk[17]

Asymptomatic bacteriuria – even in the presence of pyuria – is NOT an indication for antibiotics

Nicolle LE, et al. Clin Infect Dis. 2019 May 2;68(10):e83-e110.

Urine culture diagnostic stewardship

- Develop algorithm for urine culture ordering



Loeb M, et al. BMJ. 2005 Sep 24;331(7518):669.

Stool samples

Toxigenic *C. difficile* PCR testing – Requires ID approval

Clostridioides (Clostridium) difficile Antigen/Toxin Assay [1404221636] Stool	Final result	Component C. diff GDH C. DIFFICILE TOXIN	Value Positive Negative

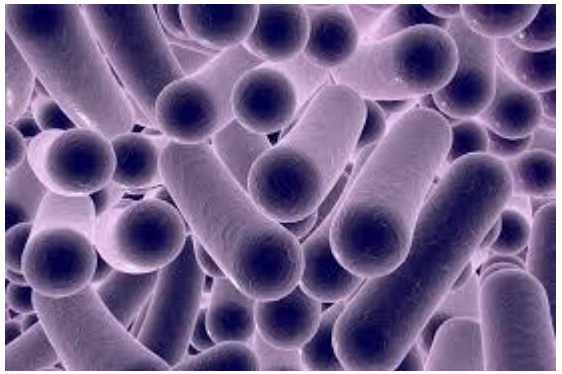
A message from BWH Infectious Diseases:
Toxin Negative, Antigen Positive for C.difficile: Treatment usually not indicated (see below).
The C.difficile antigen test does not distinguish between asymptomatic colonization and clinical disease. The negative toxin assay makes active disease unlikely

C. DIFFICILE PCR [1406799980] (Abnormal)	Edited Result - FINAL	Component C.DIFFICILE PCR	Value POSITIVE for TOXIGENIC C.DIFFICILE ! NOTIFIED RN BM485 06/22/2024 @1401

If you wish to get a PCR please call the Clostridium difficile Approval pager (30880) unless ID has been consulted, in which case you can discuss with the ID

C. DIFFICILE PCR [1223467835]	Final result	Component C.DIFFICILE PCR	Value NEGATIVE for TOXIGENIC C.DIFFICILE

Non-toxigenic *C. difficile* colonization may be protective against toxigenic *C. difficile*



ARTICLES

Primary symptomless colonisation by *Clostridium difficile* and decreased risk of subsequent diarrhoea

Janet K Shim, Stuart Johnson, Matthew H Samore, Donna Z Bliss, Dale N Gerding

Summary

Background Little is known about whether patients who develop *Clostridium-difficile*-associated diarrhoea (CDAD) are culture-positive or culture-negative before illness. The most important risk factor is antibiotic exposure. We aimed to find

C difficile and development of CDAD are likely to be influenced by several host factors. Previous studies have documented rates of acquisition and rates of CDAD during epidemic and non-epidemic periods from different hospitals.[5,8–10] The proportion of symptom-free *C. difficile* carriers among hospital patients are commonly

Review article

A clinical and epidemiological review of non-toxigenic *Clostridium difficile*

Mukil Natarajan [a], Seth T. Walk [a b], Vincent B. Young [a c], David M. Aronoff [a c]

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https://doi.org/10.1016/j.anaerobe.2013.05.005 Get rights and content

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Evaluation of an Oral Suspension of VP20621, Spores of Nontoxigenic *Clostridium difficile* Strain M3, in Healthy Subjects

Stephen A. Villano,[a] Michael Seiberling,[b] Walter Tatarowicz,[a] Elizabeth Monnot-Chase,[a] and Dale N. Gerding[c]

ViroPharma Incorporated, Exton, Pennsylvania, USA[a]; Covance Clinical Research Unit AG, Basel, Switzerland[b]; and Hines VA Hospital, Hines, Illinois, USA, and Division of Infectious Diseases, Loyola University Chicago Stritch School of Medicine, Maywood, Illinois, USA[c]

Shim JK, et al. Lancet. 1998 Feb 28;351(9103):633-6.
Natarajan M, et al. Anaerobe. 2013 Aug;22:1-5.
Villano SA, et al. Antimicrob Agents Chemother. 2012 Oct;56(10):5224-9.

Take home points!

- Recognizing when susceptibility testing of commensals flora is clinically necessary can be challenging
- Development of ordering algorithms to guide appropriate testing and work-up for certain specimens can reduce laboratory costs and reduce antimicrobial exposure
- Improvement in specimen collection methods and use of novel collection devices may reduce contamination of culture samples

Obj. 3 Identify new and emerging antimicrobial agents against multi-drug resistant organisms

Workshop Scenario #1

Your institution is evaluating cefepime-enmetazobactam for formulary consideration. The infectious diseases and antimicrobial stewardship groups reach out to discuss the process for susceptibility testing.

1. Which rapid diagnostics would prompt susceptibility testing consideration?
2. Would this be a reflex susceptibility test or restrict to request only?
    - If reflex, for all specimens or only specific sources?
    - If restricted, who would be authorized to request?
3. Any other considerations prior to performing susceptibility testing?

Workshop Scenario #2

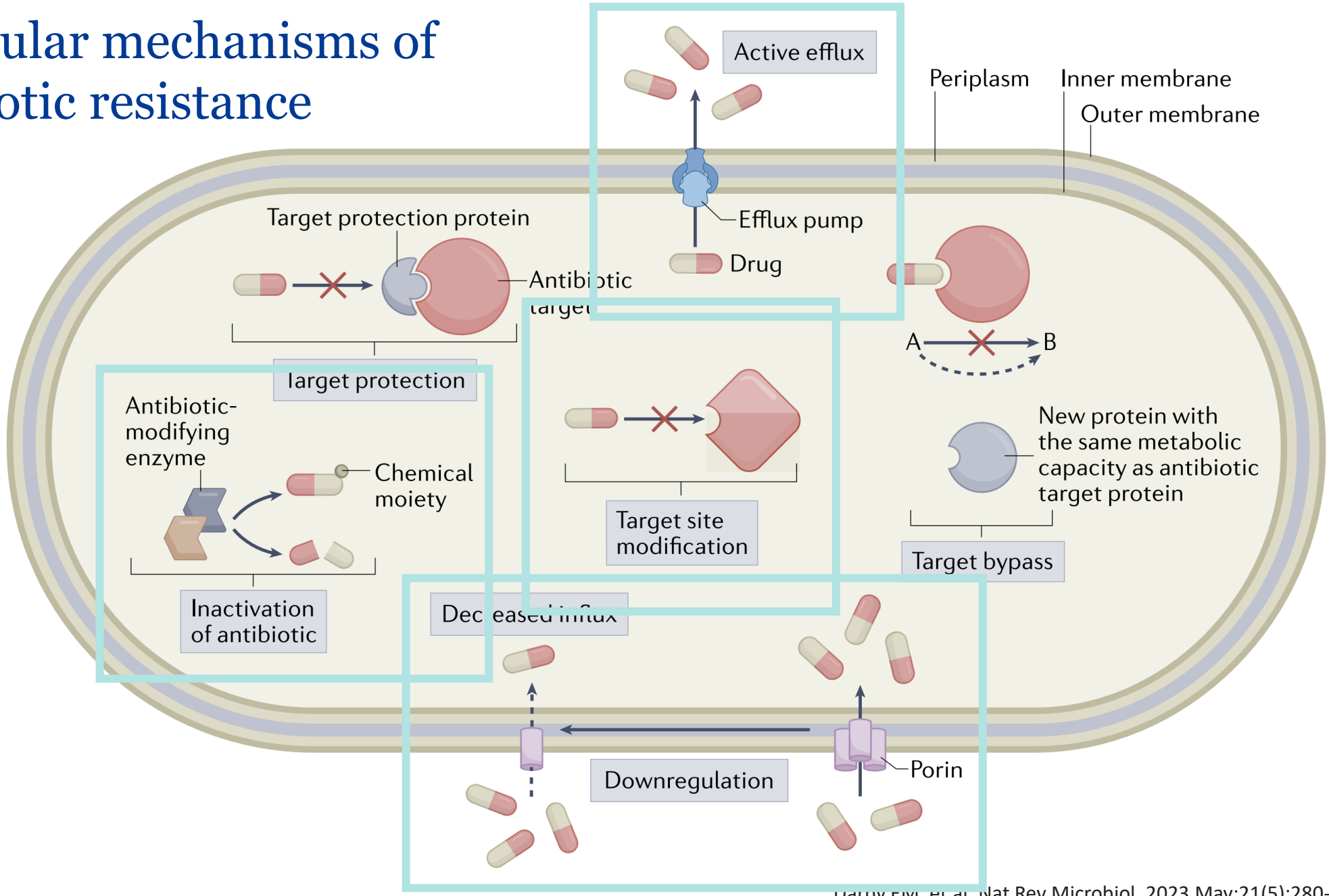
Your institution has recently implemented a multiplex-PCR for blood cultures. How would you tailor your subsequent susceptibility testing based for the following results?

- Positive for KPC-producing *E. coli*
- Positive for NDM-producing *K. pneumoniae*
- Positive for OXA-48-producing *E. cloacae*
- Positive for vanA/B *E. faecium*

Pathogens of Interest

- Extended Spectrum beta-lactamases (ESBLs)
- Carbapenem resistant Enterobacterales (CRE)
  - Ambler class A: KPC
  - Ambler class B: NDM, IMP, VIM
  - Ambler class D: OXA-48
- Difficult-to-treat *Pseudomonas aeruginosa* (DTR-PsA)
- Carbapenem-resistant *Acinetobacter Baumanii* (CRAB)
- *Stenotrophomonas maltophilia*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Vancomycin-resistant *Enterococcus* spp. (VRE)

Molecular mechanisms of antibiotic resistance



Beta-lactamases

Ambler Class	Bush Jacoby Classification	Example Enzyme Genotypes	Resistance Mechanisms
A (serine β-lactamase)	2b	TEM-1, SHV-1 (ESBLs)	Penicillinase, cephalosporinase
	2be	TEM-10, SHV-12, **CTX-M (ESBLs)**	
	2f	**KPC**, IMI	Penicillinase, cephalosporinase carbapenemase
B (metallo-β-lactamase)	3a	**IMP, VIM, NDM**	Penicillinase, cephalosporinase carbapenemase
C (serine β-lactamase)	1	**AmpC**, CMY-2	Penicillinase, cephalosporinase
D (serine β-lactamase)	2de	OXA-11, OXA-15 (ESBLs)	Penicillinase, cephalosporinase
	2df	**OXA-48**, OXA-23, OXA-24/40	Penicillinase, cephalosporinase carbapenemase

Bush K. *Antimicrob Agents Chemother*. 2010 Mar;54(3):969-76.

IDSA Guidance Document

JOURNAL ARTICLE ACCEPTED MANUSCRIPT

Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections FREE

Pranita D Tamma ✉, Emily L Heil, Julie Ann Justo, Amy J Mathers, Michael J Satlin, Robert A Bonomo

Clinical Infectious Diseases, ciae403, https://doi.org/10.1093/cid/ciae403

Published: 07 August 2024 **Article history** ▾

Tamma PD et al, *Clin Infect Dis*. 2024 Aug 7:ciae403.

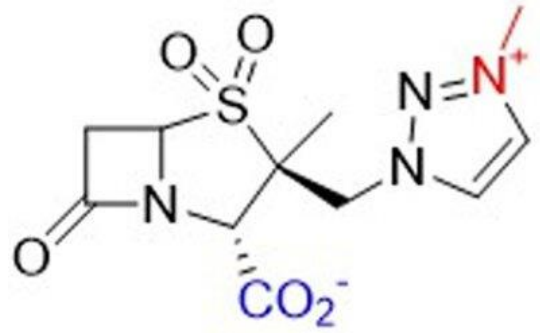
Novel Antimicrobial Agents

Cefepime-enmatazobactam

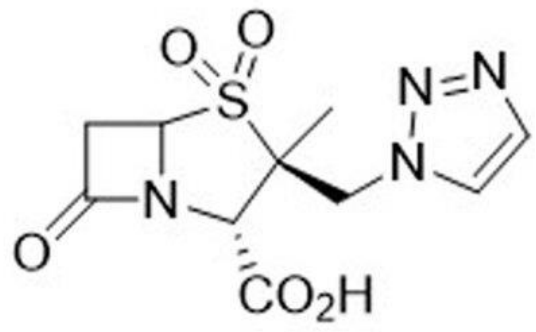
Novel mechanism: methyl group of triazole moiety improves cell penetration

Place in therapy

- Active against Ambler class A ESBLS
- Superior to piperacillin-tazobactam for complicated urinary tract infections
- Potential alternative for severe ESBL infections
- Not available for clinical use yet



Enmetazobactam



Tazobactam

Papp-Wallace KM et al *Antimicrob Agents Chemother*. 2019 Apr 25;63(5):e00105-19
Morrissey I et al *Antimicrob Agents Chemother*. 2019 Jun 24;63(7):e00514-19
Kaye KD et al *JAMA*. 2022 Oct 4;328(13):1304-1314

Enmatazobactam (AA101) *In Vitro* Activity

β-lactamase (classification) (amino acid substitutions present)	FEP	FEP-AAI101 (4 µg/ml)	FEP-AAI101 (8 µg/ml)	TZP (4 µg/ml)	PIP-AAI101 (4 µg/ml)	PIP-AAI101 (8 µg/ml)	IPM	MEM
E. coli DH10B	≤ 0.06	≤ 0.06	≤ 0.06	2	2	2	0.25	≤ 0.06
Class A								
SHV-1 (penicillinase)	2	0.25	≤ 0.06	> 256	16	8	0.25	≤ 0.06
SHV-2 (ESBL) (G238S)	4	≤ 0.06	0.12	32	4	4	0.25	≤ 0.06
SHV-5 (ESBL) (G238S, E240K)	8	≤ 0.06	≤ 0.06	256	4	4	0.25	≤ 0.06
SHV-7 (ESBL) (I8F, R43S, G238S, E240K)	8	≤ 0.06	≤ 0.06	32	4	4	0.25	≤ 0.06
SHV-8 (ESBL) (D179N)	2	≤ 0.06	≤ 0.06	2	2	2	0.25	≤ 0.06
SHV-10 (IR) (S130G)	≤ 0.06	≤ 0.06	≤ 0.06	> 256	> 256	256	0.25	≤ 0.06
SHV-14 (penicillinase) (I8F, R43S)	0.25	≤ 0.06	≤ 0.06	> 256	4	4	0.25	≤ 0.06
SHV-26 (penicillinase) (A187T)	0.25	≤ 0.06	≤ 0.06	> 256	4	4	0.25	≤ 0.06
SHV-30 (ESBL) (I8F, R43S, G238S)	2	0.12	0.12	32	2	2	0.25	≤ 0.06
SHV-49 (IR) (M69I)	≤ 0.06	≤ 0.06	≤ 0.06	> 256	> 256	128	0.25	≤ 0.06
SHV-84 (IR) (K234R)	0.12	≤ 0.06	≤ 0.06	8	8	8	0.25	≤ 0.06
SHV-102 (ESBL) (G238A)	16	0.12	≤ 0.06	> 256	8	2	0.25	≤ 0.06
SHV-106 (ESBL) (I8F, G238S)	4	≤ 0.06	≤ 0.06	16	2	2	0.25	≤ 0.06
SHV-120 (ESBL) (E240K)	0.25	≤ 0.06	≤ 0.06	> 256	16	8	0.25	≤ 0.06
SHV-129 (ESBL) (G238S, E240K, R275L, N276D)	16	≤ 0.06	≤ 0.06	128	4	2	0.25	≤ 0.06
SHV-141 (ESBL) (R43S, G238S)	0.25	≤ 0.06	≤ 0.06	2	2	2	0.12	≤ 0.06
SHV-154 (ESBL) (R43S, G238S, E240K)	8	≤ 0.06	≤ 0.06	4	4	4	0.25	≤ 0.06
SHV-161 (penicillinase) (R43S)	0.5	≤ 0.06	≤ 0.06	> 256	8	4	0.25	≤ 0.06
TEM-10 (ESBL) (R164S, E240K)	4	≤ 0.06	≤ 0.06	4	4	4	0.25	≤ 0.06
TEM-26 (ESBL) (E104K, R164S)	0.5	≤ 0.06	≤ 0.06	2	2	2	0.12	≤ 0.06
TEM-30 (IR) (R244S)	≤ 0.06	≤ 0.06	≤ 0.06	256	64	16	0.25	≤ 0.06
CTX-M-14 (ESBL)	8	≤ 0.06	0.12	2	2	2	0.12	≤ 0.06
CTX-M-15 (ESBL)	32	≤ 0.06	≤ 0.06	2	2	2	0.25	≤ 0.06
KPC-2 (carbapenemase)	4	0.12	0.12	256	16	8	4	2
KPC-3 (carbapenemase)	4	0.25	≤ 0.06	256	32	8	2	0.5

Papp-Wallace KM et al *Antimicrob Agents Chemother*. 2019 Apr 25;63(5):e00105-19

Vitek 2 Error and ESBL

- 304 ESBL *E. coli* clinical isolates
- Compared Vitek 2 vs broth-microdilution for cefepime susceptibility breakpoints
- Sensitivity, specificity, and positive and negative predictive value
  - MIC 8: 94.9%,61.2%,72.3%, 91.8%
  - MIC 2: 83.8%, 65.3%, 41%, 93.3%

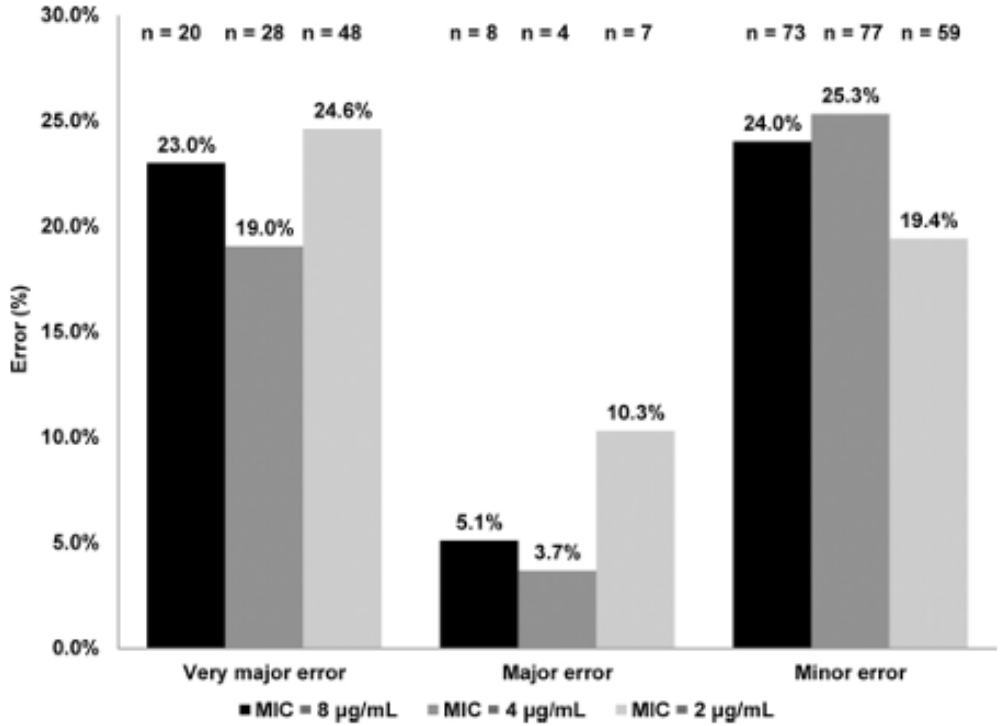


FIG 1 Error rates of Vitek 2 compared to those of agar dilution for cefepime MICs.

Rhodes NJ et al *Antimicrob Agents Chemother*. 2014 Jul;58(7):3757-61

ESBL Treatment Considerations

Urinary tract infections

- Preferred: nitrofurantoin (cystitis), trimethoprim-sulfamethoxazole, fluoroquinolones (cUTI/pyelonephritis)
- Alternative: carbapenems, fosfomycin, single-dose aminoglycosides (cystitis)

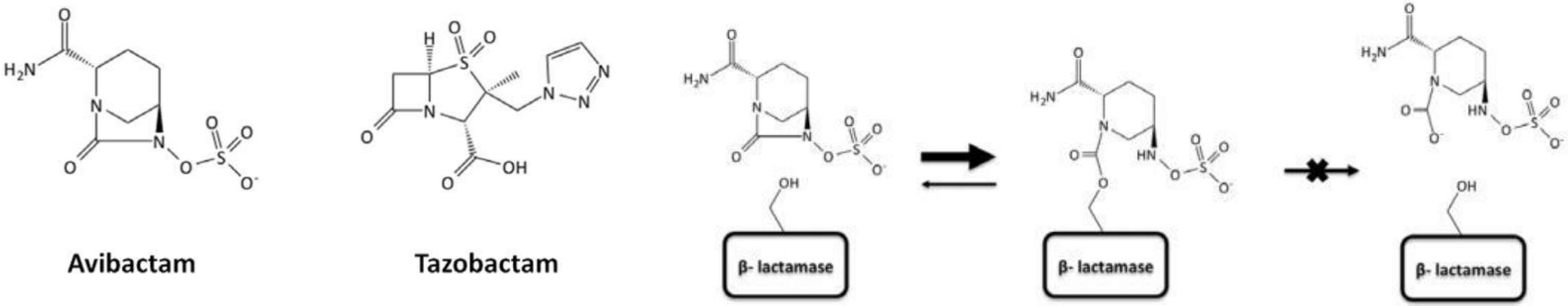
Infections outside the urinary tract

- Preferred: carbapenems
- Oral step-down therapy: trimethoprim-sulfamethoxazole, quinolones
- Not recommended: cefepime, piperacillin-tazobactam, aminoglycosides

Tamma PD et al, *Clin Infect Dis*. 2024 Aug 7:ciae403.

Ceftazidime-avibactam

Novel mechanism: diaza-bicyclo octane structure, recycles original active form



Place in therapy

- Carbapenemase producing Enterobacterales, Ambler class A, C, and D
- Active against DTR-PsA isolates

Zasowski EJ et al *Pharmacotherapy.* 2015 Aug;35(8):755-70

Ceftazidime-avibactam + Aztreonam

Novel mechanism

- Aztreonam stable to zinc groups in metallo-beta-lactamases (MBL)
- Ceftazidime-avibactam inhibits co-produced serine beta-lactamases

Place in therapy

- Metallo-beta-lactamase producing organisms; CRE and *S. maltophilia*
- Confirmatory susceptibility testing remains an operational challenge

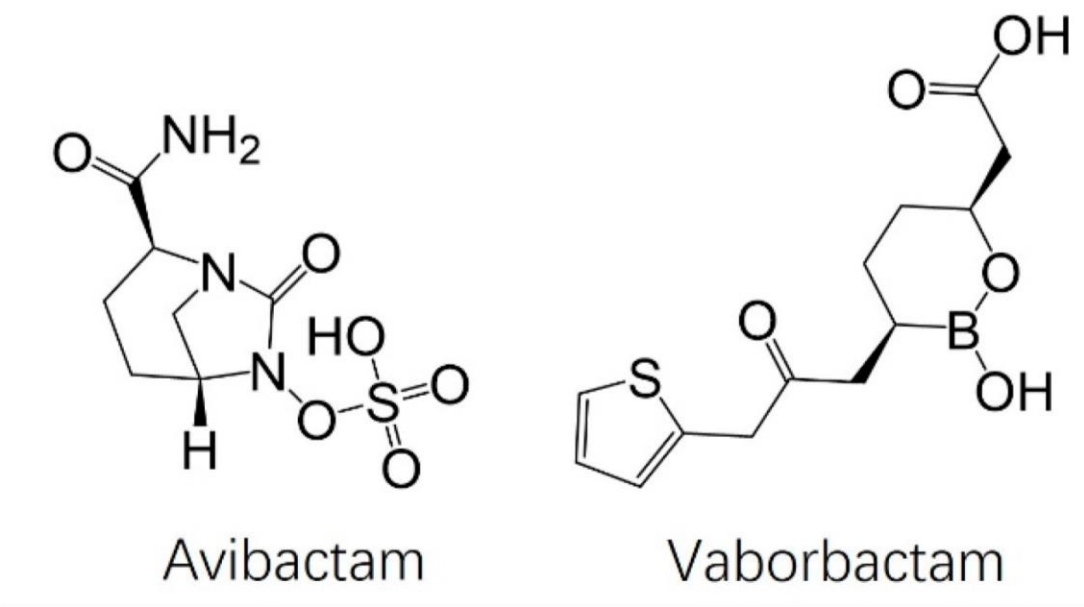
Shields RK et al *Clin Infect Dis.* 2020 Aug 14;71(4):1099-1101

Meropenem-vaborbactam

Novel mechanism: cyclic boronic acid moiety, reversible beta-lactamase inhibition

Place in therapy

- Carbapenemase producing Enterobacterales, Ambler class A and C
- No benefit:
  - DTR-PsA
  - Ambler Class D (Oxa-48)



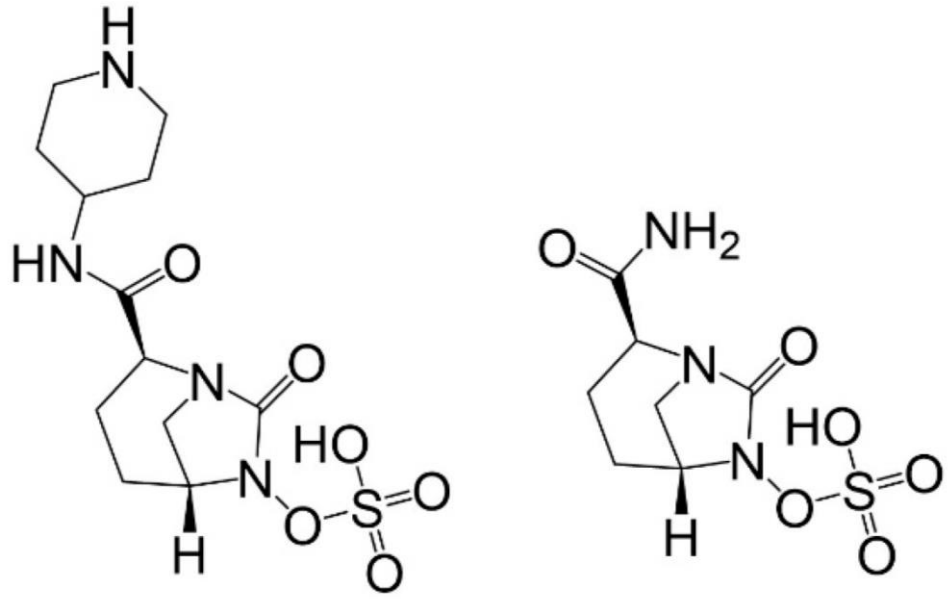
Hillyer T et al *Antibiotics (Basel)*. 2024 May 21;13(6):472
Dhillon S *Drugs*. 2018 Sep;78(13):1383

Imipenem-relebactam

Novel mechanism: diaza-bicyclo octane structure, recycles original active form

Place in therapy

- Carbapenemase producing Enterobacterales, Ambler class A and C
- Active against DTR-PsA isolates
- No benefit: Ambler Class D (Oxa-48)



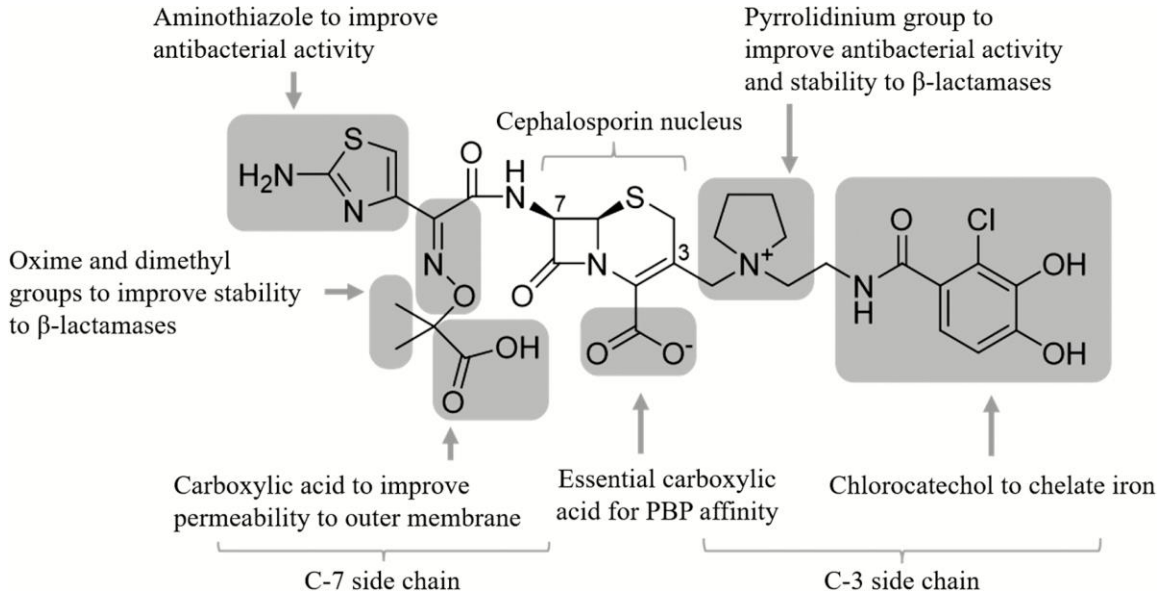
Hillyer T et al *Antibiotics (Basel)*. 2024 May 21;13(6):472
Smith JR et al *Pharmacotherapy*. 2020 Apr;40(4):343-356

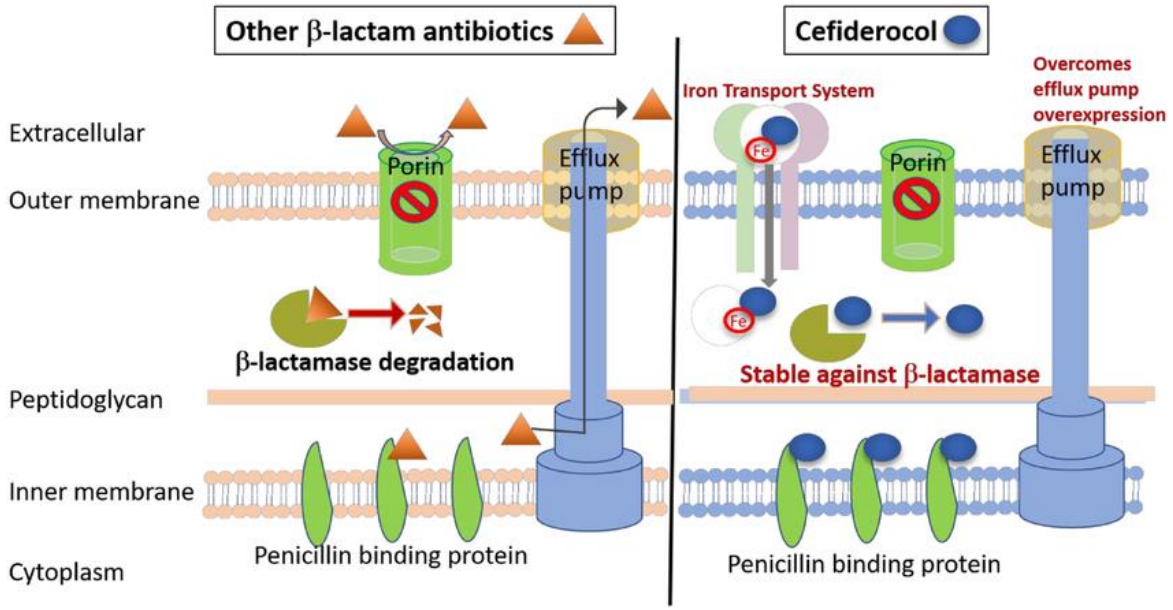
Cefiderocol

Novel mechanism: catechol moiety binds with iron allowing active transport into the periplasmic space

Place in therapy

- Wide spectrum against all Ambler classes, DTR-PsA, CRAB, and *S. maltophilia*
- Clinical data controversial





Sato T et al *Clin Infect Dis*. 2019 Nov 13;69(Suppl 7):S538-S543.

Novel Beta-lactams Indications for CRE

Agent	KPC	NDM	VIM	IMP	OXA-48
Ceftazidime-avibactam	✓				✓
Ceftazidime-avibactam + aztreonam		✓	✓	✓	
Meropenem-vaborbactam	✓				
Imipenem-relebactam	✓				
Cefiderocol	✓	✓	✓	✓	✓

Tamma PD et al, *Clin Infect Dis*. 2024 Aug 7:ciae403.

In Vitro Activity rates

- Review of International Network for Optimal Resistance Monitoring (INFORM) and the SENTRY Antimicrobial Surveillance Programs
- 35,360 Enterobacterales isolates from 2018 – 2022

β-Lactamase	% Susceptible per CLSI		
(no. of isolates)	Ceftazidime-avibactam	Meropenem-vaborbactam	Imipenem-relebactam
KPC producers (179)	97.8	98.3	98.8
MBL producers (38)[a]	2.6	15.8	0.0
OXA-48 type producers (13)	69.2[b]	15.4	0.0
2 carbapenemases (6)	0.0	16.7	0.0
No carbapenemase producer (50)	96.0	86.0	73.9
All CPE producers (224)[b]	82.6	81.7	76.9

[a] Includes NDM (33 isolates), IMP (3), and VIM (2) producers (see Table 3).
[b] All ceftazidime-avibactam resistant isolates (4 of 13) harbored an NDM in addition to the OXA-48–like.

Sader HS et al *Diagn Microbiol Infect Dis*. 2023 Jun;106(2):115945

Ceftazidime-avibactam vs Meropenem Vaborbactam for KPC

- Retrospective review of patients with confirmed CRE outside the urinary tract
- Primary outcomes; 30- and 90-day mortality, adverse events (AE), 90-day CRE infection recurrence, and development of resistance

	Ceftazidime-avibactam group (*n* = 105)	Meropenem-vaborbactam group (n = 26)	*P* value
No. of clinical successes[b] (%)	65 (61.9)	18 (69.2)	0.49
No. of failures to resolve signs and symptoms of infection (%)	4 (3.8)	1 (3.8)	1.0
Failure to sterilize blood cultures within 7 days of treatment initiation [no. of failures/no. of bacteremias (%)]	1/44 (2.3)	1/9 (11.1)	0.31
No. of 30-day mortalities (%)	20 (19.1)	3 (11.5)	0.57
No. of 90-day mortalities (%)	30 (28.6)	7 (26.9)	0.48
Median length of hospital stay[c] (days) (IQR)	15.3 (9.3–28.5)	15.6 (9.5–33.1)	0.99
Median length of ICU stay (days) (IQR)	15.0 (5.0–32.0)	12.0 (5.0–22.0)	0.53
No. of recurrences of CRE infection (%)	15 (14.3)	3 (11.5)	1.0
No. of increases in study drug MIC in mg/liter (%)	6 (40.0)	0	0.51
No. of emergences of study drug resistance (%)	3 (20.0)	0	1.0

Ackley R et al *Antimicrob Agents Chemother*. 2020 Apr 21;64(5):e02313-19

CRE Treatment Considerations

Urinary tract infection: non-beta-lactams as described in ESBL

Non-carbapenemase producing

- Preferred: meropenem, imipenem if susceptible (MIC ≤1) via prolonged infusion
- Alternative: ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam

Carbapenemase producing

- KPC: meropenem-vaborbactam, ceftazidime-avibactam, imipenem-relebactam, cefiderocol (alternative)
- MBL: ceftazidime-avibactam + aztreonam, cefiderocol
- OXA-48: ceftazidime-avibactam, cefiderocol (alternative)

Tamma PD et al, *Clin Infect Dis*. 2024 Aug 7:ciae403.

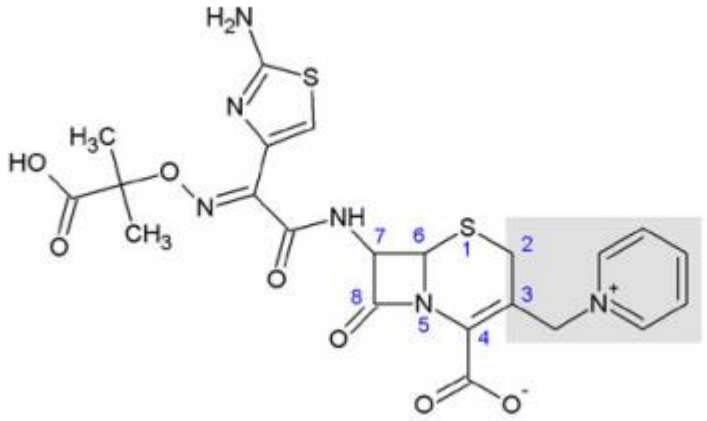
Ceftolozane-tazobactam

Novel mechanism: R-2 side chain at the 3’ position improves pseudomonal activity

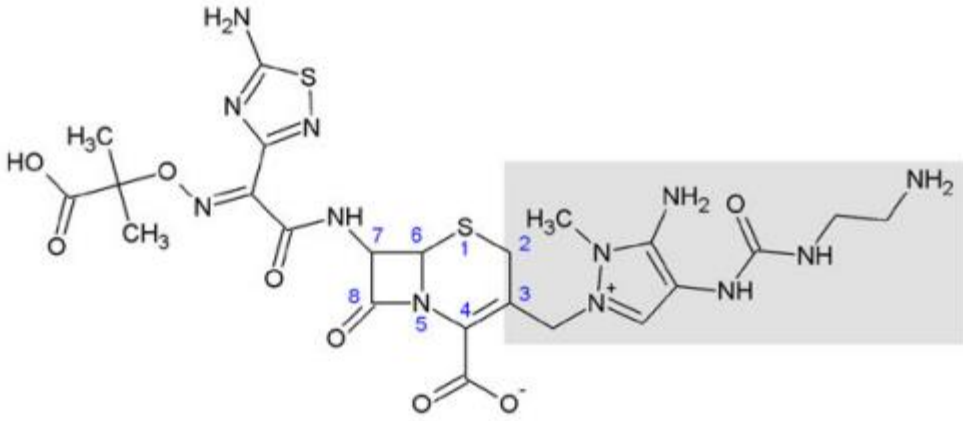
Place in therapy

- Treatment of choice for DTR-PsA
- Activity against ESBL Enterobacterales

Ceftazidime



Ceftolozane



Zhanel GG et al *Drugs*. 2014 Jan;74(1):31-51.
Bassetti M et al *Open Forum Infect Dis*. 2020 Apr 21;7(5):ofaa139

Ceftolozane-tazobactam vs ceftazidime-avibactam for Multi-drug-resistant *P. aeruginosa*

- Retrospective review of patients with MDR *P. aeruginosa* bacteremia or pneumonia
- Clinical success at 30-days

All patients (n = 420)	**Ceftolozane/tazobactam N (%)**	**Ceftazidime/avibactam N (%)**	**Odds Ratio (OR) (95% CI)**	**Adjusted OR[1] (95% CI)**
Clinical success	128 (61)	109 (52)	1.50 (1.00 – 2.26)	1.97 (1.10 – 3.53)
30-day mortality	48 (23)	50 (24)	0.94 (0.59 – 1.51)	0.88 (0.46 – 1.67)
90-day mortality	79 (38)	77 (37)	1.04 (0.70 – 1.56)	1.08 (0.63 – 1.83)
Recurrence within 30 days	31 (15)	44 (21)	0.65 (0.39 – 1.09)	0.51 (0.26 – 1.01)
Recurrence within 90 days	53 (25)	65 (31)	0.73 (0.47 – 1.15)	0.59 (0.33 – 1.07)
Emergence of resistance[2]	38 (22)	40 (23)	0.96 (0.58 – 1.60)	0.92 (0.54 – 1.57)
Pneumonia subgroup (n = 350)	**Ceftolozane/tazobactam N (%)**	**Ceftazidime/avibactam N (%)**	**Odds Ratio (OR) (95% CI)**	**Adjusted OR[1] (95% CI)**
Clinical success	110 (63)	89 (51)	1.68 (1.08 – 2.62)	2.23 (1.17 – 4.26)
30-day mortality	39 (22)	41 (23)	0.93 (0.56 – 1.56)	1.00 (0.50 – 1.63)
90-day mortality	59 (34)	66 (38)	0.84 (0.55 – 1.30)	0.91 (0.51 – 1.63)
Recurrence within 30 days	26 (15)	40 (23)	0.58 (0.33 – 1.01)	0.47 (0.22 – 1.01)
Recurrence within 90 days	45 (26)	61 (35)	0.62 (0.38 – 1.01)	0.50 (0.26 – 0.96)
Emergence of resistance[2]	30 (21)	37 (26)	0.78 (0.45 – 1.35)	0.73 (0.41 – 1.31)

https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4891722

DTR-PsA Treatment Considerations

Definition: resistant to ≥3 of following classes – penicillins, cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems

Treatment options

- Preferred: ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-relebactam
- Alternative: cefiderocol (preferred if MBL identified), tobramycin/amikacin (urinary tract only)

Tamma PD et al, *Clin Infect Dis*. 2024 Aug 7:ciae403.

Sulbactam-durlobactam

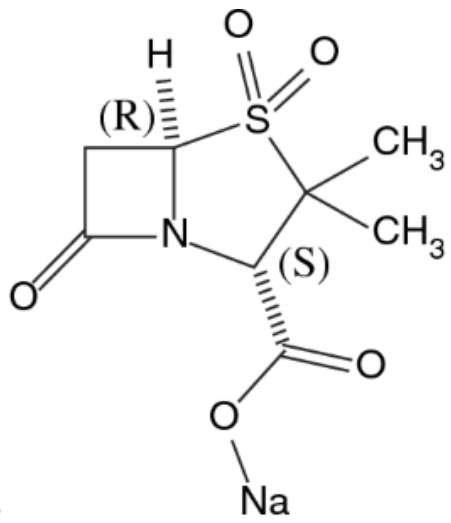
Mechanism

- Sulbactam: beta-lactamase with inhibition of penicillin-binding protein 2 (PBP2)
- Durlobactam: diaza-bicyclo octane structure, recycles original active form

Place in therapy

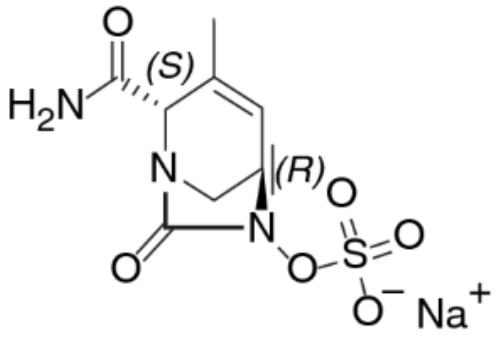
- Active against MDR *A. baumannii*
- First line agent against CRAB

Sulbactam



a

Durlobactam



b

Keam SJ *Drugs*. 2023 Sep;83(13):1245-1252
Papp-Wallace KM et al *Clin Infect Dis*. 2023 May 1;76(Suppl 2):S194-S201

Ampicillin-sulbactam Susceptibility Errors

- Review of eight *Acinetobacter* spp. isolates across 48 centers
- Highest discrepancies; Etest (18.5%) Sensititre (14.3%), Vitek 2 (14.3%)
- Unacceptable error seen with ampicillin-sulbactam using CLSI breakpoints

	Discrepancies (%)[a]		mE (%)		ME (%)		VME (%)	
Antimicrobial agent	CLSI	EUCAST	CLSI	EUCAST	CLSI	EUCAST	CLSI	EUCAST
Piperacillin/tazobactam	2.6	0.0	85.7	0.0	0.0	0.0	14.3	0.0
Ampicillin/sulbactam	**56.2**[b]	0.0	89.3	0.0	0.0	0.0	10.7	0.0

mE, minor error; ME, major error; VME, very major error.

Fernandez-Cuenca F et al *J Antimicrob Chemother*. 2018 Mar 1;73(3):692-697

CRAB Treatment Considerations

Some experts recommend using combination therapy for severe CRAB infections

Therapy options

- Backbone agent: Sulbactam-durlobactam, high dose ampicillin-sulbactam (27g/day vs 12g/day), cefiderocol
- Second agent (controversial)
  - If using sulbactam-durlobactam: meropenem, imipenem
  - If using ampicillin-sulbactam or cefiderocol: tetracycline analogs, polymyxins

Tamma PD et al, *Clin Infect Dis*. 2024 Aug 7:ciae403.

S. maltophila Treatment Considerations

No novel agents specific for *S. maltophilia* infections

Mild infections

- Can consider monotherapy
- Agents: minocycline, levofloxacin, trimethoprim-sulfamethoxazole

Moderate-severe infections

- Can consider combination therapy per expert opinion
- Ceftazidime-avibactam + aztreonam
- Two of the following: cefiderocol, minocycline, levofloxacin, trimethoprim-sulfamethoxazole

Tamma PD et al, *Clin Infect Dis*. 2024 Aug 7:ciae403.

Novel Beta-lactams Indications

Agent	ESBL	CRE	DTR-PsA	CRAB	*S. maltophilia*
Cefepime-Enmetazobactam	✓				
Ceftazidime-avibactam	✓	✓	✓		
Ceftazidime-avibactam + aztreonam	✓	✓			✓
Meropenem-vaborbactam	✓	✓			
Imipenem-relebactam	✓	✓			
Cefiderocol	✓	✓	✓	✓	✓
Ceftolozane-tazobactam			✓		
Sulbactam-durlobactam				✓	

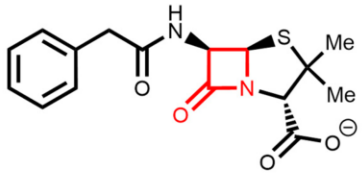
Tamma PD et al, *Clin Infect Dis*. 2024 Aug 7:ciae403.

Ceftibiprole

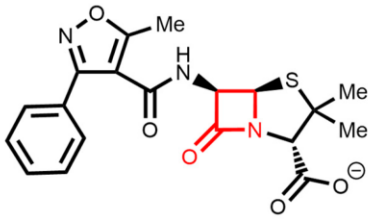
Novel mechanism: vinyl-pyrrolidinone moiety at ‘3 position improves PBP2a affinity

Place in therapy

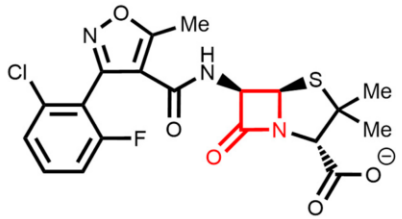
- Alternative to severe *S. aureus* infections
- Positive data for MRSA bacteremia
- Activity against *P. aeruginosa*
- Not yet available in the US



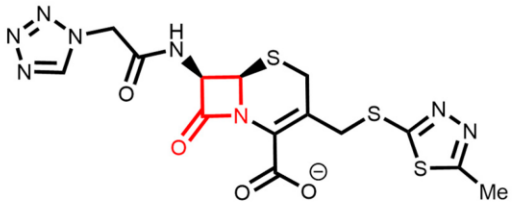
Penicillin G
(1st-generation penicillin)



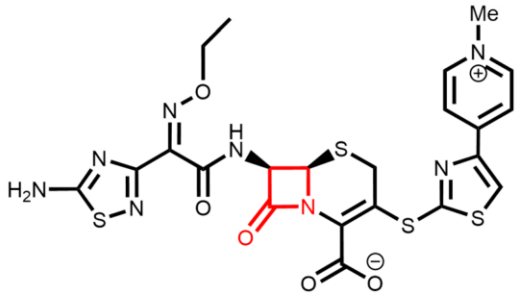
Oxacillin
(2nd-generation penicillin)



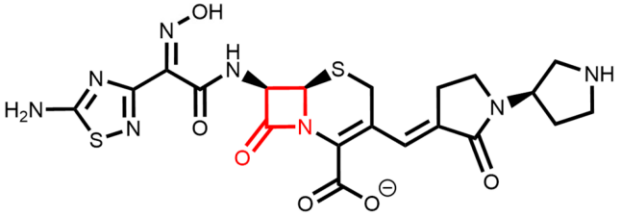
Flucloxacillin
(2nd-generation penicillin)



Cefazolin
(1st-generation cephalosporin)



Ceftaroline
(5th-generation cephalosporin)



Ceftobiprole
(5th-generation cephalosporin)

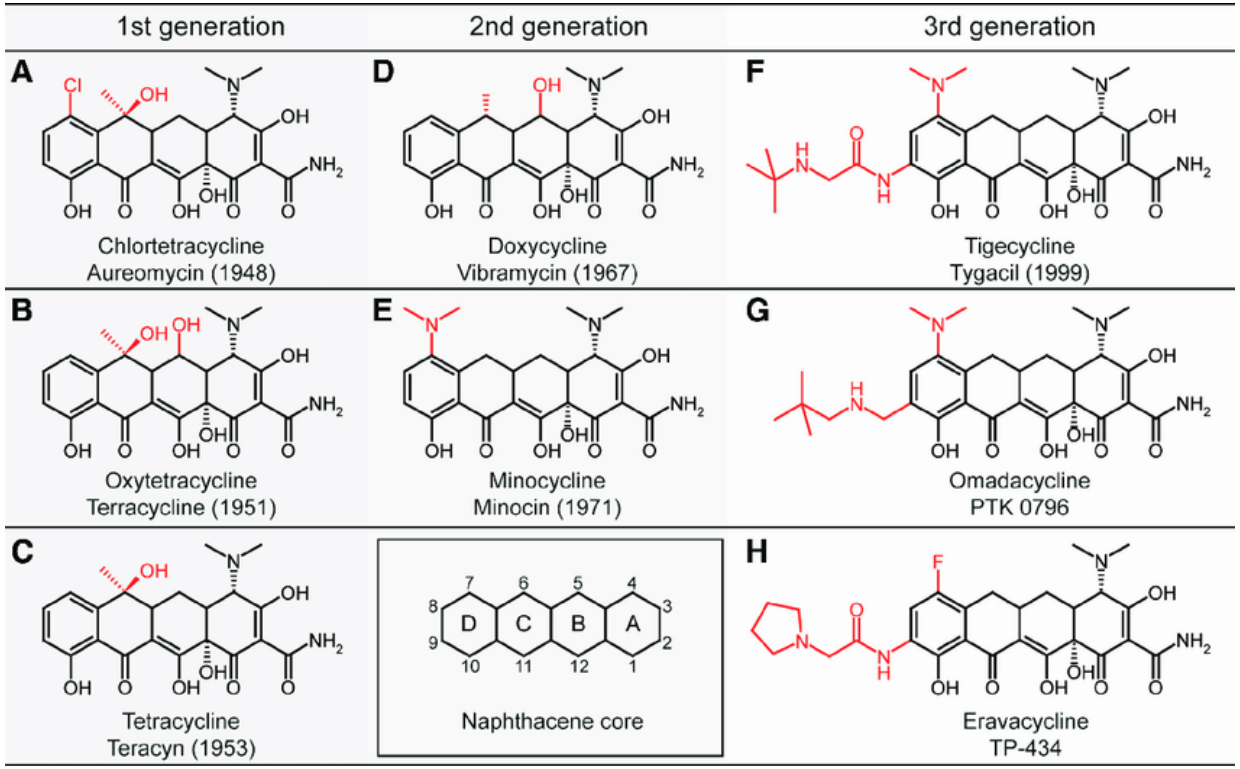
Reygaert MC et al *Clinical Medicine Insights*: Therapeutics. 2011;3.
Lade H et al *Antibiotics (Basel)*. 2023 Aug 24;12(9):1362
Holland TL et al *N Engl J Med*. 2023 Oct 12;389(15):1390-1401

Tetracycline Analogues

Novel Mechanism: modifications to ‘7 and ‘9 positions improve activity against multi-drug-resistant organisms

Place in therapy

- Broad activity against CRE, CRAB, *S. maltophilia*, MRSA, and VRE
- Clinical studies limited to intra-abdominal infections and pulmonary
- Poor serum and urinary concentrations



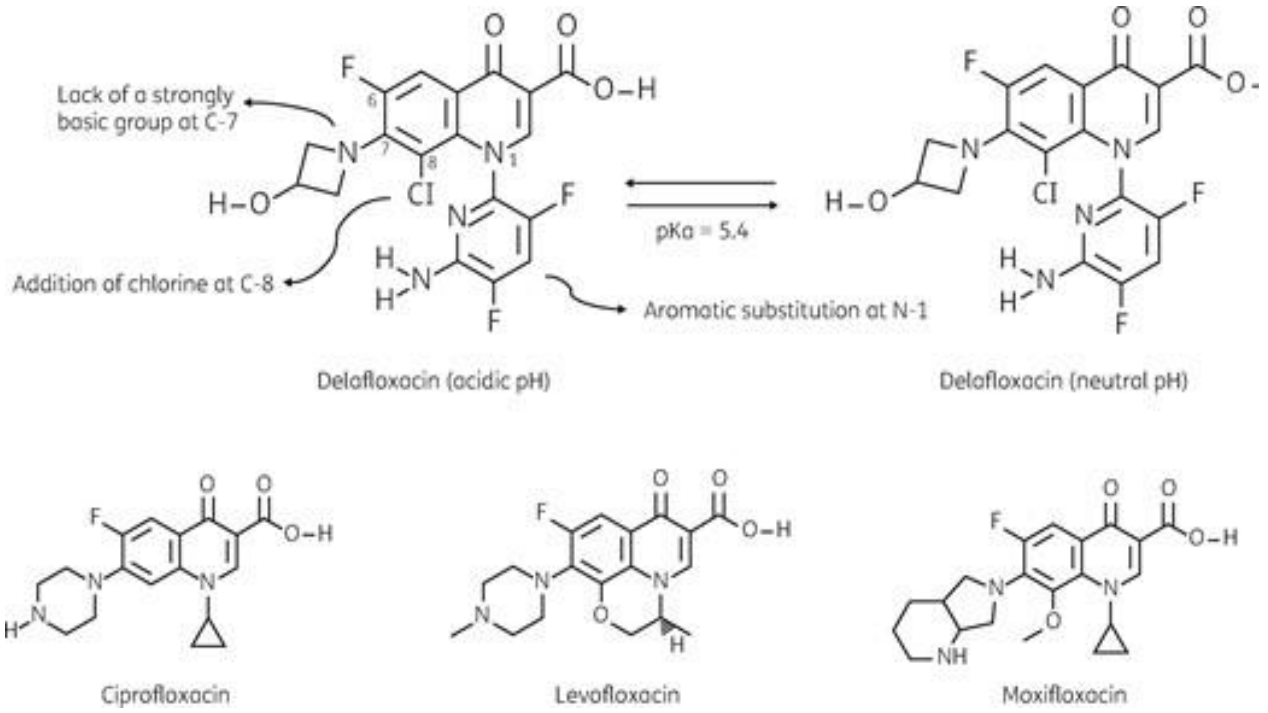
Nguyen F et al Biol Chem. 2014 May;395(5):559-75

Delafloxacin

Mechanism: modifications to core fluoroquinolone ring improves stability and membrane penetration

Place in therapy

- Improved against MRSA
- Minimal improvement against gram-negative
- Primarily used for lower risk polymicrobial infections



Mogle BT et al *J Antimicrob Chemother*. 2018 Jun 1;73(6):1439-1451

MRSA Treatment Considerations

Low risk community infections

- Traditional: doxycycline, trimethoprim-sulfamethoxazole, clindamycin (alternative)
- Novel agents: omadacycline, delafloxacin

High risk and nosocomial infections

- Traditional: vancomycin, daptomycin, linezolid, ceftaroline (alternative)
- Novel agents: ceftibiprole, tetracycline analogues (not for bacteremia or urinary tract infections)

Source: enter source copy and/or notes in this live text box
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VRE Treatment Considerations

Urinary tract infections

- Preferred uncomplicated cystitis: nitrofurantoin, Fosfomycin
- Alternatives and complicated UTI: linezolid, daptomycin

Systemic infections

- Traditional: daptomycin, linezolid, oritavancin (alternative)
- Novel agents: tetracycline analogues

Source: enter source copy and/or notes in this live text box
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Non-beta-lactam Novel Agents Indication

Agent	CRE	ESBL	CRAB	*S. maltophilia*	MRSA	VRE
Ceftibiprole					✓	
Eravacycline	✓	✓	✓	✓	✓	✓
Tigecycline	✓	✓	✓	✓	✓	✓
Omadacycline					✓	✓
Delafloxacin					✓	

Tamma PD et al, *Clin Infect Dis*. 2024 Aug 7:ciae403.

Pipeline Antimicrobial Agents

Pipeline Agents Activity

Agent	KPC	NDM	VIM	IMP	OXA-48	CRAB
Aztreonam-avibactam	+	+	+	+	+	-
Cefepime-taniborbactam	+	+	+	+	+	+
Ceftibuten-ledaborbactam	+	-	-	-	+	-
Zosurabalpin	-	-	-	-	-	+
Xeruborbactam	+	+	+	+	+	+

Obj. 4 Develop a reflex antimicrobial susceptibility testing algorithm for multi-drug-resistant organisms

Workshop Scenario #1

Your institution is evaluating cefepime-enmetazobactam for formulary consideration. The infectious diseases and antimicrobial stewardship groups reach out to discuss the process for susceptibility testing.

1. Which rapid diagnostics would prompt susceptibility testing consideration?
2. Would this be a reflex susceptibility test or restrict to request only?
    - If reflex, for all specimens or only specific sources?
    - If restricted, who would be authorized to request?
3. Any other considerations prior to performing susceptibility testing?

Workshop Scenario #2

Your institution has recently implemented a multiplex-PCR for blood cultures. How would you tailor your subsequent susceptibility testing based for the following results?

- Positive for KPC producing *E. coli*
- Positive for NDM producing *K. pneumonia*
- Positive for OXA-48 producing *E. cloacae*
- Positive for vanA/B *E. faecium*

Open Discussion

- Experience implementing new rapid diagnostic tests
  - What worked well and what could have been improved?
  - Coordination with other stakeholders?
- Process for commensal organism workups
  - How are results of potential contaminants reported in the record?
  - Which sources are worked up or not worked up?
- Presenting testing results to clinical teams
  - Cascade reporting?
  - Certain susceptibilities hidden from the general clinicians?
- What laboratory stewardship process do you have in place for novel or expensive tests?

Questions?


Mass General Brigham

Supplemental Slides

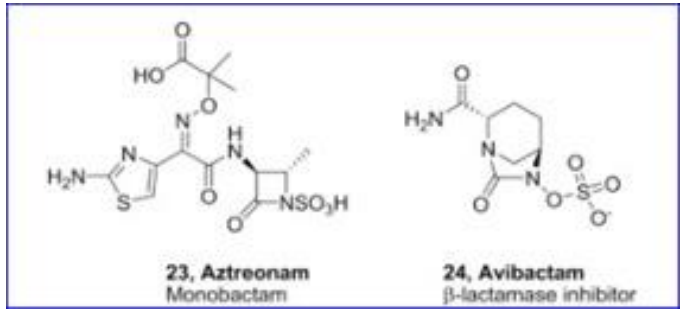
Aztreonam-avibactam

Novel mechanism

- Aztreonam stable to zinc groups in metallo-beta-lactamases (MBL)
- Ceftazidime-avibactam inhibits co-produced serine beta-lactamases

Potential place in therapy

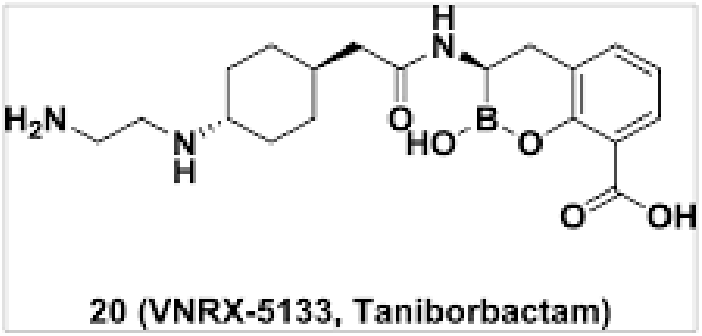
- Metallo-beta-lactamase producing organisms; CRE and *S. maltophilia*
- Ceftazidime component may improve effect



Mauri C et al *Antibiotics (Basel)*. 2021 Aug 20;10(8):1012
https://www.chemdiv.com/company/media/pharma-news/2024/pfizer-s-antibiotic-combination-receives-ec-approval-to-treat-multidrug-resistant-infections/

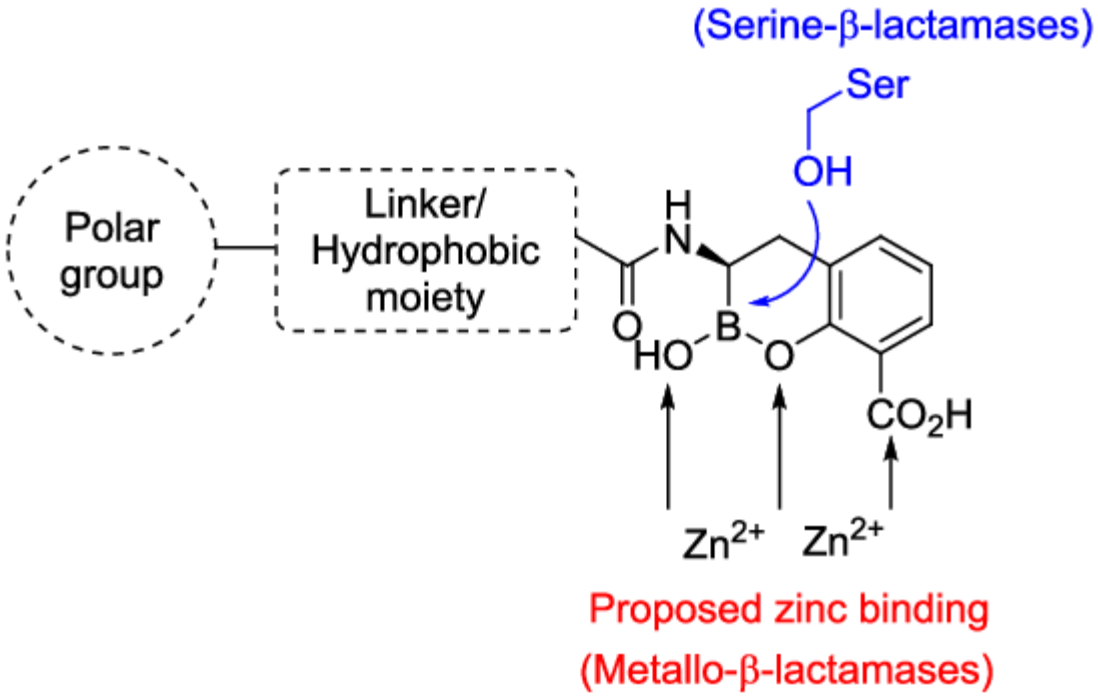
Cefepime-taniborbactam

Novel Mechanism: cyclic boronate group provides increased stability



Potential place in therapy

- Activity against serine and metallo-beta-lactamase
- Restores activity against carbapenemase producing Enterobacterales
- Potential activity against DTR-PsA, CRAB, *S. maltophilia*



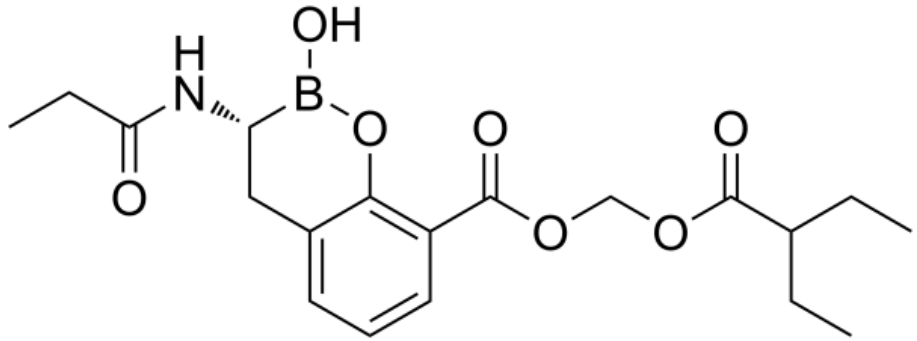
Liu B et al *J Med Chem*. 2020 Mar 26;63(6):2789-2801

Ceftibuten-ledaborbactam

Novel Mechanism: cyclic boronate group provides increased stability, prodrug formulation allows for oral absorption

Potential place in therapy

- Activity against serine beta-lactamase, including KPC and OXA-48
- Oral formulation, being developed with outpatient use in mind



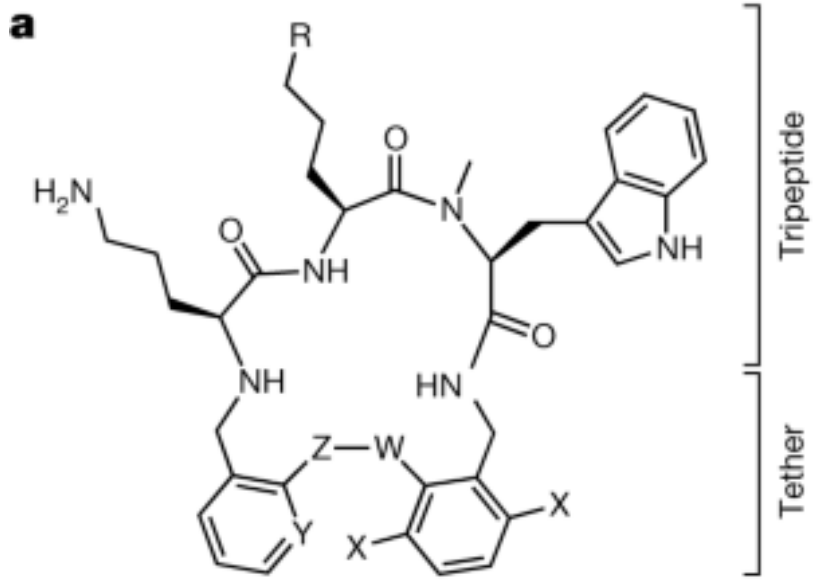
Karlowsky JA et al *Antimicrob Agents Chemother.* 2022 Nov 15;66(11):e0093422
J Antimicrob Chemother. 2022 Dec 23;78(1):93-100

Zosurabalpin

Novel Mechanism: tethered macrocyclic peptide, inhibits bacterial lipopolysaccharide transport to cell membrane

Potential place in therapy

- Targeted against *A. baumannii*
- No activity against other organisms



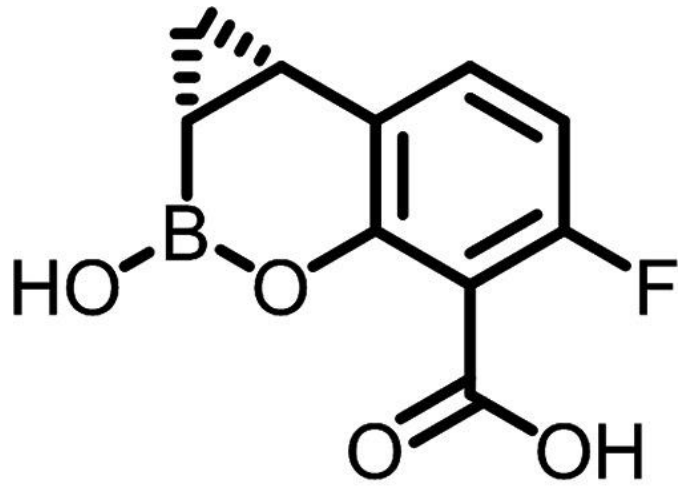
Zampaloni C et al *Nature*. 2024 Jan;625(7995):566-571

Xeruborbactam

Novel mechanisms: cyclic boronate group provides increased stability

Potential place in therapy

- Activity against all Ambler classes
- Will not be co-formulated
- Broad spectrum of activity when mixed-and-matched



Antimicrob Agents Chemother. 2022 Oct 18;66(10):e0087922