Treatment of Antimicrobial-Resistant Gram-Negative Infections

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Antimicrobial Resistance (AMR)

- The rise in antimicrobial resistance continues to be a global crisis
- Collectively, antimicrobial-resistant pathogens caused more than 2.8 million infections and over 35,000 deaths annually from 2012-2017

Source: Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2019, **2019**.

IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 1.0

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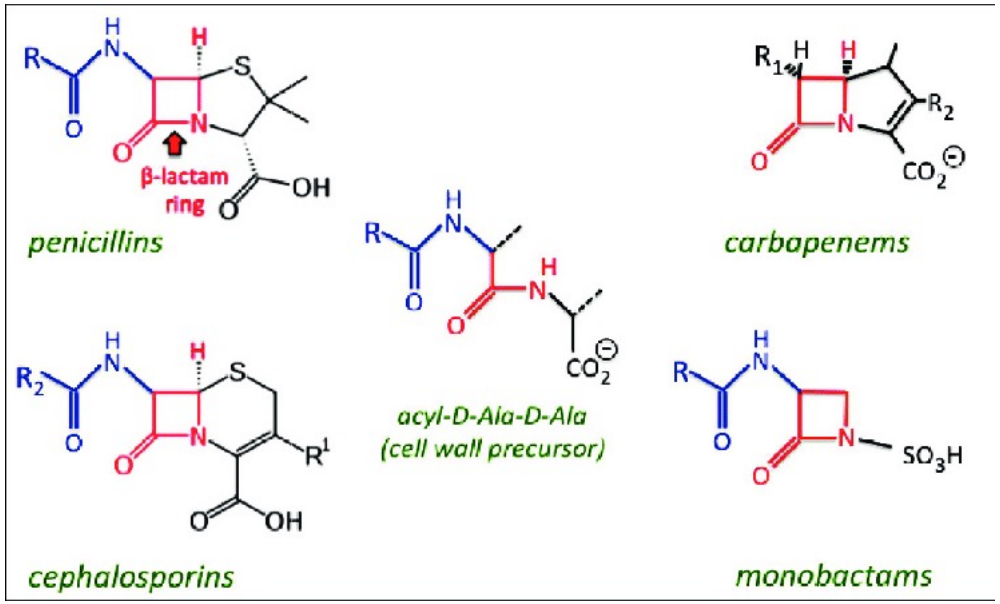
A Focus on Extended-Spectrum β-lactamase Producing Enterobacterales, Carbapenem-Resistant Enterobacterales, and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance

Extended-Spectrum Beta-lactamase-Producing Enterobacterales (ESBL-E)

- Incidence of ESBL-E identified in bacterial cultures in the US increased by 53% from 2012-17 (in large part due to increased community-acquired infections)
- ESBLs are enzymes that inactivate most penicillins, cephalosporins, and aztreonam



Extended-Spectrum Beta-lactamase-Producing Enterobacterales (ESBL-E)

- Routine EBSL testing is not performed by most clinical microbiology laboratories.
- Non-susceptibility to ceftriaxone is often used as a proxy for ESBL production, although this threshold has limitations with specificity as organisms not susceptible to ceftriaxone for reasons other than ESBL production may be falsely presumed to be ESBL-producers

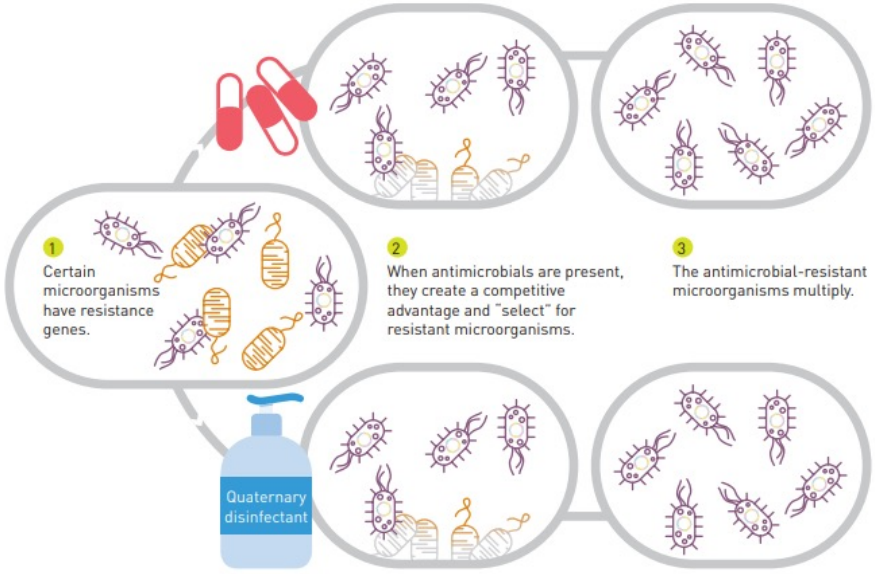


Figure 6

Selection pressure and antimicrobial resistance (United States Centers for Disease Control and Prevention [US CDC] n.d.)

Source: Tamma PD, Sharara SL, Pana ZD, et al. Molecular Epidemiology of Ceftriaxone Non-Susceptible Enterobacterales Isolates in an Academic Medical Center in the United States. Open Forum Infect Dis **2019**; 6(8): ofz353.

Question: What are preferred antibiotics for the treatment of uncomplicated cystitis caused by ESBL-E?

- A. Nitrofurantoin or trimethoprim-sulfamethoxazole
- B. Amoxicillin-clavulanate
- C. Fosfomycin
- D. Single dose aminoglycoside

Answer: What are preferred antibiotics for the treatment of uncomplicated cystitis caused by ESBL-E?

- Nitrofurantoin and trimethoprim-sulfamethoxazole have been shown to be safe and effective options for uncomplicated cystitis, including uncomplicated ESBL-E cystitis, and are considered first line
- Carbapenems and the fluoroquinolones are effective but their use for uncomplicated cystitis is discouraged when other safe and effective options are available
- Amoxicillin-clavulanate, single-dose aminoglycosides, and oral fosfomycin (fosfomycin is recommended for *E. coli* only; other organisms may have the fosA gene which can cause resistance) are alternative treatment options for uncomplicated ESBL-E cystitis but have less robust clinical data to support their use

Question: What are preferred antibiotics for the treatment of pyelonephritis and complicated urinary tract infections (cUTI) caused by ESBL-E?

- A. Ertapenem, meropenem or imipenem-cilastin
- B. Ciprofloxacin or levofloxacin
- C. Trimethoprim-sulfamethoxazole
- D. All of the above

Answer : What are preferred antibiotics for the treatment of pyelonephritis and complicated urinary tract infections caused by ESBL-E?

- Carbapenems, ciprofloxacin, levofloxacin, and trimethoprim-sulfamethoxazole are all preferred treatment options for patients with ESBL-E pyelonephritis and cUTIs based on the ability of these agents to achieve adequate and sustained concentrations in the urine, RCT results, and clinical experience
- If a carbapenem is initiated and susceptibility to ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole is demonstrated, transitioning to these agents is preferred over completing a treatment course with a carbapenem. Limiting use of carbapenem exposure will preserve their activity for future antimicrobial-resistant infections.

Source: Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis pyelonephritis in women: a randomized trial. JAMA **2000**; 283(12): 1583-90.

Fosfomycin for ESBL E. coli prostatitis

- Nitrofurantoin and oral fosfomycin do not achieve adequate concentrations in the renal parenchyma and should be avoided for pyelonephritis and cUTI
- However, fosfomycin is an alternative option for the treatment of prostatitis caused by ESBL-producing *E. coli* when preferred options cannot be tolerated or do not test susceptible
- Fosfomycin, dosed at 3 g orally daily for one week, followed by 3 g orally every 48 hours for 6-12 weeks, was associated with clinical cure in 82% of patients in an observational study of 44 males with chronic bacterial prostatitis

Source: Karaiskos I, Galani L, Sakka V, et al. Oral fosfomycin for the treatment of chronic bacterial prostatitis. J Antimicrob Chemother **2019**; 74(5): 1430-7.

Question: What are preferred antibiotics for the treatment of infections outside of the urinary tract caused by ESBL-E?

- A. Piperacillin-tazobactam
- B. Ertapenem, meropenem or imipenem-cilastin
- C. Ceftazidime-avibactam
- D. Fluoroquinolones or trimethoprim-sulfamethoxazole
- E. Any of the above options as along as the isolate is susceptible

Answer: What are preferred antibiotics for the treatment of infections outside of the urinary tract caused by ESBL-E?

- A carbapenem is recommended as first-line treatment of ESBL-E infections outside of the urinary tract, based primarily on data from a large clinical trial that randomized 391 patients with bloodstream infections due to ceftriaxone non-susceptible *E. coli* or *K. pneumoniae* (87% later confirmed to have ESBL genes) to piperacillin-tazobactam 4.5 g intravenously every six hours or meropenem 1 g intravenously every eight hours, both as standard infusions
- The primary outcome of 30-day mortality occurred in 12% and 4% of patients receiving piperacillin-tazobactam and meropenem, respectively

Source: Harris PNA, Tambyah PA, Lye DC, et al. Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With E coli or Klebsiella pneumoniae Bloodstream Infection and Ceftriaxone Resistance: A Randomized Clinical Trial. JAMA **2018**; 320(10): 984-94.

Question: Is there a role for cefepime in the treatment of infections caused by ESBL-E?

- No clinical trials comparing the outcomes of patients with ESBL-E bloodstream infections treated with cefepime or a carbapenem have been conducted. Cefepime MIC testing may be inaccurate and/or poorly reproducible if ESBL enzymes are present
- Cefepime is not recommended for the treatment of non-urinary infections caused by ESBL-E, even if susceptibility to the agent is demonstrated
- 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

Source: Smith KP, Brennan-Krohn T, Weir S, Kirby JE. Improved Accuracy of Cefepime Susceptibility Testing for Extended-Spectrum-Beta-Lactamase-Producing Enterobacteriaceae with an On-Demand Digital Dispensing Method. J Clin Microbiol **2017**; 55(2): 470-8.

Carbapenem-Resistant Enterobacterales (CRE)

- CRE account for more than 13,000 nosocomial infections and contribute to greater than 1,000 deaths in the United States annually
- The CDC defines CRE as members of the Enterobacterales order resistant to at least one carbapenem antibiotic or producing a carbapenemase enzyme
- For bacteria that are intrinsically not susceptible to imipenem (e.g., *Proteus* spp., *Morganella* spp., *Providencia* spp.), resistance to at least one carbapenem other than imipenem is required

Source: Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2019, **2019**.

Question: What are preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE resistant to ertapenem but susceptible to meropenem, when carbapenemase testing results are either not available or negative?

- The CDC characterized over 42,000 CRE isolates collected from all regions of the US between 2017-2019 and found that only ~10% of CRE isolates containing a carbapenemase gene retained susceptibility to meropenem
- Extended-infusion meropenem is recommended against infections outside of the urinary tract caused by CRE that remain susceptible to meropenem since most of these isolates do not produce carbapenemases

Question: What are the preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE resistant to both ertapenem and meropenem?

- A. Extended-infusion meropenem plus an aminoglycoside
- B. Cefiderocol
- C. Tigecycline or eravacycline
- Ceftazidime-avibactam, meropenem-vaborbactam, or imipenem-cilastatin-relebactam

Answer: What are the preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE resistant to both ertapenem and meropenem?

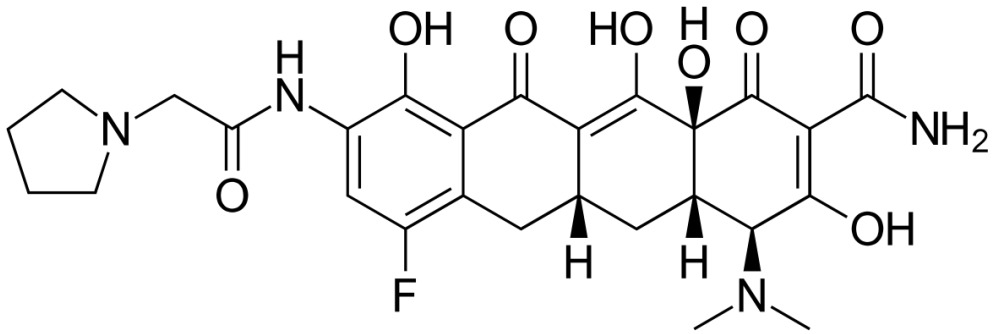
- Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam

- For patients with CRE infections who within the previous 12 months have received medical care in countries with a relatively high prevalence of metallo-β-lactamase-producing organisms (eg. India or Pakistan) or who have previously had a clinical or surveillance culture where a metallo-β-lactamase-producing isolate was identified, preferred treatment options include the combination of ceftazidime-avibactam plus aztreonam, or cefiderocol as monotherapy, if carbapenemase testing results are not available

Source : Boyd SE, Livermore DM, Hooper DC, Hope WW. Metallo-beta-Lactamases: Structure, Function, Epidemiology, Treatment Options, and the Development Pipeline. Antimicrob Agents Chemother **2020**; 64(10).

Question: What is the role of tetracycline derivatives for the treatment of infections caused by CRE?

- β-lactam agents remain preferred treatment options for CRE infections, but tigecycline and eravacycline are alternative options when β-lactam agents are either not active or unable to be tolerated
- Tetracycline-derivative agents achieve rapid tissue distribution following administration, resulting in limited urine and serum concentrations (avoid in UTI or bloodstream infections)

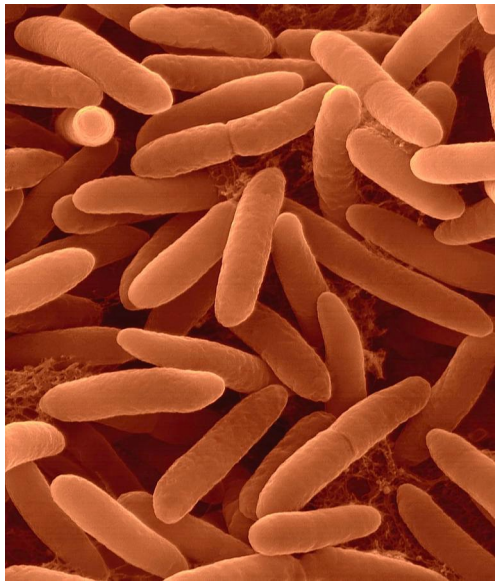


Pseudomonas aeruginosa with Difficult to Treat Resistance (DTR-*P. aeruginosa*) vs. Multidrug-resistant (MDR) *P. aeruginosa*

- **MDR** *P. aeruginosa* is defined as non-susceptibility to at least one antibiotic in at least three classes for which susceptibility is generally expected: penicillins, cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems
- **DTR** is defined as non-susceptibility to all of the following: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin

Question: What are preferred antibiotics for the treatment of uncomplicated cystitis caused by DTR-*P. aeruginosa*?

- Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, cefiderocol, or a single-dose of an aminoglycoside are all preferred agents
- Colistin, but not polymyxin B, is an alternate consideration for treating DTR-*P. aeruginosa* cystitis as it converts to its active form in the urinary tract
- Avoid fosfomycin due to the presence of the *fosA* gene, which is intrinsic to *P. aeruginosa*



Source: Sorli L, Luque S, Li J, et al. Colistin for the treatment of urinary tract infections caused by extremely drug-resistant Pseudomonas aeruginosa: Dose is critical. J Infect **2019**; 79(3): 253-61.

Question: What is the role of combination antibiotic therapy for the treatment of infections caused by DTR-*P. aeruginosa*?

- Combination antibiotic therapy is not routinely recommended for infections caused by DTR-*P. aeruginosa* if there is *in vitro* susceptibility to a first-line antibiotic (i.e., ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam)
- In cases where there is resistance to all first line agents, combination therapy (typically with an aminoglycoside plus the β-lactam-β-lactamase inhibitor agent for which the MIC is closest to its susceptibility breakpoint) could be considered
- If resistance to aminoglycosides is also present, the same strategy as above with polymixin B rather than an aminoglycoside can be considered

Source: Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with gram-negative bacteria. Clin Microbiol Rev **2012**; 25(3): 450-70.

Question: What is the role of nebulized antibiotics for the treatment of respiratory infections caused by DTR-*P. aeruginosa*?

- A. They are not recommended by the IDSA guidelines
- B. Nebulized colistin has been shown to have clinical benefit
- C. Nebulized amikacin has been shown to have clinical benefit

Answer: What is the role of nebulized antibiotics for the treatment of respiratory infections caused by DTR-*P. aeruginosa*?

- The IDSA recommends against the use of nebulized antibiotics as adjunctive therapy for DTR-*P. aeruginosa* pneumonia due to the lack of benefit observed in clinical trials, concerns regarding unequal distribution in infected lungs, and concerns for respiratory complications such as bronchoconstriction in 10-20% of patients receiving aerosolized antibiotics

Source: Maselli DJ, Keyt H, Restrepo MI. Inhaled Antibiotic Therapy in Chronic Respiratory Diseases. Int J Mol Sci **2017**; 18(5).

What can we do about AMR?

- Practice robust antimicrobial stewardship
- Adhere to national infection control practices and reporting requirements
- Avoid biologic and chemical pollution of the environment
- AMR is an emerging global health threat

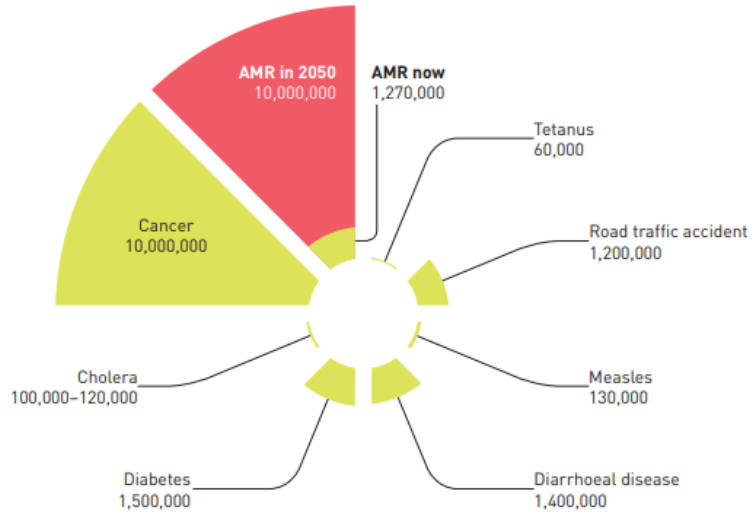


Figure 2

Predicted mortality from AMR compared with common causes of current deaths (adapted from O'Neill 2016; Murray *et al.* 2022)