trchealthcare

New Drug

Ceftobiprole Medocaril (Zevtera)

Why it matters:

Antibiotic options are limited for treating methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Ceftobiprole medocaril is a prodrug of active ceftobiprole and is the second available IV cephalosporin antibiotic that can target MRSA, similar to ceftaroline.

What else to know:

Ceftobiprole may cause nausea, vomiting, anemia, or liver injury. Avoid use in ventilator-associated pneumonia since studies suggest ceftobiprole may have higher mortality.

Manufacturer	Basilea Pharmaceutica International Ltd
Approved use	• *Staphylococcus aureus* bacteremia (including MRSA) in adults. • Acute bacterial skin and skin structure infections in adults. • Community-acquired pneumonia (CAP) in ages 3 months and up.
Approval date	April 2024
Anticipated availability	Available now
Dosage and administration (adults)	• Skin infections and CAP: 667 mg IV every 8 hours. • Blood stream infections: 667 mg IV every 6 hours for 8 days, then 667 mg IV every 8 hours thereafter. • Infuse each dose over 2 hours. • Reduce dose for CrCl <50 mL/min and increase frequency to every 6 hours if CrCl >150 mL/min, regardless of indication.
Storage requirements	• Refrigerate unopened vials and prepared doses at 2 to 8°C and protect from light. • Beyond-use dates for prepared doses range from 24 to 94 hours depending on the diluent and ceftobiprole concentration. • Light protection is not required during administration.
Prescribing information	https://innovivaspecialtytherapeutics.com/products/

Article, *Clarify the Limited Role of Ceftobiprole*. *Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber Insights.* July 2025. [410663]

Ceftobiprole Medocaril (Zevtera)

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Skin and Soft Tissue Infections

The following FAQ addresses common questions about diabetic foot infections, and antibiotic choices for cellulitis/erysipelas and necrotizing infections. A chart, *Antibiotics for MRSA Skin Infections,* is also included to help with choice of antibiotic.

--Information in chart may differ from product labelling. Information pertains to ADULTS--

Clinical Question	Pertinent Information or Suggested Approach
What are some risk factors for **foot infections in patients with diabetes**?	• Poor glycemic control[2] • Peripheral neuropathy, especially with loss of protective sensation[2] • Peripheral artery disease[2] • Foot deformity, corns, or calluses[2] • Previous foot ulceration or amputation[2] • Visual impairment[2] • Chronic kidney disease, especially for patients receiving dialysis[2] • Smoking[2]

What can be done to **prevent foot infections** in patients with **diabetes**?	• Patients should check their feet every day.[2]
	  ○ Palpate the feet.
	  ○ Visually examine all parts of the feet, using a non-breakable mirror as needed.[2]
	  ○ Enlist the help of caregivers (i.e., if the patient has visual, physical, or cognitive problems that impair their ability to assess their feet).[2]
	• Choose appropriate shoes (e.g., well-fitting walking or running shoes; no open-toe sandals).[2]
	  ○ Refer patients who may benefit for specialized shoes or orthotics (e.g., patients with plantar calluses, hammertoes, ulcers, Charcot foot, loss of protective sensation, poor circulation, history of amputation).[2]
	• Patients should avoid going barefoot.[2]
	• Advise use of a moisturizer on dry or scaly skin.[2]
	• Avoid self-treatment of ingrown toenails or calluses.[2]
	• Patients should seek urgent medical care for ulceration, redness, swelling, or skin warmth.[2]
	• Advise a comprehensive foot exam at least yearly (patients with sensory loss or prior ulceration or amputation should have their feet inspected at each visit).[2] This should include:
	  ○ documentation of risk factors.[2]
	  ○ physical exam (10 g monofilament test plus pinprick, temperature, or vibration testing; visual inspection; assessment for deformities; assessment of pulses in legs and feet).[2]
	  ○ inquiry about symptoms (e.g. pain, burning, numbness, leg fatigue, claudication).[2]

Clinical Question	Pertinent Information or Suggested Approach
What topical products have evidence for management of diabetic foot ulcers?	• Treatment of diabetic ulcers includes offloading, revascularization, debridement, treatment of infection, and physiologic wound dressings.[2] • Patients who do not achieve a 50% reduction of wound area within four weeks can be referred for "advanced" wound management.[2] o Evidence from placebo-controlled RCTs to guide selection of advanced wound therapies is lacking.[2] o Interventions with the most evidence include placental membranes, bioengineered skin substitutes, acellular matrices, and autologous platelet/leukocyte/fibrin patches.[2] Topical antibiotics or antiseptics, honey, negative pressure devices, topical or hyperbaric oxygen lack convincing evidence.[1]
How are diabetic foot infections classified?	• **Mild infections** only involve the skin or subcutaneous tissue; there are no systemic signs or symptoms.[1] Two or more of the following are present: erythema extending >0.5 to <2 cm from the wound margin; local swelling or induration; local tenderness or pain; warmth; and/or purulent discharge.[1] • **Moderate infections** have erythema extending ≥2 cm from the wound margin, and/or involve bone, joint, tendon, or muscle, without systemic symptoms.[1] • **Severe infections** are any foot infection with ≥2 of the following: temp >38°C or <36°C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute or PaCO2 <32 mmHg; WBC >12,000 per mcL or <4,000 per mcL, or ≥10% bands.[1]
What are the **empiric** antibiotic choices for **diabetic foot infections**? *Continued…*	• General considerations: o Consult surgery for patients with severe infection or moderate infection with extensive gangrene, severe ischemia, necrotizing infection, deep abscess, or compartment syndrome.[1] o Choose empiric coverage based on likely organisms, cost, adverse effects, allergies, and infection severity.[1] o Switch to targeted coverage when culture and sensitivity results (of **tissue** collected aseptically with biopsy or curettage) are available.[1] o Generally use IV instead of oral antibiotics in severe infections, or unless stepping down (when improving).[1,30] o Consider hospitalization for IV antibiotics (at least initially) in moderate infections in patients with severe peripheral artery disease or problems with adherence.[1] o Dose antibiotics as for serious infection, with dose adjustment for comorbidities (e.g., kidney insufficiency).[1] o Empiric coverage of *Pseudomonas* is not routinely needed in North America.[1] o Continue antibiotics for mild cases for one to two weeks (10 days post-debridement), or two to four weeks for more severe cases (IV initially, then oral).[1] Duration will be different for patients with bone or joint involvement.[1] • For **mild** infections, usually choose oral agents that cover streptococci and staphylococci (e.g., dicloxacillin [US], cloxacillin [Canada], cephalexin).[1] o For patients who cannot take a beta-lactam, options might include clindamycin,[a] TMP/SMX, doxycycline, levofloxacin, or moxifloxacin.[1]

Clinical Question	Pertinent Information or Suggested Approach
Empiric antibiotic choices for **diabetic foot infections,** continued	• **MRSA** coverage is recommended in: o mild infection with history of MRSA infection or colonization (oral).[1] ▪ Options might include clindamycin,[a] TMP/SMX, doxycycline, linezolid, levofloxacin, or moxifloxacin.[1] o moderate or severe infection and history of MRSA infection or colonization, or MRSA risk factors (e.g., recent antibiotic use or invasive procedure, recent hospital or nursing home stay, hemodialysis, HIV, long-term central venous access, open wounds.[1] ▪ Options might include TMP/SMX, doxycycline, vancomycin, linezolid, or daptomycin.[1] • **Gram negative** coverage is recommended or should be considered in certain scenarios:[1] o moderate or severe infection with no complicating factors. Options might include amoxicillin/clavulanic acid, ampicillin/sulbactam, cefuroxime, cefotaxime, ceftriaxone.[1] o **recent antibiotic exposure** and:[1] ▪ mild infection. Oral options might include amoxicillin/clavulanic acid, TMP/SMX, levofloxacin, or moxifloxacin.[1] ▪ moderate or severe infection (consider expert consult).[1] Options might include ticarcillin/clavulanic acid, piperacillin/tazobactam, cefuroxime, cefotaxime, ceftriaxone, or ertapenem.[1] o moderate or severe infection with risk factors for ESBL-producers.[1] Consider expert consult. Options might include ertapenem, meropenem, imipenem/cilastatin, ciprofloxacin, amikacin, colistin.[1] o moderate or severe infection with suspicion of *Pseudomonas* (macerated ulcer, warm climate, water immersion).[1,30] Options might include ticarcillin/clavulanic acid, piperacillin/tazobactam, meropenem, or imipenem/cilastatin.[1] o moderate or severe infection with ischemia, limb necrosis, or gas formation (gangrene).[1] Urgent surgical consultation is recommended for extensive gangrene, deep abscess, compartment syndrome, severe ischemia.[1] Consider anerobic coverage as well.[1] (Necrotizing infections are covered in a separate section below.) Antibiotic options might include amoxicillin/clavulanic acid, ampicillin/sulbactam, ticarcillin/clavulanic acid, piperacillin/tazobactam, ertapenem, meropenem, imipenem/cilastatin, or cephalosporin (cefuroxime, cefotaxime, ceftriaxone) plus clindamycin[a] or metronidazole.[1]
What antibiotics may be appropriate for **empiric** treatment of **cellulitis** and **erysipelas** (non-necrotizing)? *Continued…*	• General considerations: o Usually choose agents that cover *Streptococcus pyogenes*, or perhaps staphylococci (e.g., for **purulent** infections).[3,5] Due to the difficulty of determining the causative bacteria in most cellulitis cases, prescribers may choose antibiotics that target both.[25] o *Streptococcus pyogenes* is susceptible to beta-lactams.[25] o Consider MRSA coverage for severe penetrating trauma, injection drug use, unhoused persons, military personnel, correctional facility residents, athletes, history of MRSA infection or colonization, prior hospitalization for skin or soft tissue infection, antibiotic use in the past six months, recent invasive procedure (e.g., dialysis), severe infections, septic shock, age <2 yrs or >65 yrs, purulent infections, or facial erysipelas.[4-6,8]

Clinical Question	Pertinent Information or Suggested Approach
Antibiotics that may be appropriate for **empiric** treatment of **cellulitis** and **erysipelas** (non-necrotizing), continued	○ Patients with diabetes may need additional coverage (e.g., for Enterobacterales and anaerobes).[5] ○ Orbital or periorbital cellulitis may also involve *Haemophilus influenzae*, *Moraxella catarrhalis*, other gram negatives (post-trauma), or anaerobes (dental source).[5] ○ Consider additional organisms in specific situations (e.g., bite wounds, fresh water [e.g., *Aeromonas* spp; may cause necrotizing infection]; sea water or seafood exposure [*Vibrio* spp. may cause necrotizing infection])[4,6,7] ○ Associated abscess (e.g., due to staph) will require incision and drainage.[5,6] • **Milder infection** ○ A 5-day course of an oral beta-lactam (penicillin VK, amoxicillin, dicloxacillin [US]. cephalexin) may be sufficient.[3-6,25] For patients who cannot take a beta-lactam, options might include azithromycin, clindamycin,[a] linezolid, tedizolid (US), or omadacycline (US).[5,25] ▪ For MRSA coverage, options include TMP/SMX, doxycycline, clindamycin,[a] minocycline, linezolid, tedizolid (US), delafloxacin (US), or omadacycline.[5,6,8,9] ○ For mild **peri**orbital cellulitis (no systemic signs of infection), expand coverage to amoxicillin/clavulanic acid, cefpodoxime, or cefdinir (plus TMP/SMX or linezolid if MRSA coverage is needed).[5] ○ For patients with **diabetes** and mild infection (outpatient treatment), TMP/SMX should be added to penicillin VK or cephalexin.[5] Omadacycline is another option.[5] • **More severe infection** (i.e., signs of systemic infection[25])(necrotizing infections are discussed in a separate section below) ○ Moderate to severe infection: options might include IV penicillin, cefazolin, ceftriaxone, nafcillin (US), oxacillin (US).[5,6] Alternatives for patients with serious beta-lactam allergy include vancomycin, linezolid, or clindamycin.[5,6,a] ▪ For **MRSA** coverage, options include vancomycin, linezolid, daptomycin, ceftaroline, telavancin, dalbavancin, and ortiavancin.[5,6,9] ○ For severe infection, consider expanding empiric coverage by using vancomycin plus piperacillin/tazobactam.[4] For information on necrotizing infections, see the section below. ○ For orbital cellulitis (consult surgery) or periorbital cellulitis, consider vancomycin **plus** piperacillin/tazobactam or ampicillin/sulbactam or ceftriaxone and metronidazole.[5] For patients with serious beta-lactam allergy, add moxifloxacin to vancomycin in place of a beta-lactam.[5] Linezolid or daptomycin are vancomycin alternatives.[5] ○ For patients with diabetes, consider coverage for Enterobacterales (carbapenem, levofloxacin, or piperacillin/tazobactam) and staph (vancomycin, linezolid, or daptomycin).[5]

Clinical Question	Pertinent Information or Suggested Approach
What antibiotics may be appropriate for **empiric** treatment of **necrotizing** infections?	• In addition to rapid introduction of appropriate IV broad-spectrum antibiotics, surgical intervention is required.[1,6,29] • **Broad spectrum antimicrobial coverage is needed empirically**, including *Streptococcus pyogenes*, MRSA, gram negatives, and anaerobes.[5,6] o Consider vancomycin, linezolid, or daptomycin **plus** piperacillin/tazobactam, a carbapenem, or ceftriaxone plus metronidazole).[4-6] Add clindamycin,[a] or include linezolid, if a toxin-producer is suspected (see below).[5,6] • Consider coverage for *Aeromonas* (e.g., doxycycline plus ciprofloxacin) in cases involving fresh or brackish water exposure, or *Vibrio* in cases involving sea water or seafood exposure.[4,6,7] o For information on *Vibrio* treatment from the CDC, see https://www.cdc.gov/vibrio/healthcare.html. • Include a protein synthesis inhibitor (e.g., clindamycin,[a] linezolid) to block bacterial toxin production if any of the following bacteria are suspected (e.g., in rapidly progressive, severe infection; suggestive gram stain):[5,6,29] o For staph coverage in staphylococcal toxic shock syndrome (e.g., hypotension, fever, organ failure, macular rash, and later desquamation of the palms and soles), consider including vancomycin plus clindamycin,[a] or linezolid.[5,6] o *S. pyogenes* may be covered with high-dose IV penicillin (24 million units/day[c]) or ampicillin, plus high-dose clindamycin[a] (900 mg IV q8h[c]).[5,6,29] For severe necrotizing fasciitis or streptococcal toxic shock syndrome (e.g., hypotension, nausea, vomiting, diarrhea, kidney and/or respiratory failure, erythroderma), consider adjunctive IVIG (0.5 g/kg x 1, then 25 g on days 2 and 3[c]).[5,6,29] o *Clostridium* may be covered with high-dose IV penicillin plus a protein synthesis inhibitor (e.g., clindamycin[a]).[4,6]
How do **antibiotics for MRSA** compare?	See the chart below, Antibiotics for MRSA Skin Infections, below.
How is **impetigo** treated?	• Antibiotic treatment, whether oral or topical, should be aimed at both *Streptococcus pyogenes* and *Staphylococcus. aureus*. Topical antibiotics may be used when there are only a few lesions, while oral antibiotics are used for multiple lesions.[26] • Topical options: mupirocin, fusidic acid [Canada], retapamulin [*Altabax*, US].[8,27] o Ozenoxacin (*Xepi* [US]; *Ozanex* [Canada]) is not first-line due to high cost and lack of head-to-head studies with older agents.[27] The tube size available in Canada may not be sufficient for more than one treatment course in the event of recurrence.[27] • Oral options: dicloxacillin, cephalexin, erythromycin (some *Streptococcus pyogenes* and *Staphylococcus aureus* may be resistant), clindamycin,[a] amoxicillin-clavulanic acid.[4]

--Continue to the section below for a chart, *Antibiotics for MRSA Skin Infections*---

Antibiotics for MRSA Skin Infections

Drug	Considerations and Dosing[b]	Cost (see footnote d)
Ceftaroline (*Teflaro* [US])	• Parenteral formulation only. • Approved for acute bacterial skin and skin structure infections caused by *Staphylococcus aureus* (including MRSA), *E. coli*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*.[10,b] • Potential for cross-sensitivity in patients with beta-lactam allergy.[10] • Usual adult dose 600 mg IV Q12H.[10] Reduce dose for CrCl ≤50 mL/min.[10]	$490.40/day. Approved duration of therapy 5 to 14 days.[10]
Clindamycin	• Parenteral and oral formulations available. • Approved for skin and soft tissue infections with *Streptococcus pyogenes*, *Staphylococcus aureus*, and anaerobes.[11-13,b] • Usual adult PO dose: 300 to 450 mg Q6H.[4] • Adult dose for necrotizing infections: 900 mg IV Q8H.[5] • Bacteriostatic.[4] • See **footnote a** regarding resistance concerns.	**US**: ~$30/day (IV); <$10/day (PO) **Canada**: ~$75/day (IV), <$5/day (oral)
Dalbavancin (*Dalvance* [US], *Xydalba* [Canada])	• Parenteral formulation only. • A lipoglycopeptide approved for skin and soft tissue infections with Staphylococcus aureus (including MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group, and vancomycin-sensitive Enterococcus faecalis.[14,15,b] • Insufficient data for diabetic foot infection to recommend.[1] • 1,500 mg x 1, OR 1,000 mg on day one, then 500 mg on day eight.[14,15] Reduce dose for CrCl <30 mL/min.[14,15] • Because it can be given as a one-time infusion, could be used for moderately ill patients with cellulitis who refuse hospitalization, or for an outpatient who might be nonadherent.[5]	**US**: $5,337.39/course of therapy **Canada**: ~$3,101.22
Daptomycin (*Cubicin* [Canada], *Cubicin RF* [Canada], generics)	• Parenteral formulation only. • A cyclic lipopeptide approved for complicated skin and soft tissue infections caused by *Staphylococcus aureus* (including MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, (US: *Streptococcus dysgalactiae* subspecies *equisimilis*, and vancomycin-sensitive *Enterococcus faecalis*).[16,17,b] • Usual adult dose is 4 mg/kg Q24H.[16,17] Reduce dose for CrCl <30 mL/min.[16,17] • Check creatine phosphokinase weekly (more often in kidney impairment or recent statin users) and monitor for muscle pain or weakness. Also monitor for peripheral neuropathy.[16,17]	**US**: ~$55/day (for 70 kg adult); **Canada**: ~$98; Approved duration of therapy seven to 14 days.[16,17]

Drug	Considerations and Dosing[b]	Cost (see footnote d)
Delafloxacin (*Baxdela* [US])	• Parenteral and oral formulations available • A **quinolone** approved for skin and soft tissue infections with *Staphylococcus aureus* (including MRSA), *Staphylococcus haemolyticus*, *Staphylococcus lugdunensis*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, *Enterococcus faecalis*, *E. coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.[28,b] • Usual adult dose: 300 mg IV Q12H or 450 mg PO Q12H[28] • Reduce **IV** dose if eGFR <30 mL/min/1.73 m^2, due to accumulation of the IV vehicle.[16] Do not use oral or IV delafloxacin if eGFR <15 mL/min/1.73 m^2.[28] • Typical quinolone warnings: tendinitis/tendon rupture, peripheral neuropathy, central nervous system effects.[28] Interacts with di- and trivalent cations (e.g., in antacids, sucralfate, multivitamins, iron supplements).[28] • Does not appear to cause significant CYP450 drug interactions, QT prolongation, or phototoxicity.[28]	~$142/day (IV), ~$160/day (oral) Approved duration of therapy five to 14 days.[28]
Doxycycline	• Parenteral (US) and oral formulations available. • An option for MRSA coverage in diabetic foot infections or milder cellulitis.[1,6] • Usual adult dose: 100 mg PO Q12H[4]	**US**: ~$40/day (IV), <$10/day (oral) **Canada**: <$1/day (oral)
Linezolid (*Zyvox*, *Zyvoxam*, generics)	• Parenteral and oral formulations available. Approved duration of therapy 10 to 14 days (14 to 28 for VRE).[18,19] • An oxazolidinone approved for complicated skin and soft tissue infections (including diabetic foot infections without osteomyelitis) with *Staphylococcus aureus* (including MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*.[18,19,b] Also approved for uncomplicated infections caused by MSSA and *S. pyogenes*, and infections caused by VRE.[18,19,b] • Usual adult dose 600 mg IV or PO Q12H.[18,19] • Myelosuppressive; CBC required at least weekly.[18,19] • Linezolid is an MAO inhibitor and has serotonergic effects; screen for drug interactions.[18,19]	**US**: ~$90/day (IV); ~$15/day (oral); **Canada**: ~$230 (IV), ~$40/day (oral) Approved duration of therapy 10 to 14 days (14 to 28 days for diabetic foot infection [Canada] or VRE)[18,19]
Minocycline	• An option for MRSA coverage in milder cellulitis.[6] • Oral formulation only. • Usual adult dose 100 mg PO Q12H.[4]	US: <$10/day **Canada**: <$5/day

Drug	Considerations and Dosing[b]	Cost (see footnote d)
Omadacycline (*Nuzyra* [US])	• Parenteral and oral formulation available • An aminoethylcycline (a type of tetracycline) approved for acute bacterial skin and soft tissue infections caused by *Staphylococcus aureus* (including MRSA), *Staphylococcus lugdunensis*, *Streptococcus pyogenes*, *Streptococcus anginosu*s group, *Enterococcus faecalis*, *Enterobacter cloacae*, and *Klebsiella pneumoniae*.[20,b] • Usual adult IV dose: 200 mg on day one (200 mg x 1 or two separate 100 mg doses), then 100 mg Q24H.[20] • Usual adult PO dose: 450 mg Q24H x 2 days, then 300 mg Q24H.[20] • Potential for permanent tooth discoloration if used during the last half of gestation up to age eight years, or reversible inhibition of bone growth if used during the second or third trimesters, up to age eight years.[20] Breastfeeding is not recommended during treatment and for four days after the last dose.[20] • Nausea (incidence up to 30%) and vomiting (incidence up to 17%) appear to be more common in patients after an oral loading dose.[20] • No dosage adjustments needed in patients with kidney or liver impairment.[20]	~$437/day (IV), ~$510/day (oral). Approved duration of therapy seven to 14 days.[20]
Oritavancin (*Orbactiv* [US])	• Parenteral formulation only (single dose).[21] • Approved for skin and soft tissue infections caused by *Staphylococcus aureus* (including MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, *Streptococcus dysgalactiae*, and vancomycin susceptible Enterococcus faecalis.[21,b] • Long-acting (dose is 1,200 mg x 1, over three hours[c]).[21] Could be used for moderately ill patients with cellulitis who refuse hospitalization, or for an outpatient who might be nonadherent.[5] • Insufficient data for diabetic foot infections to recommend.[1] • IV heparin contraindicated for five days after use due to artificial increases in coagulation tests. Affects aPTT for up to five days and PT/INR for up to 12 hours after administration.[21] • May cause infusion reaction (flushing, itching, rash). Stop or slow infusion if this occurs.[21]	~$3,500/dose. Single-dose treatment.[21]
Tedizolid (*Sivextro* [US])	• Parenteral and oral formulations available. • An oxazolidinone approved for skin and soft tissue infections caused by *Staphylococcus aureus* (including MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, and *Enterococcus faecalis*.[22,b] • Usual adult dose: 200 mg Q24H (IV or PO).[22] • May have less tendency for interactions with MAO inhibitors and selective serotonin reuptake inhibitors (SSRIs) than linezolid.[23] • No CBC monitoring required.[22]	~$350/dose (IV) ~$420/day (oral). Approved duration of therapy six days.[22]

Drug	Considerations and Dosing[b]	Cost (see footnote d)
Telavancin (*Vibativ* [US])	• Parenteral formulation only. • A lipoglycopeptide approved for complicated skin and soft tissue infections caused by *Staphylococcus aureus* (including MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, and vancomycin-sensitive Enterococcus faecalis.[24,b] • Usual adult dose: 10 mg/kg IV Q24H.[24] Reduce dose for CrCl ≤50 mL/min.[24] • May cause infusion reaction (flushing, itching, rash).[24] Stop or slow infusion if this occurs.[24] • May cause kidney toxicity; monitor serum creatinine.[24]	~$550/day (for 70 kg patient). Approved duration of therapy seven to 14 days.[24]
TMP/SMX	• Parenteral and oral formulations available. • An option for MRSA coverage in diabetic foot infections, and milder cellulitis.[1,5] • Usual adult PO dose: one or two double-strength tablets Q12H.[4] • Usual adult IV dose: 8 to 10 mg/kg (TMP component) divided Q8H to Q12H.[9] • Reduce for CrCl <30 mL/min.[9] • TMP may cause hyperkalemia.[9]	**US**: ~$50/day (for 320 mg IV Q12 H); <$10/day (oral) **Canada**: $80/day (for 320 mg IV Q12H [*Septra*]); <$1/day oral)
Vancomycin	• Parenteral formulation only. • An option for moderate or severe skin infections.[1,4-6] • Consider a target AUC 400 to 600 mcg/mL or trough 15 to 20 mcg/mL),[5] • May cause vancomycin infusion reaction (e.g., flushing, hypotension, itching) if infused too rapidly (e.g., >10 mg/min).[9]	**US**: <$60/day (for 1 g IV Q12 H) **Canada**: ~$40/day (for 1 g IV Q12H)

Abbreviations: CBC = complete blood count; ESBL = extended-spectrum beta-lactamase; H = hours; HIV = human immunodeficiency virus; MAO = monoamine oxidase; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; PO = oral; Q = every; SIRS = systemic inflammatory response syndrome; TMP/SMX = trimethoprim/sulfamethoxazole; VRE = vancomycin-resistant *Enterococcus*

a. Clindamycin: *Streptococcus pyogenes* may be resistant to clindamycin; consider local resistance patterns and use with caution in severe cases.[6] MRSA resistance to clindamycin can be inducible, so some isolates that show sensitivity *in vitro* may not be clinically susceptible to clindamycin.[4] Erythromycin-resistant MRSA may also be resistant to clindamycin.[4] The lab can use the "D test" to check for inducible resistance.[5] There is also a concern for *Clostridioides difficile* colitis.[8]
b. Bacterial coverage noted in the chart may not reflect the full spectrum of coverage for each drug.
c. Dosing is for adults.
d. Wholesale acquisition cost (WAC) of adult dose denoted. US medication pricing by Elsevier, accessed January 2024.

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.]

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Managing Community-Acquired Pneumonia and Aspiration Pneumonia in Adults

last modified June 2025

The chart below is based on the 2019 guideline for the management of community-acquired pneumonia in adults from the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA).[1] Antibiotic dosing is provided for **adults**. The second chart below provides answers to common questions about aspiration pneumonia.

Community-Acquired Pneumonia Treatment Basics
• The **need for hospitalization** should be based on clinical judgment plus results of a validated prognostic tool.[1] Use of the PSI is recommended over CURB-65.[1] PSI is better than the CURB-65 at identifying patients who can safely be treated as outpatients, but CURB-65 is easier to use.[1] PSI may underestimate severity in younger patients.[1] The PSI is available at https://www.mdcalc.com/psi-port-score-pneumonia-severity-index-cap and the CURB-65 is available at https://www.mdcalc.com/curb-65-score-pneumonia-severity.
• Patients with **severe pneumonia** are typically those requiring intensive/critical care. See **footnote b** for guideline criteria for severe pneumonia.
• Patients with CAP should be treated with antibiotics **for at least five days** (**seven days** for MRSA or *Pseudomonas*).[1] Antibiotics should not be stopped **until the patient is clinically stable**.[1] This means abnormalities in vitals (heart rate, blood pressure, respiratory rate, oxygen saturation, body temperature) and cognition have resolved, and the patient is eating.[1]
• The most common **bacterial causes** of community-acquired pneumonia in outpatients are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Staphylococcus aureus*, *Legionella* species, *Chlamydia pneumoniae*, and *Moraxella catarrhalis*.[1]
• It is suggested that anaerobic coverage not be routinely added in cases of **aspiration pneumonia** unless lung abscess or empyema is suspected.[1] Our chart below covering aspiration pneumonia has more considerations.
• **Blood culture** yield is low in patients with nonsevere CAP.[1] Blood cultures are not recommended in outpatients, and it is suggested that they not be routinely done in the hospital setting in nonsevere CAP.[1] Blood cultures are recommended in severe CAP, and in patients being treated empirically for, or previously infected with, *Pseudomonas aeruginosa* or MRSA, or who had been hospitalized and received parenteral antibiotics within the prior 90 days.[1]
• **Sputum gram stain and culture** is recommended in severe CAP, in patients being treated empirically for, or previously infected with, *Pseudomonas aeruginosa* or MRSA, and perhaps in those hospitalized and treated with antibiotics within the prior 90 days.[1] Collection of lower respiratory tract secretions for *Legionella* culture or nucleic acid amplification testing is suggested in severe CAP.[1]
• **Urine antigen testing** for *Pneumococcus* and *Legionella* is suggested in severe CAP.[1] *Legionella* testing is also suggested if epidemiology indicates exposure (e.g., travel or overnight stay in a healthcare facility in the previous 14 days; outbreak).[1,2]
• If **influenza** is circulating in the community, testing with a rapid molecular assay (preferred over an antigen test) is suggested.[1] Coverage for influenza is suggested for outpatients who test positive, and is recommended for inpatients who test positive.[1]
• **Procalcitonin** is not recommended to determine need for initial, empiric antibiotic treatment (**see footnote g**).[1]
• Guidelines suggest not using **corticosteroids routinely** for severe CAP.[1] See **footnote f** for newer data and situations where they might be considered.

Patient Characteristics (see footnote a)	**Outpatient Oral Antibiotic Regimen (see footnote a)**

Previously healthy without comorbidities (see below) and without risk factors for *Pseudomonas aeruginosa* or MRSA (e.g., prior respiratory isolation of MRSA or *Pseudomonas aeruginosa*, or hospitalization and receipt of parenteral antibiotics within the 90 days prior. See **footnote d** for additional risk factors).	• Amoxicillin 1 g TID (high dose targets resistant *Streptococcus pneumoniae*[3])
	OR
	• Macrolide (if local pneumococcal resistance is <25% [resistance is >30% in most of US])
	  • Azithromycin 500 mg x 1, then 250 mg once daily, or
	  • Clarithromycin 500 mg BID or 1,000 mg once daily (extended-release)
	OR
	• Doxycycline 100 mg BID (less data) (consider a loading dose of 200 mg)
	
	Note: patients with risk factors for MRSA or *Pseudomonas* are not commonly managed as outpatients, but if they are, they will need coverage for these pathogens as well.

With comorbidities:
• Heart disease
• Lung disease
• Liver disease
• Kidney disease
• Diabetes
• Alcoholism
• Cancer
• Asplenia
 	
Regimens for patients with comorbidities target resistant *Streptococcus pneumoniae*, atypicals, beta-lactamase-producing *Haemophilus influenzae* and *Moraxella catarrhalis*, enteric gram negatives, and methicillin-susceptible *Staphylococcus aureus*.
	Beta-lactam
	• Amoxicillin/clavulanate (500 mg/125 mg TID or 875 mg/125 mg BID, 2,000 mg/125 mg BID)
	OR
	• Cephalosporin (cefpodoxime 200 mg BID or cefuroxime axetil 500 mg BID)
	PLUS
	Macrolide
	  • Azithromycin 500 mg x 1, then 250 mg once daily, or
	  • Clarithromycin 500 mg BID or 1,000 mg once daily (extended-release)
	OR
	Doxycycline 100 mg BID (less data) (consider a loading dose of 200 mg)
	
	OR
	
	Monotherapy with a respiratory quinolone: levofloxacin 750 mg once daily, moxifloxacin 400 mg once daily, gemifloxacin 320 mg once daily (US), delafloxacin 450 mg orally every 12 h[5] (US; new indication post-guideline publication[5]). Consider adverse effects.
	
	Note: patients with risk factors for MRSA or Pseudomonas are not commonly managed as outpatients, but if they are, they will need coverage for these pathogens as well.

a. If the patient has recently received (i.e., within the past 90 days) an antibiotic, pick an option from a different class.[1,3] Dosing is for oral tablets/capsules for **adults** with normal kidney/liver function. Based on ATS/IDSA guideline unless otherwise referenced. Information may differ from product labeling. Most antibiotics available generically, at lower cost. Brand only available for gemifloxacin (*Factive*, US).

Patient Characteristics (see footnote c)	Inpatient Antibiotic Regimen (see footnote c)
Nonsevere pneumonia without risk factors for Pseudomonas aeruginosa or MRSA (e.g., prior respiratory isolation of MRSA or Pseudomonas aeruginosa, or hospitalization and receipt of parenteral antibiotics within the 90 days prior. **See footnote d** for additional risk factors.)	**Beta-lactam** • Ampicillin/sulbactam (1.5 to 3 g every 6 h) OR • Cephalosporin (cefotaxime 1 to 2 g every 8 h, ceftriaxone 1 to 2 g once daily, or ceftaroline 600 mg every 12 h [US], or possibly ceftobiprole 667 mg every 8 h [US][19]). **PLUS** **Macrolide** • Azithromycin 500 mg once daily, or • Clarithromycin 500 mg BID OR **Doxycycline** 100 mg BID (less data) **OR** **Monotherapy with a respiratory quinolone**: levofloxacin 750 mg once daily, moxifloxacin 400 mg once daily, or delafloxacin 300 mg IV every 12 h[5] (US; new indication post-guideline publication[5]). Evidence favors beta-lactam/macrolide combination. Consider adverse effects.
Severe pneumonia without risk factors for Pseudomonas aeruginosa or MRSA (e.g., prior respiratory isolation of MRSA or Pseudomonas aeruginosa, or hospitalization and receipt of parenteral antibiotics within the 90 days prior. **See footnote d** for additional risk factors.)	Beta-lactam plus a macrolide, or a beta-lactam plus a respiratory quinolone. Dosing as above. Use of HCAP criteria (e.g., nursing home residence, recent hospitalization) should no longer be used to broaden coverage for resistant organisms (e.g., MRSA, resistant gram negatives), and use of this term is no longer recommended.[1,4]
Prior respiratory isolation of MRSA, or hospitalization and parenteral antibiotics within 90 days prior and locally validated risk factors for MRSA. **See footnote d** for additional risk factors. MRSA coverage generally not needed if nasal swab is negative, especially for nonsevere CAP. If positive, cover pending culture results.	**Prior respiratory MRSA isolation: add** MRSA coverage* to above inpatient regimen and use cultures/nasal PCR to guide need for continuation/discontinuation of MRSA coverage. **Recent hospitalization and parenteral antibiotics and locally validated risk factors for MRSA (see footnote e)** • **Severe** pneumonia: **add** MRSA coverage* to above inpatient regimen and use cultures/nasal PCR to guide need for continuation/discontinuation of MRSA coverage. • **Nonsevere: add** MRSA coverage* to above inpatient regimen only if cultures or PCR are positive. ***MRSA coverage** = linezolid 600 mg BID, or vancomycin 15 mg/kg every 12 h with dose adjusted per levels.

Patient Characteristics (see footnote c)	Inpatient Antibiotic Regimen (see footnote c)
Prior respiratory isolation of Pseudomonas aeruginosa, or hospitalization and parenteral antibiotics within 90 days prior and locally validated risk factors for Pseudomonas aeruginosa. **See footnote d** for additional risk factors to consider.	**Prior respiratory Pseudomonas aeruginosa isolation**: change beta-lactam in above inpatient regimen to one with pseudomonal coverage,** and use cultures/nasal PCR to guide need for continuation/discontinuation of pseudomonal coverage. **Recent hospitalization and parenteral antibiotics and locally validated risk factors for Pseudomonas aeruginosa** (see footnote e) • **Severe** pneumonia: change beta-lactam in above inpatient regimen to one with pseudomonal coverage** and use culture to guide need for continuation/discontinuation of pseudomonal coverage. • **Nonsevere**: change beta-lactam in above inpatient regimen to one with pseudomonal coverage** only if culture-positive. ****Pseudomonal coverage** = piperacillin/tazobactam 4.5 g every 6 h, cefepime 2 g every 8 h, ceftazidime 2 g every 8 h, imipenem 500 mg every 6 h, meropenem 1 g every 8 h, aztreonam 2 g every 8 h

b. ATS/IDSA guideline criteria for **severe pneumonia**: septic shock with need for vasopressors, respiratory failure requiring mechanical ventilation, or three or more minor criteria: respiratory rate ≥30 breaths/min., PaO2/FiO2 ratio ≤250, multilobar infiltrates, confusion or disorientation, BUN ≥20 mg/dL, white blood cell count <4,000 cells/mm^3 (not due to chemo), platelets <100,000/mm^3, core temperature <36°C, hypotension requiring aggressive fluid resuscitation.[1]

c. If the patient has recently received (i.e., within the past 90 days) an antibiotic, pick an option from a different class.[1,3] Dosing is for adults with normal kidney/liver function. Based on ATS/IDSA guideline unless otherwise referenced. Information may differ from product labeling. Most antibiotics available generically, at lower cost. Brand only available for ceftaroline (*Teflaro* [US]) and ceftobiprole (*Zevtera* [US]).

d. **Examples of additional risk factors to consider:** COPD with bronchiectasis, chronic kidney disease, antibiotic use within the past 30 to 60 days, tube feeding, nursing home residence.[7,11] Nursing home residence is not consistently a risk factor.[7]

e. **"Local validation"** means using local data to determine the prevalence of MRSA and *Pseudomonas* patients with CAP and identifying risk factors for infection locally (e.g., at your local hospital). If local data are unavailable and empiric coverage for MRSA or *Pseudomonas* is instituted on the basis of published risk factors (e.g., footnote d), continue or deescalate the regimen based on culture results.[1]

f. Role of **corticosteroids**. Corticosteroids can be considered in refractory septic shock, patients on high-flow supplemental oxygen, a pneumonia severity score over 130, and for steroid-responsive comorbidities (e.g., COPD, asthma, autoimmune disease, etc).[1,12] Corticosteroids may reduce mortality in severe CAP (NNT = 18), although mortality benefit is not consistent across studies.[1,8] Another, larger study showed reduction in mortality with early initiation of hydrocortisone in one in 17 ICU patients (N = 795).[12] Corticosteroids may reduce time to clinical stability and length of stay by about one day, and reduce the need for mechanical ventilation.[6,9] More study is needed to identify which subgroups benefit the most (e.g., patients with high inflammatory response).[10] Consider corticosteroids for patients who are clinically unstable or not responding to treatment, and perhaps those with elevated markers of inflammation (e.g., C-reactive protein).[6,9,10]

g. Empiric antibiotics should be started if CAP is clinically suspected and radiographically confirmed, regardless of **procalcitonin** level; new evidence suggests that sensitivity is inadequate to determine when initial antibiotic therapy can be safely deferred in this setting.[1]

Aspiration Pneumonia	
Question	**Answer/Pertinent Information**
What is aspiration pneumonia?	• Aspiration pneumonia is a lung infection caused by large-volume inhalation of pathologically-colonized oropharyngeal or upper GI secretions. Think of aspiration pneumonia as part of the pneumonia spectrum including community-acquired pneumonia, and hospital-acquired pneumonia, rather than its own entity.[13] • Microaspiration (small-volume aspiration) of oropharyngeal secretions is normal, especially during sleep. However, microaspiration is involved in the pathogenesis of most pneumonias.[13] • Aspiration pneumonia is DIFFERENT from chemical pneumonitis from aspiration.[13] o Chemical pneumonitis from aspiration leads to **inflammation** due to aspiration of irritating acidic gastric contents.[13] This inflammation can lead to a sudden onset (almost immediate) of symptoms that can easily be confused with pneumonia (e.g., fever, cough, elevated white blood cell count, wheezing, tachycardia).[13,14] Chemical pneumonitis can also appear like acute respiratory distress syndrome (ARDS) with bronchospasms and frothy sputum with bilateral patchy infiltrates on chest x-ray.[15] o Aspiration pneumonia is a **secondary infection** that develops over a few days due to the combination of aspirated microorganisms and damaged lung tissue.[13,14] Infiltrates on chest x-ray may not be seen early in cases of pneumonia.[13] • Aspiration pneumonia is linked to a higher mortality rate (29.4%) compared to community-acquired pneumonia (11.6%).[13]
What are **risk factors** for aspiration pneumonia?	• Patients with multiple risk factors for large-volume aspiration are at increased risk for aspiration pneumonia and death.[13] These risk factors include:[13,15,16] o alcohol use o poor dentition (increases bacterial load, not necessarily risk of aspiration) o dysphagia and gastroesophageal reflux o head, neck, and esophageal cancer o esophageal strictures o chronic obstructive pulmonary disease (COPD) o seizures o degenerative neurologic disease (e.g., multiple sclerosis, Parkinson's disease; dementia) o impaired consciousness o enteral feeding (especially if associated with impaired gastric motility, poor cough reflex, and altered mental status)
How do **chest x-rays** help diagnose aspiration pneumonia?	• Aspiration pneumonia is difficult to diagnose and differentiate from other aspiration syndromes, community-acquired pneumonia, and hospital-acquired pneumonia.[13] • Chest x-rays, along with clinical history, are used to diagnose aspiration pneumonia.[13] • Infiltrates on chest x-ray seen in gravity-dependent locations can be a clue that a patient with pneumonia has an aspiration pneumonia.[13]

Aspiration Pneumonia	
Question	**Answer/Pertinent Information**
	○ Aspiration from a supine position leads to infiltrates in the superior lower lobe or posterior upper lobes.[13] ○ Aspiration from an upright position leads to infiltrates in the basal segments of the lower lobes.[13]
What role do **proton pump inhibitors** play in aspiration pneumonia?	• PPIs reduce gastric acid and have the potential to promote an environment more favorable for bacterial growth in secretions that may be aspirated.[15] • It is not known if PPIs increase the risk of aspiration pneumonia. However, PPIs seem to **reduce** the risk of chemical pneumonitis.[13,15] • See our chart, *Proton Pump Inhibitors: Appropriate Use and Safety Concerns*, for how PPIs impact pneumonias.
What **microorganisms** are typically responsible for aspiration pneumonia?	• The bacteria most often involved in aspiration pneumonia appear to be similar to the bacteria involved in non-aspiration pneumonias.[13] ○ Bacteria associated with **community-acquired cases of aspiration pneumonia** are commonly *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, and Enterobacteriaceae.[13] ○ Bacteria associated with **hospital-acquired cases of aspiration pneumonia** are commonly gram-negative organisms, including *Pseudomonas aeruginosa*.[13] • It was previously thought (i.e., in the 1970s) that anaerobes (alone or in combination with aerobes) were involved in a large number of cases of aspiration pneumonia (45% to 48%).[13,14,17] Common anaerobes include *Bacteroides*, *Peptostreptococcus*, *Porphyromonas*, *Prevotella melaninogenica*, and *Fusobacterium* species.[15]
When should therapy be **started** after aspiration?	• Follow hospital protocols for when to initiate antibiotics with suspected pneumonias. • If it is not clear if a patient has chemical pneumonitis versus aspiration pneumonia after an acute episode of aspiration:[13] ○ Can consider waiting about 48 hours before starting antibiotics in patients who display mild to moderate symptoms if the chest x-ray is clear. ○ Can consider empirically starting antibiotics in patients with severe symptoms. Re-evaluate the need for continued antibiotics in two to three days based on clinical course and chest x-ray.

Aspiration Pneumonia	
Question	**Answer/Pertinent Information**
Which **antibiotics** are most appropriate for suspected aspiration pneumonia?	• Choice of antibiotics will depend on where the pneumonia developed (e.g., community, hospital, long-term care facility), risk factors for resistant infections, and the likelihood that anaerobes are involved.[13] • There are limited data to guide anaerobic coverage when treating pneumonia.[17] Avoid empirically covering for anaerobes in most patients with suspected aspiration pneumonia (including pneumonia patients with aspiration risks) as they may not improve clinical outcomes.[13,17] Instead, choose antibiotics based on hospital protocols for CAP, HAP, and VAP. Consider initially covering for anaerobes in patients with: o risk factors for aspiration AND highest risk for an anaerobic infection (e.g., severe gum disease or poor dentition).[13] o foul smelling sputum or drainage from an abscess or empyema.[17] **Antibiotic Selection** • Most beta-lactam/beta-lactamase inhibitor combos (e.g., piperacillin/tazobactam), carbapenems, and some fluoroquinolones (e.g., moxifloxacin), already cover many anaerobes.[13,15,18,19] (Note ceftazidime/avibactam and levofloxacin, a common formulary fluoroquinolone, should not be used for anaerobic coverage.) In addition, antibiotics used to treat CAP, HAP, or VAP can be changed to an antibiotic that covers typical CAP pathogens and anaerobes. For example, beta-lactams can be changed to ampicillin/sulbactam or amoxicillin/clavulanate.[19] • Note that data using metronidazole to treat pneumonias are very limited. However, if adding specific anaerobic coverage to existing therapy, consider metronidazole over clindamycin. **Metronidazole** has good oral bioavailability (>90%), covers anaerobes from both "**above and below the belt,**" and has a lower risk of *C. difficile* infections compared to clindamycin.[20] **Clindamycin** also has good oral bioavailability (~90%), has a higher risk of *C. difficile* infections, and only covers gram-positive organisms and anaerobes from "above the belt."[21] o If using metronidazole, be sure to combine with a beta-lactam. Metronidazole lacks coverage of organisms commonly associated with pneumonia, such as gram-positive bacteria (e.g., *S. pneumoniae*).[16,19] • Can consider a **fluoroquinolone** (e.g., moxifloxacin [covers anaerobes], levofloxacin plus metronidazole if covering for anaerobes), in patients with a severe penicillin allergy. Also, see our chart, *Managing Beta-Lactam Allergies*, when considering a beta-lactam in a patient who reports a penicillin allergy. **Assessment and Follow-up** • Promote antibiotic stewardship and adjust antibiotic therapy based on culture and sensitivity results. o Sputum cultures are easy to get (noninvasive) and inexpensive, but are often inconclusive. However, they can be used to guide therapy when organisms are able to be identified.[14] • In addition, follow hospital protocols to convert patients to oral therapy once stable, clinically improving, and able to take things by mouth. For example, patients on an intravenous beta-lactam (e.g., ampicillin/sulbactam) can usually be converted to oral amoxicillin/clavulanate.[22]

Aspiration Pneumonia	
Question	**Answer/Pertinent Information**
How long should patients with aspiration pneumonia be treated?	• Treat most patients with aspiration pneumonia like you would for CAP (at least five days) or HAP and VAP (seven days total) [Evidence Level C].[3,13,23] Can consider longer durations of treatment for patients:[13] o who are not responding well to antibiotic therapy. o with necrotizing pneumonia (destruction of the underlying lung tissue, leading to multiple small, thin-walled cavities). o with lung abscesses. o with empyema (a collection of pus in the pleural cavity). • Expect patients with an abscess or empyema to require drainage in addition to antibiotic therapy.[13]
What **prevention strategies** can be used?	• Use the following to minimize post-operative chemical pneumonitis:[13] o Ensure patients fast for at least EIGHT hours, and avoid clear liquids for at least two hours, prior to surgery. o If possible, avoid using medications that increase risk of aspiration or interfere with swallowing (e.g., sedatives, antipsychotics). • Though data are not conclusive, can consider promoting oral intake with a mechanical soft diet with thickened liquids over pureed foods to reduce the risk of aspiration pneumonia in patients with dysphagia.[13,15] • When enteral feedings are needed, ensure patients are semirecumbent, not supine to reduce the risk of gastric aspiration.[13] • Follow hospital protocols for elevating the head of the bed in ventilated patients, to reduce the risk of aspiration.[15] • For patients with swallowing disorders, promote nutritional rehab with swallowing exercises and early mobilization.[13] • The data are weak to support oral hygiene in preventing aspiration pneumonia, but these efforts are unlikely to lead to harm.[13,15] Promote good oral hygiene (e.g., tooth brushing, cleaning dentures, gargling disinfectant solution, extraction of nonviable teeth).[15,16]

Abbreviations: BID = twice daily; BUN = blood urea nitrogen; CAP = community-acquired pneumonia; COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; h = hour or hours; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; ICU = intensive care unit; MRSA = methicillin-resistant *Staphylococcus aureus*; PaO2/FiO2 = arterial oxygen partial pressure/fractional inspired oxygen; PCR = polymerase chain reaction; PPI = proton pump inhibitor; PSI = pneumonia severity index; TID = three times daily; VAP = ventilator-associated pneumonia.

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 Feb 1;69(3):548-56.
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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
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] 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. 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] ○ **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] ○ **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] ○ **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] ○ **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] ○ **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]	• 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]
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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.

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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) 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.]

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