# Resistant Gram-Negative Bacterial Infections

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

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| Risk factors, continued | • Additional risk factors specific to **CRE-related infections** include:[10,11]<br>o antibiotic use within previous three months<br>o use of third- or fourth-generation cephalosporins and/or carbapenems<br>o trauma<br>o diabetes<br>o malignancy<br>o organ transplantation |
| Which organisms are most likely to produce **ESBL**? | • Only gram-negative organisms are capable of producing ESBL.<br>• *Klebsiella pneumoniae, Klebsiella oxytoca*, and *Escherichia coli* are the most common organisms that produce ESBL.[7]<br>• 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]<br>• Carbapenem-resistant infections have also been caused by *Acinetobacter baumannii*, *Enterobacter cloacae*, and *Pseudomonas aeruginosa*.[12-15]<br>• The most commonly reported carbapenemase is *Klebsiella pneumoniae* carbapenemase (KPC).[3,33] This carbapenemase is not limited to *Klebsiella pneumoniae* isolates.[33]<br>• 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]<br>• 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]<br>• Bacteria produce enzymes that hydrolyze the beta-lactam ring of beta-lactam antibiotics, or cleave other antibiotics, rendering them ineffective.[7,40]<br>o **ESBL**-producing organisms inactivate penicillins, cephalosporins, and aztreonam; and may be co-resistant to fluoroquinolones and aminoglycosides.[7,9]<br>o **CRE** are resistant to carbapenems and co-resistant to fluoroquinolones, as well as some aminoglycosides.[15,16] |

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| 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]<br>o carbapenems (e.g., meropenem, imipenem/cilastatin, ertapenem); preferred for severe or invasive ESBL infections.<br>o ceftazidime/avibactam (however, preferentially reserved for organisms with carbapenem resistance)<br>o high-dose cefepime (**Use is controversial**. For more details, see row titled, *Are beta-lactam antibiotics ever appropriate for ESBL-related infections*?)<br>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*?)<br><br>• **CRE**-related infections may be susceptible to:[12,19,20,23,40]<br>o ceftazidime/avibactam<br>o meropenem/vaborbactam<br>o imipenem/cilastatin/relebactam<br>o cefiderocol<br>o colistin or Polymyxin B<br>o aminoglycosides (including the newest aminoglycoside, plazomicin)<br>o high-dose tigecycline<br>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]<br>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]<br>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]<br>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]<br>o High dose (4.5 grams IV q6h), extended infusion (over 3 to 4 hours) improves treatment success rates.[30,45]<br>• Use of **cefepime** in ESBL-related infections is similarly controversial.[26-28]<br>o Cefepime MIC testing results may not be accurate or reproducible when ESBL enzymes are present.[33]<br>o Treatment success has been reported for pneumonia using cefepime 2 grams IV q8h.[26]<br>o In bacteremia, patients treated with cefepime had worse outcomes, even when MIC was ≤8 mcg/mL.[27]<br>• 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 |
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| 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.<br>o Generally, give preference to nitrofurantoin or sulfamethoxazole/trimethoprim.[33]<br>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]<br>o If using an aminoglycoside, note that CRE isolates are more likely to be susceptible to amikacin and plazomicin, compared to other aminoglycosides.[33]<br>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.<br>• 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.<br>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]<br>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]<br>• **Infections outside of the urinary tract** may be treated with meropenem, imipenem/cilastatin, or ertapenem.[33]<br>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]<br>▪ documented susceptibility to the oral agent<br>▪ patients are hemodynamically stable and without fever<br>▪ source control of infection<br>▪ no suspected issues with gastrointestinal tract absorption<br>• Options for oral step-down therapy include sulfamethoxazole/trimethoprim, levofloxacin, and ciprofloxacin.[33] |

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| What regimens are preferred to treat **CRE-related infections other than uncomplicated cystitis**?[a] | • **Complicated UTIs and pyelonephritis**:<br>o Consider ceftazidime/avibactam, meropenem/vaborbactam, imipenem/cilastatin/relebactam, or cefiderocol if CRE is resistant to ertapenem and meropenem.<br>o Consider extended-infusion meropenem for **CRE resistant to ertapenem, but susceptible to meropenem** if carbapenemase testing is negative or not available.<br>• **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:<br>o Consider **extended-infusion meropenem**, if resistant to ertapenem, **susceptible to meropenem**, and carbapenemase testing is negative or not available.[33]<br>o Consider **ceftazidime/avibactam**, **meropenem/vaborbactam**, or **imipenem/cilastatin/relebactam**:[33]<br>▪ if resistant to meropenem and ertapenem and carbapenemase testing is negative or not available.<br>▪ if KPC is identified or carbapenemase testing is positive, but the carbapenemase identify is unknown.<br>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] There is an aztreonam/avibactam drug in the pipeline (approved in the European Union in 2024).[65] More data are needed to know if the new drug is effective against MBL-producing CRE infections.<br>o Consider **ceftazidime/avibactam** if OXA-48-like carbapenemase is identified.[33]<br>• **Ceftazidime/avibactam** has been used as mono- and combination therapy.[12,23,34,46,50,51]<br>o Provides similar efficacy to meropenem when combined with metronidazole for intra-abdominal infections.[53]<br>• **Meropenem/vaborbactam** has been studied as monotherapy for treatment of suspected or documented CRE infections in the bloodstream, lungs, gastrointestinal tract, and urine.[35]<br>• **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]<br>• 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]<br>o **bloodstream**: carbapenem + colistin or polymyxin B (+/- tigecycline OR aminoglycoside OR rifampin)<br>o **pulmonary**: meropenem + colistin or polymyxin B (+/- tigecycline OR aminoglycoside OR rifampin)<br>o **gastrointestinal tract**: carbapenem + colistin or polymyxin B + tigecycline +/- rifampin |

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| 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]<br>○ **ceftazidime/avibactam**<br>▪ 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]<br>▪ 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]<br>▪ 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]<br>○ **meropenem/vaborbactam**<br>▪ 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]<br>○ **imipenem/cilastatin/relebactam**<br>▪ 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]<br>○ **plazomicin**<br>▪ 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]<br>○ **cefiderocol**<br>▪ 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] |

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| 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]<br>• DTR *P. aeruginosa*: NOT susceptible to ANY of the following: piperacillin/tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem/cilastatin, ciprofloxacin, and levofloxacin.[33]<br>• Treatment options vary based on source of infection. Consider these, accounting for susceptibility and formulary:[33]<br>o **Cystitis (uncomplicated)**: ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/cilastatin/relebactam, cefiderocol. A single dose of tobramycin or amikacin is an alternative option.<br>o **Pyelonephritis/complicated UTI**: ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/cilastatin/relebactam, cefiderocol.<br>o **Infections outside the urinary tract**: ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/cilastatin/relebactam. Cefiderocol is an alternative option.<br>• **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]<br>• *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]<br>o problems in differentiating between colonization and true pathogens in common infection sites (lungs, wounds)<br>o carbapenem resistance in *Acinetobacter baumannii* usually also means resistance to most other typical antibiotics<br>o very limited evidence for effective treatment regimens<br>• 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]<br>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]<br>• Sulbactam/durlobactam (*Xacduro*) is FDA-approved for CRAB pneumonia.[36]<br>o Consider if ampicillin/sulbactam cannot be used.<br>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] |

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| What **dosing strategies** should be used for resistant gram-negative infections, other than uncomplicated cystitis?[a] | • Higher doses are used to overcome resistance and improve success rates for ESBL- and CRE-related infections.[12]<br>o **carbapenems**<br>▪ Meropenem is preferred due to risk of seizures with high doses of imipenem/cilastatin (*Primaxin*).[12]<br>• Meropenem 2 grams IV q8h infused over 3 to 4 hours (adjust for kidney impairment).[33,36]<br>▪ Meropenem/vaborbactam (*Vabomere*) combines a beta-lactamase inhibitor, vaborbactam, with meropenem to improve activity against KPC-producing CREs.[29]<br>• Usual dose is 4 grams (2 grams meropenem/2 grams vaborbactam) IV q8h infused over 3 hours (adjust for kidney impairment).[33]<br>▪ Ertapenem 1 gram IV q24h (adjust for kidney impairment)[33,36]<br>▪ Imipenem/cilastatin 500 mg IV q6h over 3 hours[33]<br>▪ Imipenem/cilastatin/relebactam (*Recarbrio*) combines a beta-lactamase inhibitor, relebactam, with imipenem/cilastatin to improve activity against KPC-producing CREs.[29]<br>• 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]<br>o **ceftazidime/avibactam** (*Avycaz*)<br>▪ 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]<br>o **ceftolozane/tazobactam** (*Zerbaxa*)<br>▪ Usual dose is 3 grams (2 grams ceftolozane/1 gram tazobactam) IV q8h infused over 3 hours (adjust for kidney impairment).[33,36]<br>▪ **cefiderocol** (*Fetroja*): usual dose is 2 grams IV q8h infused over 3 hours (adjust for kidney impairment).[33,36]<br>o Newer tetracyclines (tigecycline, eravacycline)<br>▪ **tigecycline** (*Tygacil*)<br>• 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]<br>▪ **eravacycline** (*Xerava*): Usual dose is 1 mg/kg IV q12h.[33]<br>▪ 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]<br>▪ Avoid use for urinary or bloodstream infections due to low concentrations of drug in the urine and serum.[12,33]<br>▪ Gastrointestinal adverse effects, especially nausea and vomiting, may be more severe with high-dose regimens, and could be dose-limiting.[12,63]<br>o **sulbactam/durlobactam** (*Xacduro*):<br>▪ Usual dose is 2 grams (1 gram sulbactam/1 gram durlobactam) IV q6h over 3 hours.[36] |
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| Clinical Question | Suggested Approach/Pertinent Information |
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| Dosing strategies, continued[a] | ○ **colistin** (Note: polymyxin B is preferred over colistin for systemic invasive infections due to kinetic profile.[39])<br>▪ 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).<br>▪ Colistin achieves higher urinary concentrations, and is preferred for UTIs.[12,39]<br>▪ Risk of nephrotoxicity is 50% to 60% with standard dosing and may be even higher with high-dose regimens.[37,38]<br>▪ Note that pharmacokinetic data do not support a weight-based dosing strategy.[39]<br>▪ Colistin **loading dose**:<br>• 300 mg CBA IV x1.[39]<br>▪ Colistin **maintenance dosing**:<br>• Give 12 hours after the loading dose.[12,39]<br>• **non-dialysis patients**:<br>○ 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]<br>▪ ≥90 mL/min: 360 mg CBA<br>▪ 80 to <90 mL/min: 340 mg CBA<br>▪ 70 to <80 mL/min: 300 mg CBA<br>▪ 60 to <70 mL/min: 275 mg CBA<br>▪ 50 to <60 mL/min: 245 mg CBA<br>▪ 40 to <50 mL/min: 220 mg CBA<br>▪ 30 to <40 mL/min: 195 mg CBA<br>▪ 20 to <30 mL/min: 175 mg CBA<br>▪ 10 to <20 mL/min: 160 mg CBA<br>▪ 5 to <10 mL/min: 145 mg CBA<br>▪ 0 mL/min: 130 mg CBA<br>• **intermittent HD**:<br>○ 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]<br>• **CRRT**:<br>○ 220 mg CBA IV q12h **to achieve a target plasma colistin average steady-state level of 2 mg/L**.[39] |
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| Clinical Question | Suggested Approach/Pertinent Information |
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| Dosing strategies, continued[a] | ○ **polymyxin B**<br>▪ Structurally related to colistin, differing by only one amino acid.[12]<br>▪ Achieves higher serum concentrations faster than colistin because no conversion to active drug is needed.[12,39]<br>▪ Renal dosing adjustments are recommended by the manufacturer, but are not required.[12,36,62]<br>▪ Polymyxin B **loading dose**: 2 mg to 2.5 mg/kg, using actual body weight[12,39]<br>▪ Polymyxin B **maintenance dose** strategies:<br>• Give 12 hours after the loading dose[12]<br>• 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]<br>• Organism MIC <1 mcg/mL: 2.5 mg/kg per day divided q12h[12]<br>• Organism MIC 1 to 2 mcg/mL: 3 mg/kg per day divided q12h[12]<br>• Organism MIC ≥4 mcg/mL: consider alternative agents[12]<br>○ **aminoglycosides**<br>▪ 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]<br>▪ High-dose therapy may increase risk for nephrotoxicity and ototoxicity development, and therapy should be limited to the shortest course possible.[12]<br>▪ 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]<br>○ Use of proper handwashing, gloves, and gowns can limit patient-to-patient spread of infection.[7,11]<br>• Indwelling catheters and devices can harbor infection, and should be removed as soon as possible.[6,13]<br>• Excessive antibiotic use should be addressed by antimicrobial stewardship programs.[11]<br>○ Antibiotic coverage should be narrowed based on C&S results.<br>○ Restrict use of cefotaxime, cefpodoxime, ceftazidime, and ceftriaxone whenever possible.[7]<br>○ Restrict use of carbapenems to the Infectious Disease service.[11,13]<br>○ Avoid carbapenem or colistin monotherapy in CRE infections.[12]<br>• 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.

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***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)<br>2. Systematic review (SR)/Meta-analysis of RCTs with consistent findings<br>3. All-or-none study |
| **B** | Inconsistent or limited-quality patient-oriented evidence.* | 1. Lower-quality RCT<br>2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings<br>3. Cohort study<br>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.]

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