INFECTIOUS DISEASES SOCIETY OF AMERICA 2024 GUIDANCE ON THE TREATMENT OF ANTIMICROBIAL-RESISTANT GRAM-NEGATIVE INFECTIONS

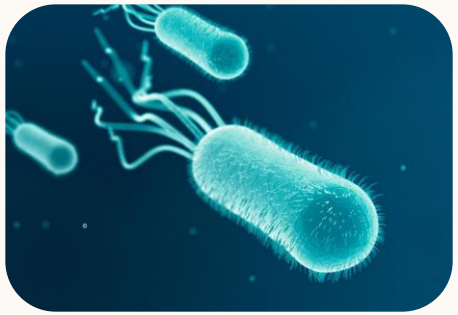
INTRODUCTION

- **Overview:** Importance of addressing antimicrobial-resistant (AMR) infections
- **Statistics:** 1.3 million global deaths (2019), 2.8 million infections, and 35,000 deaths annually in the U.S. (2012-2017)
- **Scope:** Focus on U.S. treatment of ESBL-E, AmpC-E, CRE, DTR P. aeruginosa, CRAB, and S. maltophilia

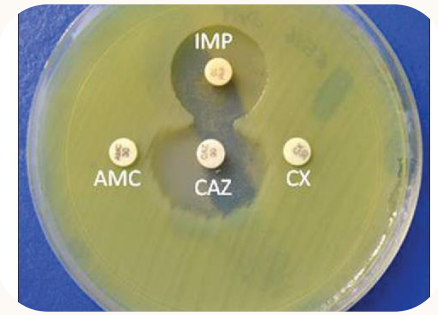
METHODOLOGY

- **Panel:** Six infectious disease specialists
- **Focus:** Preferred and alternative treatment approaches, assuming known causative organism and antibiotic susceptibility
- **Empiric Treatment:** General suggestions, not detailed

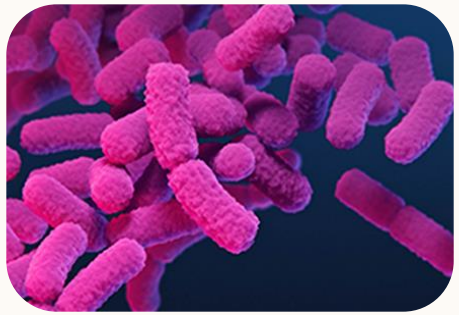
KEY PATHOGENS



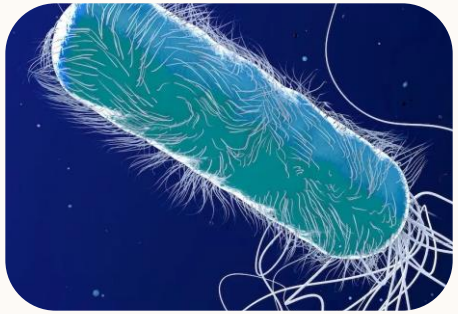
ESBL-E



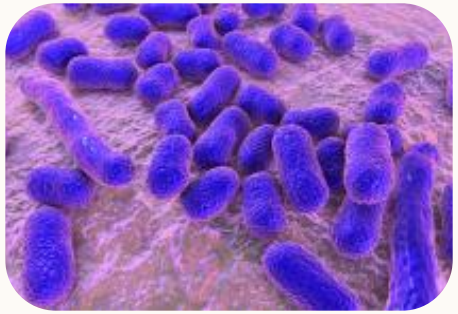
AmpC-E



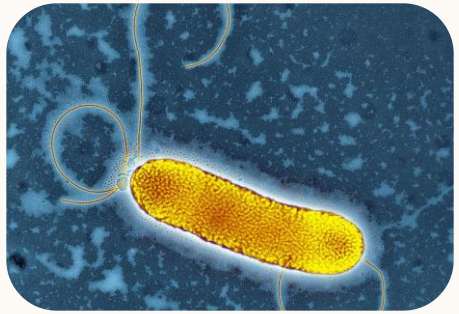
CRE



DTR P. aeruginosa



CRAB



S. maltophilia

UPDATES FROM 2023 GUIDANCE

- ESBL-E: New data on fosfomycin, amoxicillin-clavulanic acid, and piperacillin-tazobactam
- AmpC-E: Clarification on intrinsic resistance and updated recommendations for cefepime
- CRE: Increasing prevalence of metallo-beta-lactamases, new testing methods
- DTR P. aeruginosa: New recommendations for traditional agents and alternative options
- CRAB: New preferred agent sulbactam-durlobactam
- S. maltophilia: Updated agent preferences and testing methods

ESBL-E

- Fosfomycin continues to not be suggested for pyelonephritis and complicated urinary tract infections (cUTI); however, the uncertainty of the additive benefit of additional doses of oral fosfomycin for these indications was highlighted in light of recent clinical data.
- Amoxicillin-clavulanic acid continues to not be a preferred agent for uncomplicated ESBL-producing cystitis; however, it was acknowledged that there may be occasions where it is prescribed if resistance or toxicities preclude the use of alternative oral antibiotics, and **there is a preference to avoid IV antibiotics**. It is advised that caution be given to patients about the potential increased risk of recurrent infection if amoxicillin clavulanic acid is administered for this indication.

ESBL-E

- Additional details on the mechanistic reasons why piperacillin-tazobactam is not anticipated to be effective for ESBL-E infections are provided.
- Piperacillin-tazobactam continues to not be preferred for the treatment of pyelonephritis and cUTI; however, it was acknowledged that if piperacillin-tazobactam was initiated for pyelonephritis or cUTI caused and clinical improvement occurs, the decision to continue piperacillin-tazobactam should be made with the understanding that theoretically there may be an increased risk for microbiological failure with this approach.
- A re-review of available data and newer data indicate that ceftolozane-tazobactam is likely to be effective against ESBL-E; however, it suggested that this agent be preserved for the treatment of DTR P. aeruginosa or polymicrobial infections (e.g., both DTR P. aeruginosa and ESBL-E)

AMPC-E

- The term “moderate to high risk” clinically significant AmpC production was replaced with “moderate risk” throughout
- It was clarified that even without upregulation of AmpC production, basal production of AmpC βlactamases by organisms with inducible ampC expression leads to intrinsic resistance to ampicillin, amoxicillin-clavulanate, ampicillin-sulbactam, and first- and second-generation cephalosporins.
- The suggestion that cefepime is not advised for Enterobacter cloacae, Citrobacter freundii, and Klebsiella aerogenes with cefepime MICs of 4-8 µg/mL because of concerns for an increased risk of ESBL production in this cefepime MIC range was removed in light of newer data and a re review of existing data.

CRE

- An increase in the prevalence of CRE isolates producing metallo-beta-lactamases (MBL) in the United States (e.g., NDM, VIM, IMP) is acknowledged.
- A description of a Clinical and Laboratory Standards Institute (CLSI) endorsed method (i.e., broth disk elution method) to test for activity of the combination of ceftazidime-avibactam and aztreonam for MBL producing Enterobacterales is discussed.
- Dosing suggestions for ceftazidime-avibactam in combination with aztreonam are updated and Supplemental Material. Both agents are suggested to be administered every 8 hours to facilitate simultaneous administration in clinical practice

DTR P. AERUGINOSA

- For infections caused by P. aeruginosa isolates not susceptible to any carbapenem agent but susceptible to traditional β-lactams (e.g., cefepime), administration of a traditional agent as **high-dose extended-infusion therapy** continues to be suggested, although the panel no longer emphasizes the importance of repeating AST on the initial isolate before administration of the traditional agent given the frequency with which this susceptibility profile occurs.
- A new question (i.e., Question 4.2) has been added "Are there differences in percent activity against DTR P. aeruginosa across available β-lactam agents?" Differences in DTR P. aeruginosa susceptibility percentages to the newer β-lactams are described along with regional differences in enzymatic mechanisms of resistance that contribute to some of these differences.
- **Once-daily tobramycin or amikacin** were added as alternative treatment options for pyelonephritis or cUTI caused by DTR P. aeruginosa given the prolonged duration of activity of these agents in the renal cortex and the convenience of once daily dosing.

CRAB

- Sulbactam-durlobactam, in combination with meropenem or imipenem-cilastatin, was added as the preferred agent for the treatment of CRAB infections.
- High-dose ampicillin-sulbactam in combination with at least one other agent has been changed from a preferred to an alternative regimen if sulbactam-durlobactam is not available.
- The suggested dosing of high-dose ampicillin-sulbactam has been adjusted to be 27 grams of ampicillinsulbactam (18 grams ampicillin, 9 grams sulbactam) daily. (pediatric 100mg/kg Q4h ampicillin (150mg/kg Q4h ampicillin-sulbactam)

S. MALTOPHILIA

- Questions have been adjusted to list agents in order of preference (i.e., cefiderocol [with a second agent at least initially], ceftazidime-avibactam and aztreonam, minocycline [with a second agent], TMP-SMX [with a second agent], or levofloxacin [with a second agent].
- A description of a CLSI endorsed method (i.e., broth disk elution method) to test for activity of the combination of ceftazidime-avibactam and aztreonam for S. maltophilia activity is discussed.
- Tigecycline has been removed as a component of combination therapy.
- Updated guidance from the CLSI advising against the testing of ceftazidime for S. maltophilia infections has been added.

DURATION OF THERAPY AND TRANSITIONING TO ORAL THERAPY

Recommendations on durations of therapy are not provided, but clinicians are advised that the **duration of therapy should not differ for infections caused by organisms with resistant phenotypes** compared to infections caused by more susceptible phenotypes

whenever possible, transitioning to oral therapy should be considered (assuming IV therapy was initially prescribed), particularly if the following criteria are met:

1. susceptibility to an appropriate oral agent is demonstrated,
2. the patient is hemodynamically stable,
3. reasonable source control measures have occurred, and
4. concerns about insufficient intestinal absorption are not present

EXTENDED-SPECTRUM B-LACTAMASE-PRODUCING ENTEROBACTERALES

ESBLS

- ESBLs are enzymes that inactivate most penicillins, cephalosporins, and aztreonam. EBSL-E generally remain susceptible to carbapenems.
- ESBLs do not inactivate non-β-lactam agents (e.g., ciprofloxacin, trimethoprim-sulfamethoxazole [TMP-SMX], gentamicin).
  - However, organisms carrying ESBL genes often harbor additional genes or mutationsin genes expanding their resistance to a broad range of antibiotics
  - Any gram-negative organism has the potential to harbor ESBL genes; however, they are most prevalent in Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, and Proteus mirabilis

WHAT ARE PREFERRED ANTIBIOTICS FOR THE TREATMENT OF UNCOMPLICATED CYSTITIS CAUSED BY ESBL-E?

- Nitrofurantoin and TMP-SMX are preferred treatment options for uncomplicated cystitis caused by ESBL-E.
  - Ciprofloxacin, levofloxacin, and carbapenems are alternative agents for uncomplicated cystitis caused by ESBL-E.
  - Although effective, their use is discouraged when nitrofurantoin or TMP-SMX are active.

WHAT ARE PREFERRED ANTIBIOTICS FOR THE TREATMENT OF PYELONEPHRITIS OR CUTI CAUSED BY ESBL-E?

- **TMP-SMX, ciprofloxacin, or levofloxacin** are preferred treatment options for pyelonephritis or cUTIs caused by ESBL-E.
- Ertapenem, meropenem, and imipenem-cilastatin are preferred agents when **resistance or toxicities** preclude the use of TMP-SMX or fluoroquinolones.
- Aminoglycosides are alternative options for the treatment of ESBL-E pyelonephritis or cUTI.
- **Fosfomycin** is not suggested for the treatment of pyelonephritis or cUTI given its limited renal parenchymal concentrations.

WHAT ARE PREFERRED ANTIBIOTICS FOR THE TREATMENT OF INFECTIONS OUTSIDE OF THE URINARY TRACT CAUSED BY ESBL-E?

- Meropenem, imipenem-cilastatin, or ertapenem are preferred forthe treatment of infections outside of the urinary tract caused by ESBL-E.
- For patients who are critically ill and/or experiencing hypoalbuminemia, meropenem or imipenem-cilastatin are the preferred carbapenems.
- After appropriate clinical response is achieved, transitioning to oral TMP-SMX, ciprofloxacin, or levofloxacin should be considered, if susceptibility is demonstrated.

ISTHERE A ROLE FOR PIPERACILLIN-TAZOBACTAM IN THE TREATMENT OF INFECTIONS CAUSED BY ESBLE?

If piperacillin-tazobactam was initiated as empiric therapy for uncomplicated cystitis caused by an organism later identified as an ESBL-E and clinical improvement occurs, no change or extension of antibiotic therapy is necessary.

IS THERE A ROLE FOR CEFEPIME IN THE TREATMENT OF INFECTIONS CAUSED BY ESBL-E?

- If cefepime was initiated as empiric therapy for uncomplicated cystitis caused by an organism later identified as an ESBL-E and clinical improvement occurs, no change or extension of antibiotic therapy is necessary.
- The panel suggests avoiding cefepime for the treatment of pyelonephritis or cUTI. Cefepime is also not suggested for the treatment of infections outside of the urinary tract caused by ESBL-E, even if susceptibility to cefepime is demonstrated.

IS THERE A ROLE FOR THE CEPHAMYCINS IN THE TREATMENT OF INFECTIONS CAUSED BY ESBL-E?

- Cephamycins are not suggested for the treatment of ESBL-E infections until more clinical outcomes data using cefoxitin or cefotetan are available and optimal dosing has been defined

WHAT ISTHE ROLE OF NEWER B-LACTAM-B-LACTAMASE INHIBITOR COMBINATIONS AND CEFIDEROCOL FOR THE TREATMENT OF INFECTIONS CAUSED BY ESBL-E?

- The panel suggests that ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, ceftolozane-tazobactam, and cefiderocol be preferentially reserved for treating infections caused by organisms exhibiting **carbapenem resistance**.

AMPC B-LACTAMASE-PRODUCING ENTEROBACTERALES

AmpC β-lactamases are enzymes that are produced at basal levels by a number of Enterobacterales and glucose non-fermenting gram-negative organisms. Their primary function is to assist with cell wall recycling

AMPC

- Increased AmpC enzyme production resulting from inducible ampC expression can occur in the presence of specific antibiotics and results in sufficient AmpC enzyme in the periplasmic space to increase MICs to certain antibiotics (i.e., ceftriaxone, cefotaxime, ceftazidime, aztreonam, and piperacillin-tazobactam).
- In this scenario, an Enterobacterales isolate that initially tests susceptible to ceftriaxone may exhibit non-susceptibility to this agent after treatment with ceftriaxone is initiated.

WHICH COMMONLY IDENTIFIED ENTEROBACTERALES SPECIES SHOULD BE CONSIDERED AT MODERATE RISK FOR CLINICALLY SIGNIFICANT INDUCIBLE AMPC PRODUCTION?

- the most common Enterobacterales at moderate risk for clinically significant inducible AmpC production:
  - Enterobacter cloacae complex,
  - Klebsiella aerogenes, and
  - Citrobacter freundii

WHAT FEATURES SHOULD BE CONSIDERED IN SELECTING ANTIBIOTICS FOR INFECTIONS CAUSED BY ORGANISMS AT MODERATE RISK OF CLINICALLY SIGNIFICANT AMPC PRODUCTION DUE TO AN INDUCIBLE AMPC GENE?

Several β-lactam antibiotics are at moderate risk of inducing ampC genes. Both the ability to induce ampC genes and the relative stability of the agent against hydrolysis by AmpC should inform antibiotic decision-making.

MODERATE RISK OF INDUCING AMPC GENES

β-lactam antibioticsfall within a spectrum of potential forinducing ampC genes.

- Aminopenicillins(i.e., amoxicillin, ampicillin),
- narrow-spectrum (i.e., first generation) cephalosporins,and
- cephamycins are potent ampC inducers

WHAT IS THE ROLE OF CEFEPIME FOR THE TREATMENT OF INFECTIONS CAUSED BY ENTEROBACTERALES AT MODERATE RISK OF CLINICALLY SIGNIFICANT AMPC PRODUCTION DUE TO AN INDUCIBLE AMPC GENE?

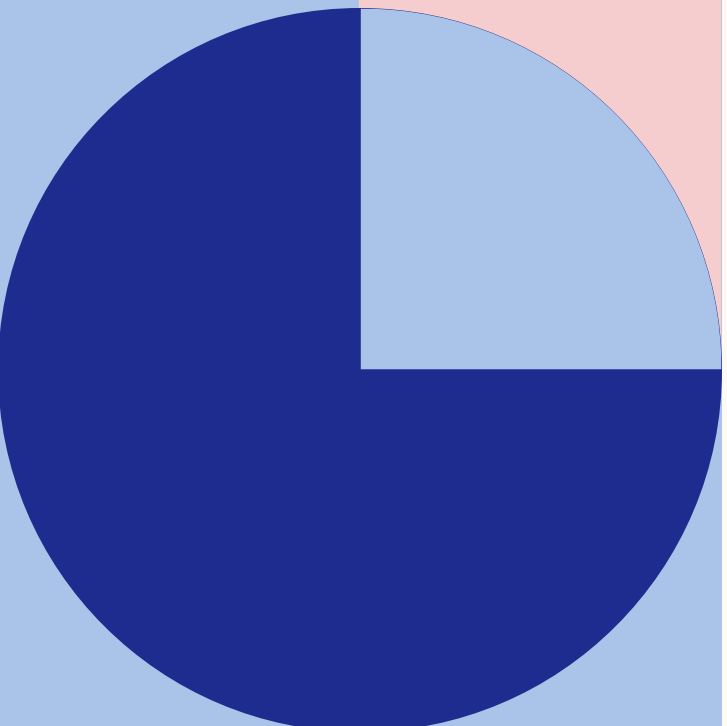
Cefepime is suggested for the treatment of infections caused by organisms at moderate risk of significant AmpC production (i.e., E. cloacae complex, K. aerogenes, and C. freundii)

- Cefepime is an oxyimino-cephalosporin that is relatively stable against AmpC enzymes and that also haslow ampC induction potential 1

WHAT IS THE ROLE OF CEFTRIAXONE FOR THE TREATMENT OF INFECTIONS CAUSED BY ENTEROBACTERALES AT MODERATE RISK OF CLINICALLY SIGNIFICANT AMPC PRODUCTION DUE TO AN INDUCIBLE AMPC GENE?

Ceftriaxone (or cefotaxime or ceftazidime) is not suggested for the treatment of invasive infections caused by organisms at moderate risk of clinically significant AmpC production (e.g., E. cloacae complex, K. aerogenes, and C. freundii).

- Ceftriaxone is reasonable for uncomplicated cystitis caused by these organisms when susceptibility is demonstrated.



WHAT IS THE ROLE OF PIPERACILLIN-TAZOBACTAM FOR THE TREATMENT OF INFECTIONS CAUSED BY ENTEROBACTERALES AT MODERATE RISK OF CLINICALLY SIGNIFICANT AMPC PRODUCTION DUE TO AN INDUCIBLE AMPC GENE?

Piperacillin-tazobactam is not suggested for the treatment of invasive infections caused by Enterobacterales at moderate risk of clinically significant inducible AmpC production.

WHAT ISTHE ROLE OF NEWER B-LACTAM-B-LACTAMASE INHIBITOR COMBINATIONS AND CEFIDEROCOL FOR THE TREATMENT OF INFECTIONS CAUSED BY ENTEROBACTERALES AT MODERATE RISK OF CLINICALLY SIGNIFICANT AMPC PRODUCTION DUE TO AN INDUCIBLE AMPC GENE?

The panel suggests that ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol be preferentially reserved fortreating infections caused by organisms exhibiting carbapenem resistance.
The panel does not suggest the use of ceftolozane-tazobactam as a treatment option for AmpC-E infections.

WHAT IS THE ROLE OF NON-B-LACTAM THERAPY FOR THE TREATMENT OF INFECTIONS CAUSED BY ENTEROBACTERALES AT MODERATE RISK OF CLINICALLY SIGNIFICANT AMPC PRODUCTION DUE TO AN INDUCIBLE AMPC GENE?

- Nitrofurantoin and TMP-SMX are preferred treatment options for uncomplicated cystitis caused by AmpC-E.
- Ciprofloxacin, levofloxacin, or an aminoglycoside (as a single dose) are alternative treatment options for AmpC-E uncomplicated cystitis.
- TMP-SMX, ciprofloxacin, or levofloxacin are preferred treatment options for pyelonephritis or cUTIs caused by AmpC-E.
- Aminoglycosides are alternative options for pyelonephritis or cUTI when resistance or toxicities preclude the use of TMP-SMX or fluoroquinolones.
    - For AmpC-E infections outside of the urinary tract, transitioning from cefepime to oral TMP-SMX, ciprofloxacin, or levofloxacin should be considered, if susceptibility is demonstrated

CARBAPENEM-RESISTANT ENTEROBACTERALES

CRE are defined as members of the Enterobacterales order resistant to at least one carbapenem antibiotic (i.e., ertapenem, meropenem, imipenem, doripenem) or producing a carbapenemase enzyme

A HETEROGENOUS GROUP OF PATHOGENS

- The most common carbapenemases in the United States are K. pneumoniae carbapenemases (KPCs), which are not limited to K. pneumoniae isolates.
- Other carbapenemases include
  - New Delhi metallo-β-lactamases (NDMs),
  - Verona integron-encoded metallo-β-lactamases (VIMs),
  - Imipenem hydrolyzing metallo-β-lactamases (IMPs), and
  - oxacillinases(e.g., OXA-48-like)
- NDM, VIM, and IMP carbapenemases are collectively referred to as metallo-β-lactamases (MBLs)

WHAT ARE PREFERRED ANTIBIOTICS FOR THE TREATMENT OF UNCOMPLICATED CYSTITIS CAUSED BY CRE?

- Nitrofurantoin, TMP-SMX, ciprofloxacin, or levofloxacin are preferred treatment options for uncomplicated cystitis caused by CRE, although the likelihood of susceptibility to any of these agents is low.
- An aminoglycoside (as a single dose), oral fosfomycin (for E. coli only), colistin, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, or cefiderocol, are alternative treatment options for uncomplicated cystitis caused by CRE

WHAT ARE PREFERRED ANTIBIOTICS FOR THE TREATMENT OF PYELONEPHRITIS OR CUTI CAUSED BY CRE?

- TMP-SMX, ciprofloxacin, or levofloxacin are preferred treatment options for pyelonephritis or cUTI caused by CRE, if susceptibility is demonstrated.
- Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are also preferred treatment options for pyelonephritis or cUTIs.
- Aminoglycosides are alternative options for the treatment of pyelonephritis or cUTI caused by CRE.

WHAT ARE THE PREFERRED ANTIBIOTICS FOR THE TREATMENT FOR INFECTIONS CAUSED BY CRE OUTSIDE OF THE URINARY TRACT THAT ARE NOT CARBAPENEMASE PRODUCING?

- For infections caused by Enterobacterales isolates that are NOT carbapenemase producing that exhibit susceptibility to meropenem and imipenem (i.e., MICs ≤1 µg/mL), but are not susceptible to ertapenem (i.e., MICs ≥1 µg/mL), the use of extended-infusion meropenem (or imipenem-cilastatin) is suggested.
- For infections caused by Enterobacterales isolates that are NOT carbapenemase producing and that do not exhibit susceptibility to any carbapenem, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are preferred treatment options.

WHAT ARE THE PREFERRED ANTIBIOTICS FORTHE TREATMENT OF INFECTIONS OUTSIDE OF THE URINARY TRACT CAUSED BY CRE IF KPC PRODUCTION IS PRESENT?

Meropenem-vaborbactam, ceftazidime-avibactam, and imipenem-cilastatinrelebactam are preferred treatment options for KPC-producing Enterobacterales infections.

Cefiderocol is an alternative option

: WHAT ARE THE PREFERRED ANTIBIOTICS FOR THE TREATMENT OF INFECTIONS OUTSIDE OF THE URINARY TRACT CAUSED BY CRE IF NDM OR OTHER MBL PRODUCTION IS PRESENT?

Ceftazidime-avibactam in combination with aztreonam, or cefiderocol as monotherapy, are preferred treatment optionsfor NDM and other MBL-producing Enterobacterales infections.

WHAT ARE THE PREFERRED ANTIBIOTICS FOR THE TREATMENT OF INFECTIONS OUTSIDE OF THE URINARY TRACT CAUSED BY CRE IF OXA-48-LIKE PRODUCTION IS PRESENT?

Ceftazidime-avibactam isthe preferred treatment option forOXA-48-like producing Enterobacterales infections.

Cefiderocol is an alternative treatment option.

WHAT IS THE LIKELIHOOD OF THE EMERGENCE OF RESISTANCE OF CRE ISOLATES TO THE NEWER BLACTAM AGENTS WHEN USED TO TREAT CRE INFECTIONS?

The emergence of resistance is a concern with all β-lactam agents used to treat CRE infections.

Available data suggest the frequency may be highest for ceftazidime-avibactam.

WHAT IS THE ROLE OF TETRACYCLINE DERIVATIVES FOR THE TREATMENT OF INFECTIONS CAUSED BY CRE?

Although β-lactam agents remain preferred treatment options for CRE infections, tigecycline and eravacycline are alternative options when β-lactam agents are either not active or unable to be tolerated.

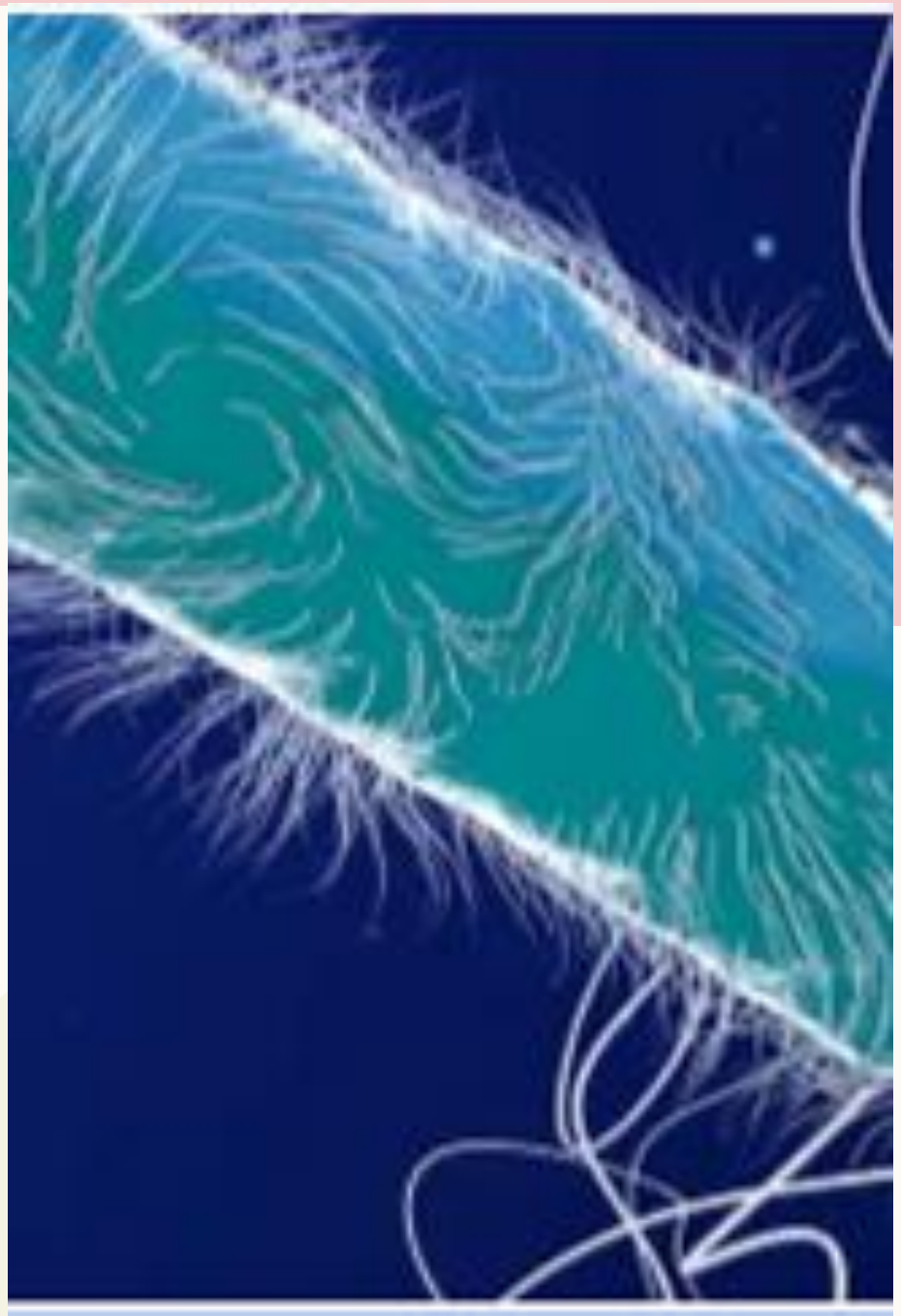
Tetracycline derivatives are not suggested for the treatment of CRE urinary tract infections or bloodstream infections

WHAT IS THE ROLE OF POLYMYXINS FOR THE TREATMENT OF INFECTIONS CAUSED BY CRE?

Combination antibiotic therapy (i.e., the use of a β-lactam agent in combination with an aminoglycoside, fluoroquinolone, tetracycline, or polymyxin) is not suggested for the treatment of infections caused by CRE

PSEUDOMONAS AERUGINOSA WITH DIFFICULT-TO-TREAT RESISTANCE

In 2018, the concept of "difficult-to-treat" resistance was proposed. In this guidance document, DTR is defined as P. aeruginosa exhibiting non-susceptibility to all of the following: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin



WHAT ARE PREFERRED ANTIBIOTICS FOR THE TREATMENT OF INFECTIONS CAUSED BY MDR P. AERUGINOSA?

- When P. aeruginosa isolates test susceptible to both traditional non-carbapenem β-lactam agents (i.e., piperacillin-tazobactam, ceftazidime, cefepime, aztreonam) and carbapenems, the former are preferred over carbapenem therapy.
- For infections caused by P. aeruginosa isolates not susceptible to any carbapenem agent but susceptible to traditional β-lactams, the administration of a traditional agent as high-dose extended-infusion therapy is suggested.
- For critically ill patients or those with poor source control with P. aeruginosa isolates resistant to carbapenems but susceptible to traditional β-lactams, use of newer β-lactam agents to which the organisms to with P. aeruginosa test susceptible (e.g., ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam) is also a reasonable treatment approach.

ARE THERE DIFFERENCES IN PERCENT ACTIVITY AGAINST DTR P. AERUGINOSA ACROSS AVAILABLE BLACTAM AGENTS?

Differences in DTR P. aeruginosa isolates susceptibility percentagesto newer βlactams exist, in part due to regional differences in enzymatic mechanisms of resistance

WHAT ARE PREFERRED ANTIBIOTICS FOR THE TREATMENT OF UNCOMPLICATED CYSTITIS CAUSED BY DTR P. AERUGINOSA?

- Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol are the preferred treatment options for uncomplicated cystitis caused by DTR P. aeruginosa.
- Tobramycin or amikacin (as a single dose) are alternative treatment options for uncomplicated cystitis caused by DTR P. aeruginosa.

WHAT ARE PREFERRED ANTIBIOTICS FOR THE TREATMENT OF PYELONEPHRITIS OR CUTI CAUSED BY DTR P. AERUGINOSA?

- Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol are preferred treatment options for pyelonephritis or cUTI caused by DTR P. aeruginosa.
- Once-daily tobramycin or amikacin are alternative agents for the treatment of DTR P. aeruginosa pyelonephritis or cUTI.

WHAT ARE PREFERRED ANTIBIOTICS FOR THE TREATMENT OF INFECTIONS OUTSIDE OF THE URINARY TRACT CAUSED BY DTR P. AERUGINOSA?

- Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam are preferred options for the treatment of infections outside of the urinary tract caused by DTR P. aeruginosa.
- Cefiderocol is an alternative treatment option for infections outside of the urinary tract caused by DTR P. aeruginosa.

WHAT ARE PREFERRED ANTIBIOTICS FOR THE TREATMENT OF DTR P. AERUGINOSA THAT PRODUCE METALLO-B-LACTAMASE ENZYMES?

For patients infected with DTR P. aeruginosa isolates that are MBL-producing, the preferred treatment is cefiderocol

WHAT IS THE LIKELIHOOD OF THE EMERGENCE OF RESISTANCE OF DTR P. AERUGINOSA ISOLATES TO THE NEWER B-LACTAM AGENTS WHEN USED TO TREAT DTR P. AERUGINOSA INFECTIONS?

The emergence of resistance is a concern with all β-lactams used to treat DTR P.aeruginosa infections. Available data suggest the frequency may be the highest for ceftolozane-tazobactam and ceftazidime-avibactam, although fewer data are available investigating this issue for imipenem-cilstatin-relebactam and cefiderocol.

WHAT IS THE ROLE OF COMBINATION ANTIBIOTIC THERAPY FOR THE TREATMENT OF INFECTIONS CAUSED BY DTR P.AERUGINOSA?

Combination antibiotic therapy is not suggested for infections caused by DTR P.aeruginosa if susceptibility to ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatinrelebactam, or cefiderocol has been confirmed.

WHAT IS THE ROLE OF NEBULIZED ANTIBIOTICS FOR THE TREATMENT OF RESPIRATORY INFECTIONS CAUSED BY DTR P. AERUGINOSA?

The panel does not suggest the use of nebulized antibiotics for the treatment of respiratory infections caused by DTR P. aeruginosa

CARBAPENEM-RESISTANT ACINETOBACTER BAUMANNII

a clear “standard of care” antibiotic regimen for CRAB infections against which to estimate the effectiveness of various treatment regimens does not exist.

WHAT IS THE GENERAL APPROACH FOR THE TREATMENT OF INFECTIONS CAUSED BY CRAB?

- The use of an antibiotic regimen which includes a sulbactam-containing agent is suggested for the treatment of CRAB infections.
- The preferred regimen is sulbactam-durlobactam in combination with a carbapenem (i.e., imipenem-cilastatin or meropenem).
- An alternative regimen is high-dose ampicillin-sulbactam (total daily dose of 9 grams of the sulbactam component) in combination with at least one other agent (i.e., polymyxin B, minocycline > tigecycline, or cefiderocol), if sulbactam-durlobactam is not available.

WHAT IS THE ROLE OF SULBACTAM-DURLOBACTAM FOR THE TREATMENT OF INFECTIONS CAUSED BY CRAB?

Sulbactam-durlobactam is a preferred agent for the treatment of CRAB infections and is suggested to be administered in combination with imipenem-cilastatin or meropenem.

WHAT IS THE ROLE OF AMPICILLIN-SULBACTAM FOR THE TREATMENT OF INFECTIONS CAUSED BY CRAB?

High-dose ampicillin-sulbactam, as a component of combination therapy, is suggested as an alternate agent for CRAB. This approach is suggested only when the unavailability of sulbactam-durlobactam precludes its use.

WHAT IS THE ROLE OF COMBINATION ANTIBIOTIC THERAPY FOR THE TREATMENT OF INFECTIONS CAUSED BY CRAB?

Combination therapy with at least two agents, whenever possible, is suggested for the treatment of CRAB infections, at least until clinical improvement is observed, because of the limited clinical data supporting any single antibiotic agent.

WHAT IS THE ROLE OF THE POLYMYXINS FOR THE TREATMENT OF INFECTIONS CAUSED BY CRAB?

Polymyxin B can be considered in combination with at least one other agent for the treatment of CRAB infections

WHAT ISTHE ROLE OF TETRACYCLINE DERIVATIVES FOR THE TREATMENT OF INFECTIONS CAUSED BY CRAB?

High-dose minocycline or high-dose tigecycline can be considered in combination with at least one other agent for the treatment of CRAB infections.
The panel prefers minocycline over tigecycline because of the long-standing clinical experience with this agent and the availability of CLSI breakpoints.

WHAT ISTHE ROLE OF CEFIDEROCOL THERAPY FOR THE TREATMENT OF INFECTIONS CAUSED BY CRAB?

Cefiderocol should be limited to the treatment of CRAB infections refractory to other antibiotics or in cases where intolerance or resistance to other agents precludes their use. When cefiderocol is used to treat CRAB infections, the panel suggests prescribing it as part of a combination regimen

WHAT IS THE ROLE OF EXTENDED-INFUSION MEROPENEM OR IMIPENEM-CILASTATIN FOR THE TREATMENT OF INFECTIONS CAUSED BY CRAB?

Meropenem or imipenem-cilastatin are not suggested for the treatment of CRAB infections, with the exception of co-administration with sulbactam-durlobactam.

WHAT IS THE ROLE OF THE RIFAMYCINS FOR THE TREATMENT OF INFECTIONS CAUSED BY CRAB?

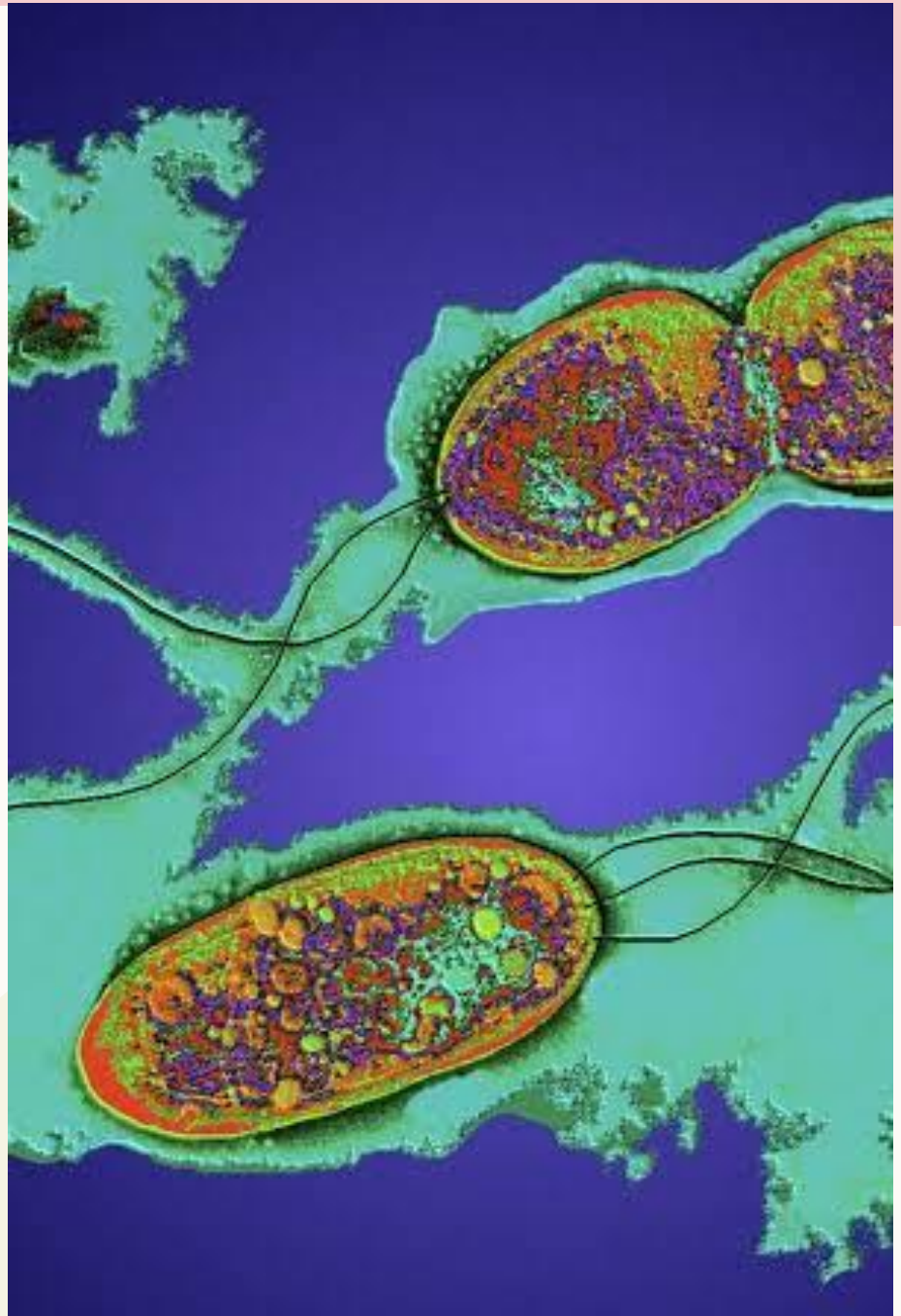
Rifampin or other rifamycins are not suggested for the treatment of CRAB infections

WHAT IS THE ROLE OF NEBULIZED ANTIBIOTICS FOR THE TREATMENT OF RESPIRATORY INFECTIONS CAUSED BY CRAB?

Nebulized antibiotics are not suggested for the treatment of respiratory infections caused by CRAB.

STENOTROPHOMONAS MALTOPHILIA

Stenotrophomonas maltophilia is an aerobic, glucose non-fermenting, gram-negative bacillus that is ubiquitous in water environments



WHAT IS A GENERAL APPROACH FOR THE TREATMENT OF INFECTIONS CAUSED BY S. MALTOPHILIA?

Any of two approaches are preferred options for the treatment of S. maltophilia infections:

- the use of two of the following agents: cefiderocol, minocycline, TMP-SMX, or levofloxacin
- the combination of ceftazidime-avibactam and aztreonam.

WHAT ISTHE ROLE OF CEFIDEROCOL FOR THE TREATMENT OF INFECTIONS CAUSED BY S. MALTOPHILIA?

Cefiderocol as a component of combination therapy, at least until clinical improvement is observed, is a preferred agent for the treatment of S. maltophilia infections.

WHAT IS THE ROLE OF CEFTAZIDIME-AVIBACTAM AND AZTREONAM FOR THE TREATMENT OF INFECTIONS CAUSED BY S. MALTOPHILIA?

Ceftazidime-avibactam and aztreonam is a preferred treatment combination for S. maltophilia infections.

WHAT IS THE ROLE OF TETRACYCLINE DERIVATIVES FOR THE TREATMENT OF INFECTIONS CAUSED BY S. MALTOPHILIA?

High-dose minocycline, as a component of combination therapy, is an option for the treatment of S. maltophilia infections.

WHAT ISTHE ROLE OF TRIMETHOPRIM-SULFAMETHOXAZOLE FOR THE TREATMENT OF INFECTIONS CAUSED BY S. MALTOPHILIA?

TMP-SMX, as a component of combination therapy, is an option for the treatment of S. maltophilia infections.

WHAT ISTHE ROLE OF FLUOROQUINOLONES FOR THE TREATMENT OF INFECTIONS CAUSED BY S.MALTOPHILIA?

Levofloxacin, as a component of combination therapy, is an option for the treatment of S. maltophilia infections.

WHAT IS THE ROLE OF CEFTAZIDIME FOR THE TREATMENT OF INFECTIONS CAUSED BY S. MALTOPHILIA?

Ceftazidime is not a suggested treatment option for S. maltophilia infections due to the presence of β-lactamase genes intrinsic to S. maltophilia that are expected to render ceftazidime inactive. As of 2024, CLSI breakpoints for S. maltophilia to ceftazidime are no longer available.

2024 CLINICAL AND LABORATORY STANDARDS INSTITUTE BREAKPOINTS FOR SELECT GRAM-NEGATIVE ORGANISMS

- 1 For full details of antibiotic susceptibility testing interpretations refer to: Clinical and Laboratory Standards Institute. 2024. M100: Performance Standards for Antimicrobial Susceptibility Testing. 34th ed. Wayne, PA. CLSI M100 document is updated annually; susceptibility criteria subject to changes in 2025.
- 2Breakpoints only available for infections originating from the urinary tract.
- 3Cefepime MICs of 4-8 µg/mL are susceptible dosedependent.
- 4No susceptible category for colistin or polymyxin B; MICs ≤2 µg/mL considered intermediate.
- 5Applies to Escherichia coli urinary tract isolates only.
- 6Piperacillin-tazobactam MICs of 16 µg/mL are considered susceptible dose-dependent.
- 7No CLSI breakpoint. FDA defines susceptibility as MICs ≤2 µg/mL.
- 8Neither CLSI nor FDA breakpoints are available.

Antibiotic	Enterobacterales (µg/mL)	*Pseudomonas aeruginosa* (µg/mL)	Carbapenem-Resistant *Acinetobacter baumannii* (µg/mL)	*Stenotrophomonas maltophilia* (µg/mL)
Amikacin	≤4	≤16[2]	--	--
Ampicillin-sulbactam	--	--	≤8/4	--
Aztreonam	≤4	≤8	--	--
Cefepime	≤2[3]	≤8	--	--
Cefiderocol	≤4	≤4	≤4	≤1
Ceftazidime	≤4	≤8	--	--
Ceftazidime-avibactam	≤8/4	≤8/4	--	--
Ceftolozane-tazobactam	≤2/4	≤4/4	--	--
Ciprofloxacin	≤0.25	≤0.5	--	--
Colistin or Polymyxin B	--[4]	--[4]	--[4]	--
Doxycycline	≤4	--	--	--
Ertapenem	≤0.5	--	--	--
Fosfomycin	≤64[5]	--	--	--
Gentamicin	≤2	--	--	--
Imipenem	≤1	≤2	--	--
Imipenem-relebactam	≤1/4	≤2/4	--	--
Levofloxacin	≤0.5	≤1	--	≤2
Meropenem	≤1	≤2	--	--
Meropenem-vaborbactam	≤4/8	--	--	--
Minocycline	≤4	--	≤4	≤1
Nitrofurantoin	≤32	--	--	--
Piperacillin-tazobactam	≤8/4[6]	≤16/4	--	--
Plazomicin	≤2	--	--	--
Sulbactam-durlobactam	--	--	≤4/4	--
Tigecycline	--[7]	--	--[8]	--[8]
Trimethoprim-sulfamethoxazole	≤2/38	--	--	≤2/38
Tobramycin	≤2	≤1	--	--

THANK YOU

“Welcome to the grim darkness of the future without antibiotics.”