Uncomplicated Gram-Negative Bacteremia in Adults

Data are growing to support using shorter durations of therapy and oral step-down therapy in the treatment of uncomplicated gram-negative bacteremia. This FAQ answers common questions about treating uncomplicated gram-negative bacteremia in adults including differentiating uncomplicated and complicated bacteremia, appropriate duration of therapy, and oral step-down therapy. See our FAQ, *Resistant Gram-Negative Bacterial Infections*, for answers to clinical questions about managing extended-spectrum beta-lactamase (ESBL)- and carbapenem-resistant Enterobacterales (CRE)-related infections.

Question	Answer/Pertinent Information
How is **uncomplicated gram-negative bacteremia** defined?	Generally, consider infections that meet ALL FOUR of the following criteria as uncomplicated gram-negative bacteremia:[1] • **Criteria 1**: bacteremia secondary to one of the following types of infections:[1] o urinary tract o intra-abdominal or biliary o catheter-related o pneumonia WITHOUT structural lung disease, empyema/abscess, or cystic fibrosis o skin and soft tissue • **Criteria 2**: source control (See row "What is the role of source control?") (See exceptions in row "Which infections are more likely to be considered complicated?")[1] • **Criteria 3**: patients WITHOUT immunocompromise and risk for an opportunistic infection[1,a,b] • **Criteria 4**: clinical improvement within 72 hours of receiving appropriate antibiotic treatment (e.g., afebrile, hemodynamic stability)[1]
Which infections are more **likely to be considered complicated**?	• Some infections may be considered complicated, regardless of source control. Examples of **complicated infections even with source control** may include:[1] o bone and joint o central nervous system (CNS) o endovascular (e.g., endocarditis, infected pacemaker, septic thrombophlebitis)
What is the role of **source control**?	• Source control consists of the following:[1] o removal of infected hardware, catheters, or devices o drainage of infected fluid collections (e.g., abscess) o assurance of no residual or metastatic sites of infection (as appropriate) via methods such as imaging

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Which IV antibiotics are usually recommended for uncomplicated gram-negative bacteremia?	• To guide IV antibiotic choice, consider C&S results, MICs, infection source, patient-specifics (e.g., renal function, allergies) in addition to following available facility protocols. Examples of IV antibiotics and dosing used to treat gram-negative bacteremia based on the causative pathogen include:[2,5,6,15,16] o *E. coli* or *Klebsiella*: ceftriaxone 2 g IV every 24 hours. See our *Beta-Lactam Allergy: FAQs*, for options in patients with penicillin allergies. ▪ ESBL-producing pathogens (often resistant to ceftriaxone): ertapenem 1 g IV every 24 hours o *Pseudomonas aeruginosa* (extended infusions given over about four hours): cefepime 2 g IV every eight hours, piperacillin/tazobactam 4.5 g IV every eight hours, or meropenem 1 g IV every eight hours o Other less common pathogens (e.g., *Citrobacter*, *Enterobacter cloacae*, *Serratia marcescens*): cefepime extended infusion 2 g IV every 8 to 12 hours (if susceptible to ceftriaxone and ceftazidime)
What is an appropriate **duration of treatment** for uncomplicated gram-negative bacteremia?	• Use seven days of antibiotics for most patients with uncomplicated gram-negative bacteremia.[3,4,7] • Clinical outcomes and microbiological cure seem similar whether using seven days of antibiotics or 14 days of antibiotics to treat uncomplicated gram-negative bacteremia [Evidence Level A-1].[1,3,4,14] o Consider **day one** as the first day of effective therapy (e.g., the first day of antibiotics with coverage of the identified pathogen).[1] ▪ However, even with antibiotics that cover the pathogen, if patients do not improve until source control is achieved, day one should be the day source control is achieved.[1] o Most data are in infections due to Enterobacterales (e.g., *Escherichia coli*, *Klebsiella* [including ESBL-producing pathogens]), but there are some data supporting seven days of antibiotics for uncomplicated gram-negative bacteremia due to *Pseudomonas*.[1,14] • Reducing antibiotic treatment duration for uncomplicated gram-negative bacteremia may be an important antimicrobial stewardship intervention.[14] Some evidence suggests shorter antibiotics courses may reduce the emergence of multidrug-resistant gram-negative bacteria.[7]
When are **oral antibiotics appropriate** to treat uncomplicated gram-negative bacteremia?	• Transitioning to oral antibiotics can reduce unnecessary IV lines and potential complications and may be associated with a reduced length of stay for patients with uncomplicated gram-negative bacteremia.[13] • It may be appropriate to transition to oral antibiotics in patients with uncomplicated gram-negative bacteremia if the following criteria are met:[1,6] o Improving clinically on IV antibiotics. (Note that if a patient is initially started on oral therapy and is improving clinically, oral therapy can be continued.) o Confirmed source of the infection. o C&S indicates sensitivity to available oral antibiotics. o Patient has an intact, functional gastrointestinal tract (e.g., able to tolerate oral intake, no concern for absorption issues).

Question	Answer/Pertinent Information
Which oral antibiotics may be appropriate to treat uncomplicated gram-negative bacteremia?	• To guide oral antibiotic choice, consider C&S results, infection source, patient-specifics, and possible adverse effects. • Preferred oral antibiotics for uncomplicated gram-negative bacteremia usually include:[1,6,8,9] o **Fluoroquinolones** (e.g., ciprofloxacin 750 mg PO bid, levofloxacin 750 mg PO once daily)[1,11] ▪ May reduce chance of infection recurrence compared to beta-lactams.[8] ▪ Gram-negative coverage usually outweighs possible risks associated with fluoroquinolones due to the short duration of therapy. o **TMP/SMX** (e.g., 2 double strength tablets PO BID or 8 to10 mg/kg/day [TMP] PO divided in 2 or 3 doses. ▪ Consider which patients may NOT be appropriate for treatment with TMP/SMX (e.g., first trimester of pregnancy, CrCl <15 mL/min) and possible side effects, such as hyperkalemia.[5] • **Oral beta-lactams** are usually NOT considered first-line oral step-down therapy due to lower bioavailability and potential for inadequate serum concentrations relative to the MIC and necessary dosing frequency.[1,9,11,12] o However, data are growing to support oral beta lactam use to complete antibiotic treatment in some cases of gram-negative bacteremia (e.g., gram-negative bacteremia from urinary source).[9,10] o If considering use of an oral beta-lactam, consult an infectious disease specialist or work with the antibiotic stewardship team to ensure appropriate choice and dose. Specific considerations may include bioavailability, source of infection, identified pathogen, MIC (if available or possibly surrogate MIC if necessary).[12] ▪ High beta-lactam doses may be necessary (e.g., cephalexin PO 1,000 mg every 6 hours, amoxicillin/clavulanate 875/125 mg PO every 8 hours).[6,12,15] o Due to concerns about meeting pharmacokinetic targets for gram-negative infections., the following beta-lactams **should NOT be routinely recommended** as oral step-down therapy for uncomplicated gram-negative bacteremia: cefadroxil, cefpodoxime, cefprozil, cefuroxime, and cefdinir.[1,12]
What is the role for **repeat blood cultures** in uncomplicated gram-negative bacteremia?	• Repeat blood cultures are not needed to confirm successful treatment in most cases of uncomplicated gram-negative bacteremia.[1] • Repeat blood cultures may be helpful in patients:[1] o who are NOT responding clinically within 72 hours of starting antibiotics. o when there is concern for an endovascular infection (e.g., endocarditis). o with limited or no source control.

a. Examples of patients who ARE considered at risk for opportunistic infections include recent solid organ transplant recipients; expected prolonged neutropenia with absolute neutrophil count (ANC) <500 cells/mL during treatment of gram-negative bacteremia; recent CD4 count <200 cells/mL; chronic corticosteroids and/or immunomodulator therapy.[1]

b. Infectious disease experts may consider some immunocompromised patients as NOT being at risk for opportunistic infections (e.g., stable patient receiving immunomodulatory therapy).[1]

Abbreviations: C&S = culture and sensitivity; IV = intravenous; MIC = mean inhibitory concentration; PO = by mouth; TMP/SMX = trimethoprim/sulfamethoxazole.

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/afp/2004/0201/p548.pdf.]

References

1. Heil EL, Bork JT, Abbo LM, et al. Optimizing the Management of Uncomplicated Gram-Negative Bloodstream Infections: Consensus Guidance Using a Modified Delphi Process. Open Forum Infect Dis. 2021 Oct 11;8(10):ofab434. doi: 10.1093/ofid/ofab434.
2. Moehring R, Anderson DJ. Gram-negative bacillary bacteremia in adults. Updated July 21, 2020. https://www.uptodate.com/. (Accessed March 2, 2022).
3. Molina J, Montero-Mateos E, Praena-Segovia J, et al. Seven-versus 14-day course of antibiotics for the treatment of bloodstream infections by Enterobacterales: a randomized, controlled trial. Clin Microbiol Infect. 2021 Sep 9:S1198-743X(21)00491-2. doi: 10.1016/j.cmi.2021.09.001.
4. von Dach E, Albrich WC, Brunel AS, et al. Effect of C-Reactive Protein-Guided Antibiotic Treatment Duration, 7-Day Treatment, or 14-Day Treatment on 30-Day Clinical Failure Rate in Patients With Uncomplicated Gram-Negative Bacteremia: A Randomized Clinical Trial. JAMA. 2020 Jun 2;323(21):2160-2169.
5. Clinical Pharmacology powered by ClinicalKey. Tampa (FL): Elsevier. 2022. http://www.clinicalkey.com. (Accessed February 23, 2022).
6. Stanford Health Care. Stanford de-escalation guide for gram-negative bacteremia. Revised September 2020. https://med.stanford.edu/content/dam/sm/bugsanddrugs/documents/clinicalpathways/SHC-GNR-Bacteremia-de-escalation-guide.pdf. (Accessed February 23, 2022).
7. Chotiprasitsakul D, Han JH, Cosgrove SE, et al. Comparing the Outcomes of Adults With Enterobacteriaceae Bacteremia Receiving Short-Course Versus Prolonged-Course Antibiotic Therapy in a Multicenter, Propensity Score-Matched Cohort. Clin Infect Dis. 2018 Jan 6;66(2):172-177.
8. Punjabi C, Tien V, Meng L, et al. Oral Fluoroquinolone or Trimethoprim-sulfamethoxazole vs. ß-lactams as Step-Down Therapy for Enterobacteriaceae Bacteremia: Systematic Review and Meta-analysis. Open Forum Infect Dis. 2019 Aug 14;6(10):ofz364. doi: 10.1093/ofid/ofz364.
9. Sutton JD, Stevens VW, Chang NN, et al. Oral β-Lactam Antibiotics vs Fluoroquinolones or Trimethoprim-Sulfamethoxazole for Definitive Treatment of Enterobacterales Bacteremia From a Urine Source. JAMA Netw Open. 2020 Oct 1;3(10):e2020166. doi: 10.1001/jamanetworkopen.2020.20166.
10. Mercuro NJ, Stogsdill P, Wungwattana M. Retrospective analysis comparing oral stepdown therapy for Enterobacteriaceae bloodstream infections: fluoroquinolones versus β-lactams. Int J Antimicrob Agents. 2018 May;51(5):687-692.
11. Kutob LF, Justo JA, Bookstaver PB, et al. Effectiveness of oral antibiotics for definitive therapy of Gram-negative bloodstream infections. Int J Antimicrob Agents. 2016 Nov;48(5):498-503.
12. Mogle BT, Beccari MV, Steele JM, et al. Clinical considerations for oral beta-lactams as step-down therapy for Enterobacteriaceae bloodstream infections. Expert Opin Pharmacother. 2019 Jun;20(8):903-907.
13. Tamma PD, Conley AT, Cosgrove SE, et al. Association of 30-Day Mortality With Oral Step-Down vs Continued Intravenous Therapy in Patients Hospitalized With Enterobacteriaceae Bacteremia. JAMA Intern Med. 2019 Mar 1;179(3):316-323.

14. Yahav D, Franceschini E, Koppel F, et al. Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial. Clin Infect Dis. 2019 Sep 13;69(7):1091-1098.
15. Cattrall JWS, Asín-Prieto E, Freeman J, et al. A pharmacokinetic-pharmacodynamic assessment of oral antibiotics for pyelonephritis. Eur J Clin Microbiol Infect Dis. 2019 Dec;38(12):2311-2321.
16. Stanford hospitals and clinics. Medication administration: extended-infusion cefepime (Maxipime) protocol. Reviewed October 2019. https://med.stanford.edu/content/dam/sm/bugsanddrugs/documents/antimicrobial-dosing-protocols/SHC-Extended-Infusion-Cefepime.pdf. (Accessed February 23, 2022).

Cite this document as follows: **Clinical Resource,** ***Uncomplicated Gram-Negative Bacteremia in Adults. Hospital Pharmacist's Letter/Pharmacy Technician's Letter.*** **March 2022. [380317]**