trchealthcare

Urinary Tract Infections

Updated August 2025

Uncomplicated UTI

Cystitis in men or women. Patient is afebrile (unless fever is due to a non-UTI cause) and has no other symptoms suggesting infection beyond the bladder (see Complicated UTI for these symptoms). Patient does NOT have neurogenic bladder or obstruction.[1]

Empiric antibiotic options[8,c]

- TMP or TMP-SMX x 3 days (avoid if resistance >20% or used within 3 months)
- Nitrofurantoin x 5 days or fosfomycin x 1 (avoid if pyelonephritis suspected)
- Alternatives: oral beta-lactam x 3 to 7 days; oral fluoroquinolone x 3 days (see "Complicated UTI" for specific agents)

Symptomatic Treatment (add-on to antibiotic)

- Used for ≤2 days.[2,5] Unclear efficacy.[4,5,7]
- Phenazopyridine poses rare risk of methemoglobinemia, hemolytic anemia, and AKI, often with inappropriate use or G6PD deficiency.[2,3]
- Cystoplus (sodium citrate [Canada]) is a urinary alkalinizer with high sodium content (1,070 mg per dose).[5,6]

Complicated UTI[1]

Pyelonephritis, CAUTI, or UTI associated with neurogenic bladder or obstruction. Symptoms may include fever, chills, rigors, flank pain/tenderness, and/or unstable vitals.

When **choosing an antibiotic**, consider any recent previous culture results, risk of resistance, local antibiograms, and severity of illness.[b] E.coli is the "default" target. Some patients can be treated as outpatients with oral antibiotics.

Empiric antibiotic options

- Preferred: TMP-SMX, ciprofloxacin*, levofloxacin*, piperacillin/tazobactam*, ceftriaxone*, ceftazidime*, cefotaxime*, cefepime*
  - **Consider avoiding fluoroquinolones if the patient has used one in the past 12 months.**
  - Alternatives: amoxicillin/clavulanate,[a] cefixime,[a] cefpodoxime (US),[a] cefuroxime,[a] cephalexin,[a] imipenem/cilastatin,* imipenem/cilastatin/relebactam*, meropenem*, meropenem/vaborbactam*, ertapenem*, ceftolozane/tazobactam*, ceftazidime/avibactam*, cefiderocol*, aminoglycosides*
  - ***Sepsis: choose among these.**[b]
- IV to oral **switch**: consider when patient is improving (e.g., afebrile, stable vitals, can take oral meds), provided an effective oral alternative is available and source is controlled.

Duration: For most patients, 7 days (5 to 7 for fluoroquinolones). A longer duration, typically up to 14 days, may be appropriate (e.g., not clinically improving, severe sepsis, immunocompromise, CKD, acute bacterial prostatitis, complete obstruction, surgery, abscess); individualize.

Considerations in Special Populations

Pregnancy

- For pyelonephritis, start with a parenteral agent and treat for a total of 14 days.[9,10] Consider ampicillin/gentamicin, ceftriaxone +/- ampicillin, cefepime, or aztreonam [for beta-lactam allergy]).[9,10] Ampicillin covers enterococcus.[10]
- See our chart, *Antibiotics in Pregnancy and Lactation*, for safety information on fluoroquinolones, nitrofurantoin, TMP-SMX, and more.
- Screen for asymptomatic bacteriuria once, early in pregnancy (e.g., 12 to 16 weeks' gestation or first prenatal visit [USPSTF]; first trimester [Canada]).[12,13] Treat for five to seven days with an appropriate oral antibiotic.[9]

Pediatric

- Be aware that hospital antibiogram data might not apply to pediatric patients.[14]
- Infants <2 months of age are **usually** treated with parenteral antibiotics. Oral antibiotics (after one parenteral dose) might be appropriate if patient is 29 to 60 days of age, looks well, is well-hydrated, has normal labs, has a dependable carer, and will follow up within 24 hours.[15]
- **Empiric options, community**-acquired: cephalexin, ceftriaxone, or nitrofurantoin (cystitis, >12 years of age). Alternatives: TMP-SMX (beta-lactam allergy; history of cefazolin-resistant, TMP-SMX susceptible infection), ciprofloxacin or levofloxacin (beta-lactam allergy).[16,24]
- **Empiric options, hospital**-acquired (CAUTI, extensive antibiotic exposure): cover for *Pseudomonas* (e.g., ceftazidime; alternatives: piperacillin/tazobactam, cefepime, ciprofloxacin, levofloxacin).[16,21,24,25]
- **Phenazopyridine**: A dose of 4 mg/kg/dose (max 200 mg) TID is suggested for children 6 to 11 years of age, but there is no pediatric formulation, and pediatric guidelines do not suggest its use.[7,17]
- **Recurrent UTIs**: reserve antibiotic prophylaxis for some patients with vesicoureteral reflux.[20,24]

Prophylaxis of Recurrent UTIs in Women

- Option for three UTI in a year or two in six months, or >2 during pregnancy.[9,18]
- Non-pharmacologic options: offer cranberry (e.g., 240 mL juice, 500 mg supplement daily); recommend vaginal estrogen (ring, cream) in peri- or postmenopausal women.[18,19]
- Daily antibiotic options: TMP 100 mg, TMP-SMX 40/200 mg (or thrice weekly), nitrofurantoin 50 to 100 mg (an option in pregnancy), cephalexin 125 to 250 mg (an option in pregnancy), fosfomycin 3 g (every 10 days)[9,18]
- Post-coital options: TMP-SMX 40/200 mg, TMP-SMX 80/200 mg, nitrofurantoin 50 to 100 mg (an option in pregnancy), cephalexin 250 mg (an option in pregnancy)[9,18]
- Six to 12 months' duration of antibiotic prophylaxis is evidence-based, but patients often continue for years.[18,26] Assess safety and efficacy periodically.[18]

Footnotes

a. For **oral beta-lactams**, use highest recommended dose.[1]
b. Sepsis: In sepsis, the initial emphasis is on mortality prevention (vs stewardship). **Consult relevant antibiogram, if available. Choose an antibiotic for which the susceptibilities of the target bacteria are ≥80% (≥90% for SHOCK). Coverage for *Pseudomonas*, MRSA, or enterococci may be appropriate.**
c. Reserve pivmecillinam (Pivya) and sulopenem etzadroxil/probenecid (Orlynvah) for when other options are not feasible (e.g., resistance).[22,23]

Abbreviations: AKI = acute kidney injury; CAUTI = Catheter-associated urinary tract infection; CKD = chronic kidney disease; G6PD = glucose-6-phosphate dehydrogenase; IV = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*; TID = three times daily; TMP = trimethoprim; TMP-SMX = trimethoprim/sulfamethoxazole; UTI = urinary tract infection

References

1. Trautner BW, Cortes-Penfield NW, Gupta K, et al. Complicated Urinary Tract Infections (cUTI): Clinical Guideline for Treatment and Management. July 17, 2025. https://www.idsociety.org/practice-guideline/complicated-urinary-tract-infections/. (Accessed August 4, 2025).
2. Coyne BM, Ishaq SM, Thota A, Thakkar B. Treatment for a rare case of phenazopyridine-induced methemoglobinemia: a case report and mini-review. Front Med (Lausanne). 2025 May 8;12:1568949.
3. Khan O, Uddin SMM, Atuaka C, et al. Syncope Following Treatment of UTI: A Case of Acute Hemolytic Anemia, Methemoglobinemia and Acute Renal Dysfunction Following Phenazopyridine Use in a Patient With G6PD Deficiency. J Community Hosp Intern Med Perspect. 2023 Jan 10;13(1):54-57.
4. O'Kane DB, Dave SK, Gore N, et al. Urinary alkalisation for symptomatic uncomplicated urinary tract infection in women. Cochrane Database Syst Rev. 2016 Apr 19;4(4):CD010745.
5. Norwell Consumer Healthcare. About Cystoplus. https://www.cystoplus.ca/about. (Accessed August 5, 2025).
6. TRC Healthcare. Cystoplus by PendoPharm (division of Pharmascience Inc). [Natural Medicines website]. Available at https://naturalmedicines.therapeuticresearch.com/Data/Commercial-Products/C/Cystoplus-161016. (Accessed August 5, 2025).
7. Eastham jH, Patel P. Phenazopyridine. [Updated 2023 May 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK580545/. (Accessed August 5, 2025).
8. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011 Mar 1;52(5):e103-20.
9. Urinary Tract Infections in Pregnant Individuals. Obstet Gynecol. 2023 Aug 1;142(2):435-445.
10. Toronto Central LHIM: Guidelines for Empiric Treatment of Urinary Tract Infection in Adults. Last revised January 2015. https://www.antimicrobialstewardship.com/uti. (Accessed August 5, 2025).
11. Briggs GG, Towers CV, Forinash AB. Drugs in Pregnancy and Lactation. 12th ed. Philadelphia, PA: Wolters Kluwer, 2022 (online version accessed August 5, 2025).
12. Canadian Task Force on Preventive Health Care. Asymptomatic bacteriuria in pregnancy (2018). https://canadiantaskforce.ca/guidelines/published-guidelines/asymptomatic-bacteriuria/. (Accessed August 5, 2025).
13. U.S. Preventive Services Task Force. Final recommendation statement. Asymptomatic bacteriuria in adults: screening. April 2019. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/asymptomatic-bacteriuria-in-adults-screening. (Accessed August 5, 2025).
14. Gerber JS, Jackson MA, Tamma PD, Zaoutis TE; AAP Committee on Infectious Diseases and Pediatric Infectious Diseases Society. Policy Statement: Antibiotic Stewardship in Pediatrics. J Pediatric Infect Dis Soc. 2021 May 28;10(5):641-649.
15. Consensus Guidelines for Management of Pediatric Urinary tract Infection (UTI): Northern California Pediatric Hospital Medicine Consortium. Last modified September 2024. https://medconnection.ucsfbenioffchildrens.org/news/consensus-guidelines-for-management-of-pediatric-urinary-tract-infection-uti#management. (Accessed August 6, 2025.)
16. University of California San Francisco. Infectious Diseases Management Program at UCSF. Urinary Tract Infections-Community Onset. Updated July 2021. https://idmp.ucsf.edu/content/urinary-tract-infections-community-onset. (Accessed August 5, 2025).
17. Clinical Pharmacology powered by ClinicalKey. Tampa (FL): Elsevier. 2025. http://www.clinicalkey.com. (Accessed August 6, 2025).
18. Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline. https://www.auanet.org/guidelines-and-quality/guidelines/recurrent-uti. (Accessed August 6, 2025).
19. TRC Healthcare. Cranberry. [Natural Medicines website]. Available at https://naturalmedicines.therapeuticresearch.com/Data/ProMonographs/Cranberry. Last updated August 6, 2025. (Accessed August 6, 2025).
20. Mattoo TK, Shaikh N, Nelson CP. Contemporary Management of Urinary Tract Infection in Children. Pediatrics. 2021 Feb;147(2):e2020012138. Erratum in: Pediatrics. 2022 Oct 1;150(4): PMID: 33479164.
21. CDC. Clinical Safety: Preventing Catheter-Associated Urinary Tract Infections (CAUTIs). June 27, 2025. https://www.cdc.gov/uti/hcp/clinical-safety/index.html. (Accessed August 6, 2025).
22. FDA. FDA approves new treatment for uncomplicated urinary tract infections in adult women who have limited or no alternative oral antibiotic treatment options. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-new-treatment-uncomplicated-urinary-tract-infections-adult-women-who-have-limited-or-no. (Accessed August 6, 2025).
23. Zering J. Pivmecillinam (Pivya): An Upcoming New Antibiotic in the Urinary Tract Infection Tool Kit. Caring for the Ages, Volume 25, Issue 7, 11. https://www.caringfortheages.com/article/S1526-4114(24)00360-3/fulltext. (Accessed August 6, 2025).
24. UC Davis Health. Children's Hospital. April 2023. https://health.ucdavis.edu/media-resources/pediatrics/documents/pdfs/clinical-guidelines/UTI-Guidelines-in-Pediatrics.pdf. (Accessed August 26, 2025).
25. Children's Hospital of Philadelphia. Urinary Tract Infections (UTI) Clinical Pathway-all settings. 2025. https://www.chop.edu/clinical-pathway/uti-antibiotic-recommendations. (Accessed August 26, 2025).
26. Albert X, Huertas I, Pereiró II, et al. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. Cochrane Database Syst Rev. 2004;2004(3):CD001209.

Resistant Gram-Negative Bacterial Infections

modified August 2025

Resistance among gram-negative bacteria is a global health threat.[1] Extended-spectrum beta-lactamase (ESBL)-producing organisms are susceptible to a limited number of antibiotics, and are classified as a serious threat by the CDC.[2] Carbapenem-resistant Enterobacterales (CRE; The "E" now stands for the order; previously the "E" stood for the family [*Enterobacteriaceae*].[33]) are susceptible to very few antibiotics, and are considered an urgent threat by the CDC.[2] Risk factors for resistant gram-negative infections can be used to identify patients in whom empiric broad spectrum antibiotic treatment is warranted.[33] Treatment failures and/or final culture and sensitivity results can identify CRE, and treatment can be escalated appropriately. It is recommended that infectious diseases specialists be consulted for the management of patients with resistant gram-negative bacterial infections.[33] The chart below answers clinical questions about managing resistant gram-negative bacterial infections.

Clinical Question	Suggested Approach/Pertinent Information
How common are resistant gram-negative infections in the United States?	• Infections from ESBL-producing organisms were identified in almost 200,000 hospitalized patients and lead to approximately 9,100 deaths in 2017.[2] ○ Between 5% to 20% of *Escherichia coli* and 3% to 35% *Klebsiella pneumoniae* in the US produce ESBL, and these rates have been steadily increasing.[5,31,32] • CRE organisms cause about 9,300 infections, leading to about 900 deaths each year.[43] In 2021, 2.7% of Enterobacterales isolates from healthcare-associated infections were identified as CRE.[3] • The CDC classifies carbapenem-resistant *Acinetobacter baumannii* (CRAB) as an urgent threat. In 2021, 39.5% of *A. baumannii* isolates were carbapenem-resistant.[56]

What are risk factors for resistant gram-negative colonization or infection?
 	
Continued…
	• Risk factors for resistant gram-negative infections are similar to those for other nosocomial infections, including:[6,7]
	  ○ severe illness; arterial or central venous catheters; indwelling urinary catheters; or mechanical ventilation
	• Additional risk factors specific to **ESBL-related infections** include:[7]
	  ○ length of hospitalization and/or intensive care unit (ICU) stay
	  ○ residence at a long-term care facility
	  ○ emergency abdominal surgery or gut colonization
	  ○ use of gastrostomy or jejunostomy tube
	  ○ hemodialysis
	  ○ prior use of any antibiotic

Clinical Question	Suggested Approach/Pertinent Information
Risk factors, continued	• Additional risk factors specific to **CRE-related infections** include:[10,11] o antibiotic use within previous three months o use of third- or fourth-generation cephalosporins and/or carbapenems o trauma o diabetes o malignancy o organ transplantation
Which organisms are most likely to produce **ESBL**?	• Only gram-negative organisms are capable of producing ESBL. • *Klebsiella pneumoniae, Klebsiella oxytoca*, and *Escherichia coli* are the most common organisms that produce ESBL.[7] • Other gram-negative organisms that may produce ESBL include: *Acinetobacter*, *Burkholderia*, *Citrobacter*, *Enterobacter*, *Morganella*, *Proteus*, *Pseudomonas*, *Salmonella*, *Serratia*, and *Shigella* species.[7-9]
Which organisms are most likely to be c**arbapenem resistant** in the United States?	• *Klebsiella pneumonia*, *Klebsiella oxytoca*, and *Escherichia coli* are the most common CRE.[12] • Carbapenem-resistant infections have also been caused by *Acinetobacter baumannii*, *Enterobacter cloacae*, and *Pseudomonas aeruginosa*.[12-15] • The most commonly reported carbapenemase is *Klebsiella pneumoniae* carbapenemase (KPC).[3,33] This carbapenemase is not limited to *Klebsiella pneumoniae* isolates.[33] • Other carbapenemase enzymes include New Delhi MBL (NDM), Verona Integron-Encoded MBL (VIM), Oxacillinase-48-type (OXA-48), and Imipenemase MBL (IMP). These carbapenemase enzymes are more common outside the US, however, they are increasingly reported in the US and are no longer only associated with exposure to healthcare in countries where they are more prevalent.[3]
What are the mechanisms of resistance among gram-negative organisms?	• Entry of antibiotics is limited due to decreased permeability of the bacterial outer membrane.[40] • Genetic mutations confer resistance through changes to drug binding sites, or by encoding for efflux pumps or loss of porin channels to effectively evade antibiotics.[7,40] • Bacteria produce enzymes that hydrolyze the beta-lactam ring of beta-lactam antibiotics, or cleave other antibiotics, rendering them ineffective.[7,40] o **ESBL**-producing organisms inactivate penicillins, cephalosporins, and aztreonam; and may be co-resistant to fluoroquinolones and aminoglycosides.[7,9] o **CRE** are resistant to carbapenems and co-resistant to fluoroquinolones, as well as some aminoglycosides.[15,16]

Clinical Question	Suggested Approach/Pertinent Information
Which classes of antibiotics remain active against resistant gram-negative organisms?	• **ESBL**-producing organisms usually maintain susceptibility to:[4,7,14,17,18,23,33] o carbapenems (e.g., meropenem, imipenem/cilastatin, ertapenem); preferred for severe or invasive ESBL infections. o ceftazidime/avibactam (however, preferentially reserved for organisms with carbapenem resistance) o high-dose cefepime (**Use is controversial**. For more details, see row titled, *Are beta-lactam antibiotics ever appropriate for ESBL-related infections*?) o high-dose, extended infusion piperacillin/tazobactam (**Use is controversial**. For more details, see row titled, *Are beta-lactam antibiotics ever appropriate for ESBL-related infections*?) • **CRE**-related infections may be susceptible to:[12,19,20,23,40] o ceftazidime/avibactam o meropenem/vaborbactam o imipenem/cilastatin/relebactam o cefiderocol o colistin or Polymyxin B o aminoglycosides (including the newest aminoglycoside, plazomicin) o high-dose tigecycline o high-dose, extended infusion meropenem
Are beta-lactam antibiotics ever appropriate for **ESBL-related infections**?	• Use of **piperacillin/tazobactam** in ESBL-related infections is controversial.[7,24,25] o Has been used successfully for ESBL-producing *E. coli* UTIs, but treatment failures were more common with urosepsis and/or bacteremia, especially with MICs >8 mcg/mL.[25] o In a large multicenter study, outcomes were not statistically significantly different when beta-lactam/beta-lactamase inhibitor combos (predominantly piperacillin/tazobactam) were compared to carbapenems (mostly meropenem) for ESBL-related bloodstream infections.[44] o Piperacillin/tazobactam was not able to demonstrate non-inferiority for 30-day mortality compared to meropenem in patients with *E. coli* or *K. pneumoniae* ceftriaxone-resistant, bloodstream infections [Evidence Level A-1].[54] o High dose (4.5 grams IV q6h), extended infusion (over 3 to 4 hours) improves treatment success rates.[30,45] • Use of **cefepime** in ESBL-related infections is similarly controversial.[26-28] o Cefepime MIC testing results may not be accurate or reproducible when ESBL enzymes are present.[33] o Treatment success has been reported for pneumonia using cefepime 2 grams IV q8h.[26] o In bacteremia, patients treated with cefepime had worse outcomes, even when MIC was ≤8 mcg/mL.[27] • The Infectious Diseases Society of America (IDSA) recommends to avoid use of piperacillin/tazobactam or cefepime in non-urinary tract infections caused by ESBL, even if they appear susceptible based on culture and sensitivity results.[33] See the exception to this in the row below "How should ESBL- and CRE-related lower UTIs (cystitis) be treated."

Clinical Question	Suggested Approach/Pertinent Information
How should ESBL- and CRE-related uncomplicated lower UTIs (cystitis) be treated?	• **Uncomplicated lower UTIs (cystitis)** may be treated with nitrofurantoin, PO fosfomycin (only when *E. coli* is the organism, due to resistance with other organisms that can hydrolyze fosfomycin), aminoglycosides, fluoroquinolones, sulfamethoxazole/trimethoprim or carbapenems when C&S shows susceptibility.[7,21,22,33] Urinary concentrations of these antibiotics are higher than organism MIC, effectively overcoming resistance. See our chart, *Urinary Tract Infections*, for more on treating urinary tract infections, including use of nitrofurantoin in patients with kidney impairment. o Generally, give preference to nitrofurantoin or sulfamethoxazole/trimethoprim.[33] o In addition, for CRE-related uncomplicated cystitis, ciprofloxacin or levofloxacin are also considered preferred antibiotics.[33] Alternatives include single dose aminoglycoside, PO fosfomycin (only if *E. coli*), colistin, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, or cefiderocol.[33] o If using an aminoglycoside, note that CRE isolates are more likely to be susceptible to amikacin and plazomicin, compared to other aminoglycosides.[33] o Only use meropenem for a CRE-related cystitis if CRE is resistant to ertapenem, susceptible to meropenem, and carbapenemase testing results are negative or not available. • If either cefepime or piperacillin/tazobactam is as started as empiric therapy for cystitis, the patient is clinically improving, and it is later determined the cystitis is caused by ESBL-Enterobacterales, it is ok to continue therapy.[33]
What regimens are preferred to treat **ESBL-related infections other than uncomplicated cystitis**?	• **Complicated UTIs and pyelonephritis**: see our chart, *Urinary Tract Infections*, for treatment. o However, note that many labs do not perform ESBL testing. Instead, ceftriaxone MICs ≥2 mcg/mL are assumed to indicate ESBL production.[33] Avoid ceftriaxone in these cases.[33] o The preferred treatment for ESBL-related complicated UTIs and pyelonephritis are a urinary fluoroquinolone (e.g., ciprofloxacin, levofloxacin), or sulfamethoxazole/trimethoprim.[33] If resistance or toxicities prevent the use of fluoroquinolones or sulfamethoxazole/trimethoprim, ertapenem, meropenem, and imipenem-cilastatin are preferred.[33] A full course of an aminoglycoside can be considered as an alternative.[33] • **Infections outside of the urinary tract** may be treated with meropenem, imipenem/cilastatin, or ertapenem.[33] o Though data are limited, consider oral step-down therapy for ESBL-related infections (based on data for bloodstream infections) under the following conditions:[33] ▪ documented susceptibility to the oral agent ▪ patients are hemodynamically stable and without fever ▪ source control of infection ▪ no suspected issues with gastrointestinal tract absorption • Options for oral step-down therapy include sulfamethoxazole/trimethoprim, levofloxacin, and ciprofloxacin.[33]

Clinical Question	Suggested Approach/Pertinent Information
What regimens are preferred to treat **CRE-related infections other than uncomplicated cystitis**?[a]	• **Complicated UTIs and pyelonephritis**: o Consider ceftazidime/avibactam, meropenem/vaborbactam, imipenem/cilastatin/relebactam, or cefiderocol if CRE is resistant to ertapenem and meropenem. o Consider extended-infusion meropenem for **CRE resistant to ertapenem, but susceptible to meropenem** if carbapenemase testing is negative or not available. • **Infections outside of the urinary tract**: Monotherapy with ceftazidime/avibactam, meropenem/vaborbactam, or imipenem/cilastatin/relebactam may be an option.[12,23,24,33,46-52] Choose therapy based on availability of carbapenemase testing and susceptibilities: o Consider **extended-infusion meropenem**, if resistant to ertapenem, **susceptible to meropenem**, and carbapenemase testing is negative or not available.[33] o Consider **ceftazidime/avibactam**, **meropenem/vaborbactam**, or **imipenem/cilastatin/relebactam**:[33] ▪ if resistant to meropenem and ertapenem and carbapenemase testing is negative or not available. ▪ if KPC is identified or carbapenemase testing is positive, but the carbapenemase identify is unknown. o Consider **ceftazidime/avibactam PLUS aztreonam** (using commercially available ceftazidime/avibactam) if MBL-producing carbapenemase (i.e., NDM, VIM, IMP) is identified.[33] Use resulted in clinical cure in several patients with MBL-producing CRE-related bacteremia.[23,33,34] Alternatively, aztreonam/avibactam (Emblaveo) is also now available.[65] Initial data shows in-vitro activity and some efficacy against MBL-producing CRE infections [Evidence Level B-1].[66,67] o Consider **ceftazidime/avibactam** if OXA-48-like carbapenemase is identified.[33] • **Ceftazidime/avibactam** has been used as mono- and combination therapy.[12,23,34,46,50,51] o Provides similar efficacy to meropenem when combined with metronidazole for intra-abdominal infections.[53] • **Meropenem/vaborbactam** has been studied as monotherapy for treatment of suspected or documented CRE infections in the bloodstream, lungs, gastrointestinal tract, and urine.[35] • **Imipenem/cilastatin/relebactam** has been studied as monotherapy for treatment of documented imipenem-nonsusceptible bacterial infections (i.e., hospital-acquired/ventilator-associated pneumonia, complicated intraabdominal infection, or complicated urinary tract infection). Note that the primary pathogen identified in more than 75% of the patients in the study was *Pseudomonas aeruginosa*.[57] • Combination therapy isn't recommended due to the availability of newer agents active against CRE. If older regimens are needed, combine meds based on the site of the infection for KPC-producing *Klebsiella pneumoniae*:[12] o **bloodstream**: carbapenem + colistin or polymyxin B (+/- tigecycline OR aminoglycoside OR rifampin) o **pulmonary**: meropenem + colistin or polymyxin B (+/- tigecycline OR aminoglycoside OR rifampin) o **gastrointestinal tract**: carbapenem + colistin or polymyxin B + tigecycline +/- rifampin

Clinical Question	Suggested Approach/Pertinent Information
How do the newer antibiotics compare to traditional regimens for **CRE-related infections**?	• Preliminary evidence suggests improved efficacy, safety, and survival outcomes with ceftazidime/avibactam-, meropenem/vaborbactam-, imipenem/cilastatin/relebactam-, plazomicin-, or cefiderocol-containing regimens versus traditional antibiotic combinations, such as one that includes a polymyxin.[35,47-49,51,52,57,59] o **ceftazidime/avibactam** ▪ Ceftazidime/avibactam-containing regimens (as monotherapy or with gentamicin) improved treatment success and survival in patients with KPC-producing CRE bacteremia vs other treatments [Evidence Level B-3].[51] Risk of acute kidney injury was significantly lower with ceftazidime/avibactam-containing regimens than with comparator treatments.[51] ▪ Ceftazidime/avibactam significantly reduced 30-day all-cause mortality in patients with CRE bacteremia, pneumonia, or wound infections vs colistin-containing regimens [Evidence Level B-3].[52] ▪ When used as salvage therapy for patients with KPC-producing CRE pneumonia, ceftazidime/avibactam-containing regimens significantly reduced mortality vs other treatments [Evidence Level B-3].[47] o **meropenem/vaborbactam** ▪ Limited data suggest better cure rates with less nephrotoxicity and possible reduced mortality of CRE infections (infections included in the study: bacteremia, hospital-acquired/ventilator-associated bacterial pneumonia, complicated intra-abdominal infection, complicated urinary tract infection, and acute pyelonephritis) with meropenem/vaborbactam monotherapy vs other regimens [Evidence Level B-1].[35] Comparator regimens included combinations of carbapenems, polymyxin B/colistin, aminoglycosides, tigecycline, or ceftazidime/avibactam monotherapy.[35] o **imipenem/cilastatin/relebactam** ▪ Limited data suggest better cure rates with less nephrotoxicity in patients with imipenem-nonsusceptible bacterial infections (infections included in the study: hospital-acquired/ventilator-associated pneumonia, complicated intraabdominal infection, or complicated urinary tract infections) with imipenem/cilastatin/relebactam monotherapy vs colistin plus imipenem [Evidence Level B-1].[57] o **plazomicin** ▪ Limited data suggest reduced 28-day mortality from bloodstream, lung, and complicated UTI CRE infections with plazomicin-containing regimens vs colistin-containing regimens [Evidence Level B-3].[29] Incidence of kidney function decline was significantly lower with plazomicin-containing regimens vs those containing colistin.[29] o **cefiderocol** ▪ Limited data suggest comparable efficacy of cefiderocol vs comparator antibiotics in critically ill patients with nosocomial pneumonia, sepsis, and complicated urinary tract infections with or at risk of multidrug-resistant and carbapenem-resistant gram-negative organisms [Evidence Level B-1].[58,60,61]

Clinical Question	Suggested Approach/Pertinent Information
What regimens are preferred to treat *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR)?	• Multidrug resistant *P. aeruginosa*: NOT susceptible to one or more antibiotic in three or more classes for which susceptibility is expected: penicillins, cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems.[33] • DTR *P. aeruginosa*: NOT susceptible to ANY of the following: piperacillin/tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem/cilastatin, ciprofloxacin, and levofloxacin.[33] • Treatment options vary based on source of infection. Consider these, accounting for susceptibility and formulary:[33] o **Cystitis (uncomplicated)**: ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/cilastatin/relebactam, cefiderocol. A single dose of tobramycin or amikacin is an alternative option. o **Pyelonephritis/complicated UTI**: ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/cilastatin/relebactam, cefiderocol. o **Infections outside the urinary tract**: ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/cilastatin/relebactam. Cefiderocol is an alternative option. • **Avoid meropenem/vaborbactam** with carbapenem-resistant pseudomonas infections. *In vitro* data suggests meropenem/vaborbactam does not provide coverage for carbapenem- or beta-lactam-resistant *Pseudomonas aeruginosa*.[23] • *P. aeruginosa* susceptibility may be more likely with ceftolozane/tazobactam than other agents. This may be because ceftolozane has independent activity against (DTR) *P. aeruginosa* (i.e., does NOT rely on an inhibitor for susceptibility), unlike ceftazidime and imipenem.[33]
What regimens are preferred to treat **CRAB-related infections**?[a]	• The management of CRAB-related infections is particularly difficult due to:[33] o problems in differentiating between colonization and true pathogens in common infection sites (lungs, wounds) o carbapenem resistance in *Acinetobacter baumannii* usually also means resistance to most other typical antibiotics o very limited evidence for effective treatment regimens • Preferred regimen for CRAB usually includes ampicillin/sulbactam 9 grams IV q8h (this high-dose regimen may be effective even if C&S show *Acinetobacter* resistance) in combination with a second antibiotic.[33] o Choose the second agent (consider polymyxin B, minocycline, tigecycline, or cefiderocol) based on site of infection (e.g., a tetracycline for pneumonia, polymyxin for bloodstream infections, colistin for urinary tract infections).[33] • Sulbactam/durlobactam (Xacduro) is FDA-approved for CRAB pneumonia.[36] o Consider if ampicillin/sulbactam cannot be used. o Evidence suggests sulbactam/durlobactam is non-inferior to colistin (both given in combination with imipenem-cilastatin) for the primary endpoint of 28-day all-cause mortality, in the treatment of hospital-acquired or ventilator-associated pneumonia caused by CRAB.[64]

Clinical Question	Suggested Approach/Pertinent Information
What **dosing strategies** should be used for resistant gram-negative infections, other than uncomplicated cystitis?[a] *Continued…*	• Higher doses are used to overcome resistance and improve success rates for ESBL- and CRE-related infections.[12] o **carbapenems** ▪ Meropenem is preferred due to risk of seizures with high doses of imipenem/cilastatin (Primaxin).[12] • Meropenem 2 grams IV q8h infused over 3 to 4 hours (adjust for kidney impairment).[33,36] ▪ Meropenem/vaborbactam (Vabomere) combines a beta-lactamase inhibitor, vaborbactam, with meropenem to improve activity against KPC-producing CREs.[29] • Usual dose is 4 grams (2 grams meropenem/2 grams vaborbactam) IV q8h infused over 3 hours (adjust for kidney impairment).[33] ▪ Ertapenem 1 gram IV q24h (adjust for kidney impairment)[33,36] ▪ Imipenem/cilastatin 500 mg IV q6h over 3 hours[33] ▪ Imipenem/cilastatin/relebactam (Recarbrio) combines a beta-lactamase inhibitor, relebactam, with imipenem/cilastatin to improve activity against KPC-producing CREs.[29] • Usual dose is 1.25 grams (imipenem 500 mg/cilastatin 500 mg/relebactam 250 mg) IV q6h infused over 30 minutes (adjust for kidney impairment).[33,36] o **ceftazidime/avibactam** (Avycaz) ▪ Usual dose is 2.5 grams (ceftazidime 2 grams/0.5 grams avibactam) IV q8h infused over 2 to 3 hours (adjust for kidney impairment).[33,36] o **ceftolozane/tazobactam** (Zerbaxa) ▪ Usual dose is 3 grams (2 grams ceftolozane/1 gram tazobactam) IV q8h infused over 3 hours (adjust for kidney impairment).[33,36] ▪ **cefiderocol** (Fetroja): usual dose is 2 grams IV q8h infused over 3 hours (adjust for kidney impairment).[33,36] o Newer tetracyclines (tigecycline, eravacycline) ▪ **tigecycline** (Tygacil) • Loading dose of 200 mg, followed by 100 mg IV q12h to q24h (this high-dose regimen is recommended when using for treatment of CRE infections).[12,33] ▪ **eravacycline** (Xerava): Usual dose is 1 mg/kg IV q12h.[33] ▪ Consider as alternatives for intra-abdominal infections, skin and soft tissue infections, osteomyelitis, and respiratory infections.[33] Note that eravacycline has less evidence for CRE infections compared to tigecycline.[33] ▪ Avoid use for urinary or bloodstream infections due to low concentrations of drug in the urine and serum.[12,33] ▪ Gastrointestinal adverse effects, especially nausea and vomiting, may be more severe with high-dose regimens, and could be dose-limiting.[12,63] o **sulbactam/durlobactam** (Xacduro): ▪ Usual dose is 2 grams (1 gram sulbactam/1 gram durlobactam) IV q6h over 3 hours.[36]

Clinical Question	Suggested Approach/Pertinent Information
Dosing strategies, continued[a]	○ **colistin** (Note: polymyxin B is preferred over colistin for systemic invasive infections due to kinetic profile.[39]) ▪ Colistimethate (CMS) is a prodrug of colistin, and has more data supporting its use in CRE infections than does polymyxin B.[12] Dose in mg is derived from colistin base activity (CBA). ▪ Colistin achieves higher urinary concentrations, and is preferred for UTIs.[12,39] ▪ Risk of nephrotoxicity is 50% to 60% with standard dosing and may be even higher with high-dose regimens.[37,38] ▪ Note that pharmacokinetic data do not support a weight-based dosing strategy.[39] ▪ Colistin **loading dose**: • 300 mg CBA IV x1.[39] ▪ Colistin **maintenance dosing**: • Give 12 hours after the loading dose.[12,39] • **non-dialysis patients**: ○ Daily dose according to creatinine clearance, **to achieve a target plasma colistin average steady-state level of 2 mg/L** (divide daily dose q12h):[39] ▪ ≥90 mL/min: 360 mg CBA ▪ 80 to <90 mL/min: 340 mg CBA ▪ 70 to <80 mL/min: 300 mg CBA ▪ 60 to <70 mL/min: 275 mg CBA ▪ 50 to <60 mL/min: 245 mg CBA ▪ 40 to <50 mL/min: 220 mg CBA ▪ 30 to <40 mL/min: 195 mg CBA ▪ 20 to <30 mL/min: 175 mg CBA ▪ 10 to <20 mL/min: 160 mg CBA ▪ 5 to <10 mL/min: 145 mg CBA ▪ 0 mL/min: 130 mg CBA • **intermittent HD**: ○ Supplement on dialysis days with 40 mg CBA IV for a 3-hour dialysis session, or 50 mg CBA IV for a 4-hour dialysis session, in addition to a total daily dose of 130 mg CBA IV (divided q12h) **to achieve a target plasma colistin average steady-state level of 2 mg/L**.[39] • **CRRT**: ○ 220 mg CBA IV q12h **to achieve a target plasma colistin average steady-state level of 2 mg/L**.[39]
Continued…	

Clinical Question	Suggested Approach/Pertinent Information
Dosing strategies, continued[a]	○ **polymyxin B** ▪ Structurally related to colistin, differing by only one amino acid.[12] ▪ Achieves higher serum concentrations faster than colistin because no conversion to active drug is needed.[12,39] ▪ Renal dosing adjustments are recommended by the manufacturer, but are not required.[12,36,62] ▪ Polymyxin B **loading dose**: 2 mg to 2.5 mg/kg, using actual body weight[12,39] ▪ Polymyxin B **maintenance dose** strategies: • Give 12 hours after the loading dose[12] • For patients with severe infections, 1.25 to 1.5 mg/kg q12h, using actual body weight. (Note that dose adjustment is not recommended for patients with kidney impairment).[39] • Organism MIC <1 mcg/mL: 2.5 mg/kg per day divided q12h[12] • Organism MIC 1 to 2 mcg/mL: 3 mg/kg per day divided q12h[12] • Organism MIC ≥4 mcg/mL: consider alternative agents[12] ○ **aminoglycosides** ▪ Gentamicin or tobramycin (7 mg/kg), amikacin (15 mg/kg), or plazomicin (15 mg/kg) IV x one dose, then tailor additional doses to serum levels.[12,33,55] ▪ High-dose therapy may increase risk for nephrotoxicity and ototoxicity development, and therapy should be limited to the shortest course possible.[12] ▪ Gentamicin may be more effective for *Klebsiella* species, and amikacin and plazomicin are more active than others for CRE.[12,41,42]
What infection control strategies and stewardship practices can help limit the spread of resistant gram-negative infections?	• Strict isolation precautions should be followed for patients with ESBL- or CRE-related infections.[11] ○ Use of proper handwashing, gloves, and gowns can limit patient-to-patient spread of infection.[7,11] • Indwelling catheters and devices can harbor infection, and should be removed as soon as possible.[6,13] • Excessive antibiotic use should be addressed by antimicrobial stewardship programs.[11] ○ Antibiotic coverage should be narrowed based on C&S results. ○ Restrict use of cefotaxime, cefpodoxime, ceftazidime, and ceftriaxone whenever possible.[7] ○ Restrict use of carbapenems to the Infectious Disease service.[11,13] ○ Avoid carbapenem or colistin monotherapy in CRE infections.[12] • See our toolbox, *Antimicrobial Stewardship*, for additional infection control strategies.

a. Work with your lab for susceptibility testing. Some labs may only run susceptibility for newer antibiotics if specifically requested to do so.

Abbreviations: CDC = Centers for Disease Control and Prevention; CRAB = carbapenem-resistant *Acinetobacter baumannii*; CrCl = creatinine clearance; CRE = carbapenem-resistant Enterobacterales; CRRT = continuous renal replacement therapy; C&S = culture and sensitivity; ESBL = extended-spectrum beta-lactamase; HD = hemodialysis; ICU = intensive care unit; IV = intravenously; KPC = *Klebsiella pneumoniae* carbapenemase; MBL = metallo-beta-lactamase; MIC = minimum inhibitory concentration; PO = by mouth; UTI = urinary tract infection.

Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*	1. High-quality randomized controlled trial (RCT) 2. Systematic review (SR)/Meta-analysis of RCTs with consistent findings 3. All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*	1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).

[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. Am Fam Physician 2004;69:548-56. https://www.aafp.org/pubs/afp/issues/2004/0201/p548.html.]

References

1. World Health Organization. Antimicrobial resistance. November 21, 2023. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance. (Accessed May 8, 2024).
2. CDC. Antibiotic resistance threats in the United States. 2019. https://www.cdc.gov/antimicrobial-resistance/media/pdfs/2019-ar-threats-report-508.pdf?CDC_AAref_Val=https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf. (Accessed May 23, 2024).
3. CDC. Carbapenem-resistant Enterobacterales. https://arpsp.cdc.gov/profile/arln/cre. (Accessed May 23, 2024).
4. Zhanel GG, Lawrence CK, Adam H, et al. Imipenem-Relebactam and Meropenem-Vaborbactam: Two Novel Carbapenem-β-Lactamase Inhibitor Combinations. Drugs. 2018 Jan;78(1):65-98.
5. Thaden JT, Fowler VG, Sexton DJ, Anderson DJ. Increasing Incidence of Extended-Spectrum β-Lactamase-Producing Escherichia coli in Community Hospitals throughout the Southeastern United States. Infect Control Hosp Epidemiol. 2016 Jan;37(1):49-54.
6. Kanj SS, Kanafani ZA. Current concepts in antimicrobial therapy against resistant gram-negative organisms: extended-spectrum beta-lactamase-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, and multidrug-resistant Pseudomonas aeruginosa. Mayo Clin Proc. 2011 Mar;86(3):250-9.
7. Jacoby GA, Munoz-Price LS. The new beta-lactamases. N Engl J Med. 2005 Jan 27;352(4):380-91.
8. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. Clin Microbiol Rev. 2005 Oct;18(4):657-86.
9. Thomson KS. Controversies about extended-spectrum and AmpC beta-lactamases. Emerg Infect Dis. 2001 Mar-Apr;7(2):333-6.
10. Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, et al. Predictors of carbapenem-resistant Klebsiella pneumoniae acquisition among hospitalized adults and effect of acquisition on mortality. Antimicrob Agents Chemother. 2008 Mar;52(3):1028-33.
11. Marchaim D, Chopra T, Bhargava A, et al. Recent exposure to antimicrobials and carbapenem-resistant Enterobacteriaceae: the role of antimicrobial

stewardship. Infect Control Hosp Epidemiol. 2012 Aug;33(8):817-30.
12. Morrill HJ, Pogue JM, Kaye KS, LaPlante KL. Treatment Options for Carbapenem-Resistant Enterobacteriaceae Infections. Open Forum Infect Dis. 2015 May 5;2(2):ofv050.
13. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. Clin Infect Dis. 2011 Jul 1;53(1):60-7.
14. Sader HS, Castanheira M, Flamm RK, et al. Antimicrobial activity of ceftazidime-avibactam against Gram-negative organisms collected from U.S. medical centers in 2012. Antimicrob Agents Chemother. 2014;58(3):1684-92.
15. Fraimow HS, Tsigrelis C. Antimicrobial resistance in the intensive care unit: mechanisms, epidemiology, and management of specific resistant pathogens. Crit Care Clin. 2011 Jan;27(1):163-205.
16. Bratu S, Tolaney P, Karumudi U, et al. Carbapenemase-producing Klebsiella pneumoniae in Brooklyn, NY: molecular epidemiology and in vitro activity of polymyxin B and other agents. J Antimicrob Chemother. 2005 Jul;56(1):128-32.
17. Farrell DJ, Flamm RK, Sader HS, Jones RN. Antimicrobial activity of ceftolozane-tazobactam tested against Enterobacteriaceae and Pseudomonas aeruginosa with various resistance patterns isolated in U.S. Hospitals (2011-2012). Antimicrob Agents Chemother. 2013 Dec;57(12):6305-10.
18. Harris PN, Tambyah PA, Paterson DL. β-lactam and β-lactamase inhibitor combinations in the treatment of extended-spectrum β-lactamase producing Enterobacteriaceae: time for a reappraisal in the era of few antibiotic options? Lancet Infect Dis. 2015 Apr;15(4):475-85.
19. Castanheira M, Farrell SE, Krause KM, et al. Contemporary diversity of β-lactamases among Enterobacteriaceae in the nine U.S. census regions and ceftazidime-avibactam activity tested against isolates producing the most prevalent β-lactamase groups. Antimicrob Agents Chemother. 2014;58(2):833-8.
20. Metan G, Akova M. Reducing the impact of carbapenem-resistant Enterobacteriaceae on vulnerable patient groups: what can be done? Curr Opin Infect Dis. 2016 Dec;29(6):555-560.
21. Salvatore DJ, Resman-Targoff BH. Treatment options for urinary tract infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*. *J Acad Hosp Med* 2015;7:1-4. https://medicine.missouri.edu/sites/default/files/Treatment%20Options%20for%20Urinary%20Tract%20Infections%20Caused%20by%20Extended-Spectrum%20%CE%92-Lactamase-Producing%20Esch.pdf. (Accessed May 23, 2024).
22. Pullukcu H, Tasbakan M, Sipahi OR, et al. Fosfomycin in the treatment of extended spectrum beta-lactamase-producing Escherichia coli-related lower urinary tract infections. Int J Antimicrob Agents. 2007 Jan;29(1):62-5.
23. Pogue JM, Bonomo RA, Kaye KS. Ceftazidime/Avibactam, Meropenem/Vaborbactam, or Both? Clinical and Formulary Considerations. Clin Infect Dis. 2019 Jan 18;68(3):519-524.
24. Bassetti M, Peghin M, Pecori D. The management of multidrug-resistant Enterobacteriaceae. Curr Opin Infect Dis. 2016 Dec;29(6):583-594.
25. Retamar P, López-Cerero L, Muniain MA, et al. Impact of the MIC of piperacillin-tazobactam on the outcome of patients with bacteremia due to extended-spectrum-β-lactamase-producing Escherichia coli. Antimicrob Agents Chemother. 2013 Jul;57(7):3402-4.
26. Zanetti G, Bally F, Greub G, et al. Cefepime versus imipenem-cilastatin for treatment of nosocomial pneumonia in intensive care unit patients: a multicenter, evaluator-blind, prospective, randomized study. Antimicrob Agents Chemother. 2003 Nov;47(11):3442-7.
27. Lee NY, Lee CC, Huang WH, et al. Cefepime therapy for monomicrobial bacteremia caused by cefepime-susceptible extended-spectrum beta-lactamase-producing Enterobacteriaceae: MIC matters. Clin Infect Dis. 2013 Feb;56(4):488-95.
28. Chopra T, Marchaim D, Veltman J, et al. Impact of cefepime therapy on mortality among patients with bloodstream infections caused by extended-spectrum-β-lactamase-producing Klebsiella pneumoniae and Escherichia coli. Antimicrob Agents Chemother. 2012 Jul;56(7):3936-42.
29. Durante-Mangoni E, Andini R, Zampino R. Management of carbapenem-resistant Enterobacteriaceae infections. Clin Microbiol Infect. 2019 Aug;25(8):943-950.
30. Ng TM, Khong WX, Harris PN, et al. Empiric Piperacillin-Tazobactam versus Carbapenems in the Treatment of Bacteraemia Due to Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae. PLoS One. 2016 Apr 22;11(4):e0153696.
31. Raphael E, Glymour MM, Chambers HF. Trends in prevalence of extended-spectrum beta-lactamase-producing Escherichia coli isolated from patients with community- and healthcare-associated bacteriuria: results from 2014 to 2020 in an urban safety-net healthcare system. Antimicrob Resist Infect Control. 2021 Aug 11;10(1):118.
32. McDanel J, Schweizer M, Crabb V, et al. Incidence of Extended-Spectrum β-Lactamase (ESBL)-Producing Escherichia coli and Klebsiella Infections in the United States: A Systematic Literature Review. Infect Control Hosp Epidemiol. 2017 Oct;38(10):1209-1215.
33. Tamma PD, Aitken SL, Bonomo RA, et al. Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections. Clin Infect Dis. 2023 Jul 18:ciad428.
34. Science News. Novel antibiotic combination therapy overcomes deadly drug-resistant bacteria. March 9, 2017. https://www.sciencedaily.com/releases/2017/03/170309171129.htm. (Accessed May 23, 2024).
35. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and Safety of Meropenem-Vaborbactam

versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial. Infect Dis Ther. 2018 Dec;7(4):439-455.
36. Clinical Pharmacology powered by ClinicalKey. Tampa (FL): Elsevier. 2024. http://www.clinicalkey.com. (Accessed May 23, 2024).
37. Vicari G, Bauer SR, Neuner EA, Lam SW. Association between colistin dose and microbiologic outcomes in patients with multidrug-resistant gram-negative bacteremia. Clin Infect Dis. 2013 Feb;56(3):398-404.
38. Pogue JM, Lee J, Marchaim D, et al. Incidence of and risk factors for colistin-associated nephrotoxicity in a large academic health system. Clin Infect Dis. 2011 Nov;53(9):879-84.
39. Tsuji BT, Pogue JM, Zavascki AP, et al. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy. 2019 Jan;39(1):10-39.
40. Suay-García B, Pérez-Gracia MT. Present and Future of Carbapenem-resistant *Enterobacteriaceae* (CRE) Infections. Antibiotics (Basel). 2019 Aug 19;8(3):122.
41. Livermore DM, Mushtaq S, Warner M, et al. Activity of aminoglycosides, including ACHN-490, against carbapenem-resistant Enterobacteriaceae isolates. J Antimicrob Chemother. 2011 Jan;66(1):48-53.
42. Castanheira M, Sader HS, Jones RN. Antimicrobial susceptibility patterns of KPC-producing or CTX-M-producing Enterobacteriaceae. Microb Drug Resist. 2010 Mar;16(1):61-5.
43. Bradley N, Lee Y. Practical Implications of New Antibiotic Agents for the Treatment of Carbapenem-Resistant Enterobacteriaceae. Microbiol Insights. 2019 Apr 4;12:1178636119840367.
44. Gutierrez-Gutierrez B, Perez-Galera S, Salamanca E, et al. A Multinational, Preregistered Cohort Study of β-Lactam/β-Lactamase Inhibitor Combinations for Treatment of Bloodstream Infections Due to Extended-Spectrum-β-Lactamase-Producing Enterobacteriaceae. Antimicrob Agents Chemother. 2016 Jun 20;60(7):4159-69.
45. Patel GW, Patel N, Lat A, et al. Outcomes of extended infusion piperacillin/tazobactam for documented Gram-negative infections. Diagn Microbiol Infect Dis. 2009 Jun;64(2):236-40.
46. Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Machuca I, Pascual A. Treatment of Infections Caused by Extended-Spectrum-Beta-Lactamase-, AmpC-, and Carbapenemase-Producing Enterobacteriaceae. Clin Microbiol Rev. 2018 Feb 14;31(2):e00079-17.
47. Tumbarello M, Trecarichi EM, Corona A, et al. Efficacy of Ceftazidime-Avibactam Salvage Therapy in Patients With Infections Caused by Klebsiella pneumoniae Carbapenemase-producing K. pneumoniae. Clin Infect Dis. 2019 Jan 18;68(3):355-364.
48. Mackow NA, van Duin D. Reviewing novel treatment options for carbapenem-resistant *Enterobacterales*. Expert Rev Anti Infect Ther. 2024 Jan-Jun;22(1-3):71-85.
49. McKinnell JA, Dwyer JP, Talbot GH, et al. Plazomicin for Infections Caused by Carbapenem-Resistant Enterobacteriaceae. N Engl J Med. 2019 Feb 21;380(8):791-793.
50. King M, Heil E, Kuriakose S, et al. Multicenter Study of Outcomes with Ceftazidime-Avibactam in Patients with Carbapenem-Resistant Enterobacteriaceae Infections. Antimicrob Agents Chemother. 2017 Jun 27;61(7):e00449-17.
51. Shields RK, Nguyen MH, Chen L, et al. Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant Klebsiella pneumoniae Bacteremia. Antimicrob Agents Chemother. 2017 Jul 25;61(8):e00883-17.
52. van Duin D, Lok JJ, Earley M, et al. Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae. Clin Infect Dis. 2018 Jan 6;66(2):163-171.
53. Thaden JT, Pogue JM, Kaye KS. Role of newer and re-emerging older agents in the treatment of infections caused by carbapenem-resistant Enterobacteriaceae. Virulence. 2017 May 19;8(4):403-416.
54. 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 Sep 11;320(10):984-994. doi: 10.1001/jama.2018.12163. Erratum in: JAMA. 2019 Jun 18;321(23):2370.
55. Connolly L, Riddle V, Cebrik D, et al. A Multicenter, Randomized, Double-Blind, Phase 2 Study of the Efficacy and Safety of Plazomicin Compared with Levofloxacin in the Treatment of Complicated Urinary Tract Infection and Acute Pyelonephritis. Antimicrob Agents Chemother. 2018 Mar 27;62(4):e01989-17.
56. CDC. Carbapenem-resistant Acinetobacter. https://arpsp.cdc.gov/profile/antibiotic-resistance/carbapenem-resistant-acinetobacter. (Accessed May 24, 2024).
57. Motsch J, Murta de Oliveira C, Stus V, et al. RESTORE-IMI 1: A Multicenter, Randomized, Double-blind Trial Comparing Efficacy and Safety of Imipenem/Relebactam vs Colistin Plus Imipenem in Patients With Imipenem-nonsusceptible Bacterial Infections. Clin Infect Dis. 2020 Apr 15;70(9):1799-1808.
58. Wu JY, Srinivas P, Pogue JM. Cefiderocol: A Novel Agent for the Management of Multidrug-Resistant Gram-Negative Organisms. Infect Dis Ther. 2020 Mar;9(1):17-40.
59. Viale P, Sandrock CE, Ramirez P, et al. Treatment of critically ill patients with cefiderocol for infections caused by multidrug-resistant pathogens: review of the evidence. Ann Intensive Care. 2023 Jun 15;13(1):52.

60. Wunderink RG, Matsunaga Y, Ariyasu M, et.al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis. 2021 Feb;21(2):213-225.
61. Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. Lancet Infect Dis. 2021 Feb;21(2):226-240.
62. Product information for polymyxin B injection. Eugia US. E. Windsor, NJ 08520. June 2023.
63. Huang PY, Hsu CK, Tang HJ, Lai CC. Eravacycline: a comprehensive review of in vitro activity, clinical efficacy, and real-world applications. Expert Rev Anti Infect Ther. 2024 May 8:1-12.
64. Kaye KS, Shorr AF, Wunderink RG, et al. Efficacy and safety of sulbactam-durlobactam versus colistin for the treatment of patients with serious infections caused by Acinetobacter baumannii-calcoaceticus complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK). Lancet Infect Dis. 2023 Sep;23(9):1072-1084.
65. Pfizer. European Commission approves Pfizer's Emblaveo for patients with multidrug-resistant infections and limited treatment options. April 22, 2024. https://www.pfizer.com/news/press-release/press-release-detail/european-commission-approves-pfizers-emblaveor-patients. (Accessed May 25, 2024).
66. Papp-Wallace KM, Sader HS, Maher JM, et al. Aztreonam-avibactam Demonstrates Potent Activity Against Carbapenem-resistant Enterobacterales Collected From US Medical Centers Over a 6-year Period (2017-2022). Open Forum Infect Dis. 2025 Apr 25;12(5):ofaf250.
67. Daikos GL, Cisneros JM, Carmeli Y, et al. Aztreonam-avibactam for the treatment of serious infections caused by metallo-β-lactamase-producing Gram-negative pathogens: a Phase 3 randomized trial (ASSEMBLE). JAC Antimicrob Resist. 2025 Jul 28;7(4):dlaf131.

Cite this document as follows: **Clinical Resource,** ***Resistant Gram-Negative Bacterial Infections. Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights.*** **June 2024. [400619]**

Considerations for IV-to-PO Conversions

Converting patients from IV to oral meds has a number of benefits. For example, it can help reduce drug costs and workload for nurses and pharmacy staff, IV lines can be removed earlier, and it can possibly provide another option when an IV medication is in short supply. There are three different types of IV-to-PO conversions: sequential (replacing an IV med with its oral formulation), switching (replacing an IV med with an oral formulation that has the same effects), and step-down (replacing an IV med with an oral formulation that has similar effects).[1,2,11] The following table lists considerations for IV-to-PO conversions of commonly used meds. Keep in mind, **you'll need to consider multiple factors when looking at the possibility of conversion** (e.g., renal/hepatic dosing adjustments, indication, disease severity). In addition, consider interactions between oral meds and enteral feeding (for more details see our algorithm, *A Stepwise Approach: Selecting Meds for Feeding Tube Administration*).

NOTE: Doses in this chart do not take into consideration adjustments for kidney or liver dysfunction, or for weight. Some of the dose conversions below are approximations. As appropriate, monitor and adjust the oral dose.

Med	IV-to-PO Considerations	Comments
Acetazolamide	Doses for IV and immediate-release tabs are the same.[3]	NA
Amiodarone	If <1 week IV infusion: switch to 400 to 1,600 mg/day PO.[14] If 1 to 2 weeks IV: switch to 400 to 800 mg/day PO.[14] If >2 weeks IV: switch to 100 mg to 400 mg/day PO.[14] Administer above oral doses until total load (IV plus PO) of 6 g to 10 g is reached, then start oral maintenance dose (100 mg to 400 mg once daily, depending on the indication).[14]	Oral dosing is dependent on the indication.[14] Oral doses can be given once daily or divided BID if patients have GI intolerance or total daily dose is 800 mg to 1,000 mg or higher.
Ampicillin	Convert to PO amoxicillin.[6] Dose conversion will depend on indication. Ampicillin and amoxicillin have nearly identical spectrums of activity.[4]	Amoxicillin has better GI absorption than PO ampicillin.[4]
Ampicillin-sulbactam	Convert to PO amoxicillin-clavulanic acid. Dose conversion will depend on indication. Ampicillin-sulbactam and amoxicillin–clavulanic acid have nearly identical spectrums of activity.[4]	NA
Azithromycin	500 mg IV Q24H to 500 mg PO Q24H.[6]	NA
Bumetanide	Dose of IV and PO bumetanide are the same.[3]	Up to 85% to 95% of oral bumetanide is absorbed.[3]

Med	IV-to-PO Considerations		Comments
Cefazolin	Convert cefazolin 1 g IV Q8H to cephalexin 500 mg PO Q6H.[6]		NA
Ciprofloxacin	200 mg IV Q12H to 250 mg PO Q12H.[3] 400 mg IV Q12H to 500 mg PO Q12H.[3] 400 mg IV Q8H to 750 mg PO Q12H.[3]		NA
Clindamycin	Convert 600 mg IV Q8H to 300 to 450 mg PO Q6H.[6]		NA
Dexamethasone	Doses of IV and PO dexamethasone are the same.[7]		The bioavailability of oral dexamethasone has been reported as 60% to 100%.[3]
Digoxin	50 mcg IV to 62.5 mcg (0.0625 **mg**) PO. 100 mcg IV to 125 mcg (0.125 **mg**) PO. 200 mcg IV to 250 mcg (0.25 **mg**) PO. 400 mcg IV to 500 mcg (0.5 **mg**) PO.		Digoxin oral tablets are 60% to 80% bioavailable.
Diltiazem	**For an IV infusion rate of:**	**Convert to PO dose of**:[10]	Oral dose = (IV drip rate [mg/hr] x 3 + 3) x 10.[10] Divide daily doses of oral products as appropriate per formulation.
	3 mg/hr	120 mg/day	
	5 mg/hr	180 mg/day	
	7.5 mg/hr	260 mg/day	
	10 mg/hr	330 mg/day	
	15 mg/hr	480 mg/day	
Doxycycline	Dose and frequency of IV and immediate-release PO are the same.[5]		NA
Enalaprilat	**For Hypertension:** Enalaprilat 1.25 mg IV Q6H to enalapril 5 mg/day PO. Enalaprilat 0.625 mg IV Q6H to enalapril 2.5 mg/day PO.		Adjust initial dose based on blood pressure response. Oral enalapril doses may be given once daily or divided twice daily.[3]
Esomeprazole	Dose and frequency of IV and PO esomeprazole are similar.[5]		Bioavailability of oral esomeprazole is around 90% with repeated daily dosing.[3]

Med	IV-to-PO Considerations	Comments
Famotidine	Dose and frequency of IV and PO famotidine are the same.[5]	NA
Fluconazole	Doses of IV and PO fluconazole are the same.[6]	NA
Furosemide	IV to PO conversion is ~1 mg IV to 2 mg PO.[12]	Bioavailability is ~50% for furosemide tablets and oral solution.[12]
Hydrocortisone	Doses of IV and PO hydrocortisone are the same.[7]	Corticosteroid dose and dose frequency is determined by disease severity.
Hydromorphone	1.5 mg IV is equianalgesic to 6 to 7.5 mg of immediate-release PO.[8,13] Dose conversions are approximate. Titrate to response.	See our chart, *Equianalgesic Dosing of Opioids for Pain Management*, for more details.
Hydralazine	Double the IV dose and administer orally, then titrate to effect.[3]	NA
Isavuconazonium	Doses and frequency of IV and PO isavuconazonium are the same.[3]	NA
Labetalol	Following inpatient IV treatment, start PO treatment with 200 mg PO x1, then 200 or 400 mg PO 6 to 12 hours later depending on blood pressure response. Titrate PO dose up to 1,200 mg Q12H if needed.	Administer an oral dose once blood pressure has started to increase following discontinuation of IV labetalol.
Lacosamide	Dose and frequency of IV and PO lacosamide are the same.[3]	NA
Levetiracetam	Dose and frequency of IV and PO (immediate-release) are the same.[5]	NA
Levofloxacin	Dose and frequency of IV and PO are the same.[6]	NA
Levothyroxine	Increase the IV dose by ~20% to 25% for oral administration. Dose should then be titrated based on clinical status and lab results.[3]	Bioavailability of oral levothyroxine is about 50% to 75%.[3]

Med	IV-to-PO Considerations	Comments
Linezolid	600 mg IV Q12H to 600 mg PO BID.[6]	NA
Methylprednisolone	Dose of IV and PO methylprednisolone are the same.[3,7] Methylprednisolone 4 mg is equivalent to prednisone or prednisolone 5 mg.[3,7]	Corticosteroid dose and dose frequency is determined by disease severity.
Metoprolol	Equivalent maximal beta-blocking effect may be achieved with IV and PO doses (mg) in a ratio of 1:2.5. Note that patient variability may exist and caution should be used if converting patients on large chronic oral doses to intravenous metoprolol. For example, consider converting an oral daily dose of 50 mg to 2.5 mg to 5 mg IV Q6H (ratio range of 5:1 to 2.5:1).[14]	The duration of action is shorter with the IV formulation, compared to oral. Monitor and adjust dose as needed.[9] Divide daily doses of oral products as appropriate per formulation.
Metronidazole	Doses of IV and PO are the same.[6]	NA
Morphine	10 mg IV is equianalgesic to 30 mg PO.[8,13] Dose conversions are approximate. Titrate to response.	See our chart, *Equianalgesic Dosing of Opioids for Pain Management*, for more details.
Moxifloxacin	400 mg IV Q24H to 400 mg PO Q24H.[5]	NA
Pantoprazole	Dose and frequency of IV and PO pantoprazole are the same.[5]	NA
Phenytoin	The total daily dose of IV and PO phenytoin are the same.[5] Note that frequency differs. IV is often administered Q8H while oral forms should be administered based on the formulation (which may be once daily if extended-release).	Bioavailability of oral phenytoin is 90% to 100%; however, absorption rates vary between different products.[3]
Rifampin	Dosing recommendations for IV and PO rifampin are the same.[5]	NA
Trimethoprim-sulfamethoxazole	Dose and frequency of IV and PO are the same.[6]	NA

Med	IV-to-PO Considerations	Comments
Valproate sodium	The total daily dose of IV valproate sodium and oral valproic acid/divalproex products are the same.[3]	Divide daily doses of oral products as appropriate per formulation.
Voriconazole	Convert 200 mg IV Q12H to 200 mg PO Q12H.[5,6]	NA

Abbreviations: BID = twice daily; GI = gastrointestinal; NA = not applicable; PO = oral; IV = intravenous; TID = three times daily.

Information in the above chart is from the following US product labeling, unless otherwise specified: *Pacerone* (September 2020); digoxin tablet (Amneal Pharmaceuticals, February 2019); enalaprilat injection (Hikma Pharmaceuticals, May 2022); labetalol injection (Hospira, November 2022); metoprolol injection (Baxter Healthcare, February 2023).

Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*	1. High-quality randomized controlled trial (RCT) 2. Systematic review (SR)/Meta-analysis of RCTs with consistent findings 3. All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*	1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).

[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. Am Fam Physician 2004;69:548-56. https://www.aafp.org/pubs/afp/issues/2004/0201/p548.html.]

References

1. Shrayteh ZM, Rahal MK, Malaeb DN. Practice of switch from intravenous to oral antibiotics. Springerplus. 2014 Dec 9;3:717.
2. Wetzstein GA. Intravenous to oral (iv:po) anti-infective conversion therapy. Cancer Control. 2000 Mar-Apr;7(2):170-6.
3. Clinical Pharmacology powered by ClinicalKey. Tampa (FL): Elsevier. 2024. http://www.clinicalkey.com. (Accessed April 29, 2024).
4. Gilbert DN, Chambers HF, Eliopoulos GM, et al, Eds. Sanford Guide Web Edition. Sperryville, VA: Antimicrobial Therapy, Inc., 2024. https://webedition.sanfordguide.com/en. (Accessed April 29, 2024).
5. Cyriac JM, James E. Switch over from intravenous to oral therapy: A concise overview. J Pharmacol Pharmacother. 2014 Apr;5(2):83-7.
6. Sunnybrook Health Sciences Centre. Intravenous to oral conversion. Last updated April 18, 2018. https://sunnybrook.ca/content/?page=antimicrobial-stewardship-iv-oral. (Accessed May 6, 2024).
7. Furst DE, Saag KG. Overview of the pharmacologic use of glucocorticoids. Last updated March 11, 2024. In UpToDate, Post TW (ed), UpToDate, Waltham, MA 02013.
8. Clinical Resource, *Equianalgesic Dosing of Opioids for Pain Management. Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber's Letter*. March 2023. [390329].
9. Dasta JF, Boucher BA, Brophy GM, et al. Intravenous to oral conversion of antihypertensives: a toolkit for guideline development. Ann Pharmacother. 2010 Sep;44(9):1430-47.
10. UW Health. Atrial fibrillation – rate control drugs. March 20, 2019. https://www.uwhealth.org/cckm/cpg/cardiovascular/related/Atrial-Fibrillation-Mgt---Rate-Control-Drugs-190312.pdf. (Accessed April 29, 2024).
11. Mazumder SA. Intravenous-to-oral switch therapy. Updated November 13, 2023. https://emedicine.medscape.com/article/237521-overview#a2. (Accessed April 29, 2024).
12. Ezekowitz JA, O'Meara E, McDonald MA, et al. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the

Management of Heart Failure. Can J Cardiol. 2017 Nov;33(11):1342-1433.
13. Tan S, Lee E, Lee S, et al. Morphine Equianalgesic Dose Chart in the Emergency Department. J Educ Teach Emerg Med. 2022 Jul 15;7(3):L1-L20.
14. Lexi-Drugs. UpToDate LexiDrug. UpToDate Inc. https://online.lexi.com. (Accessed May 8, 2024).

Cite this document as follows: **Clinical Resource*, Considerations for IV-to-PO Conversions. Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights.* June 2024. [400618]**