Gram-Negative BSI Adult IV to PO Step-Down Guideline

Disclaimer: Practice guidelines are intended to assist with clinical decision-making for common situations but cannot replace evaluation and management decisions based on individual patient factors. All patients should be carefully evaluated and treated for suspected focal infection if identified. Consult Infectious Diseases (ID) or Adult Antimicrobial Stewardship Program (ASP) if you have clinical questions or questions about antibiotic selection. Additionally, the information below reflects the best available data at the time the guideline was prepared. The results of future studies may prompt revisions to this guideline.

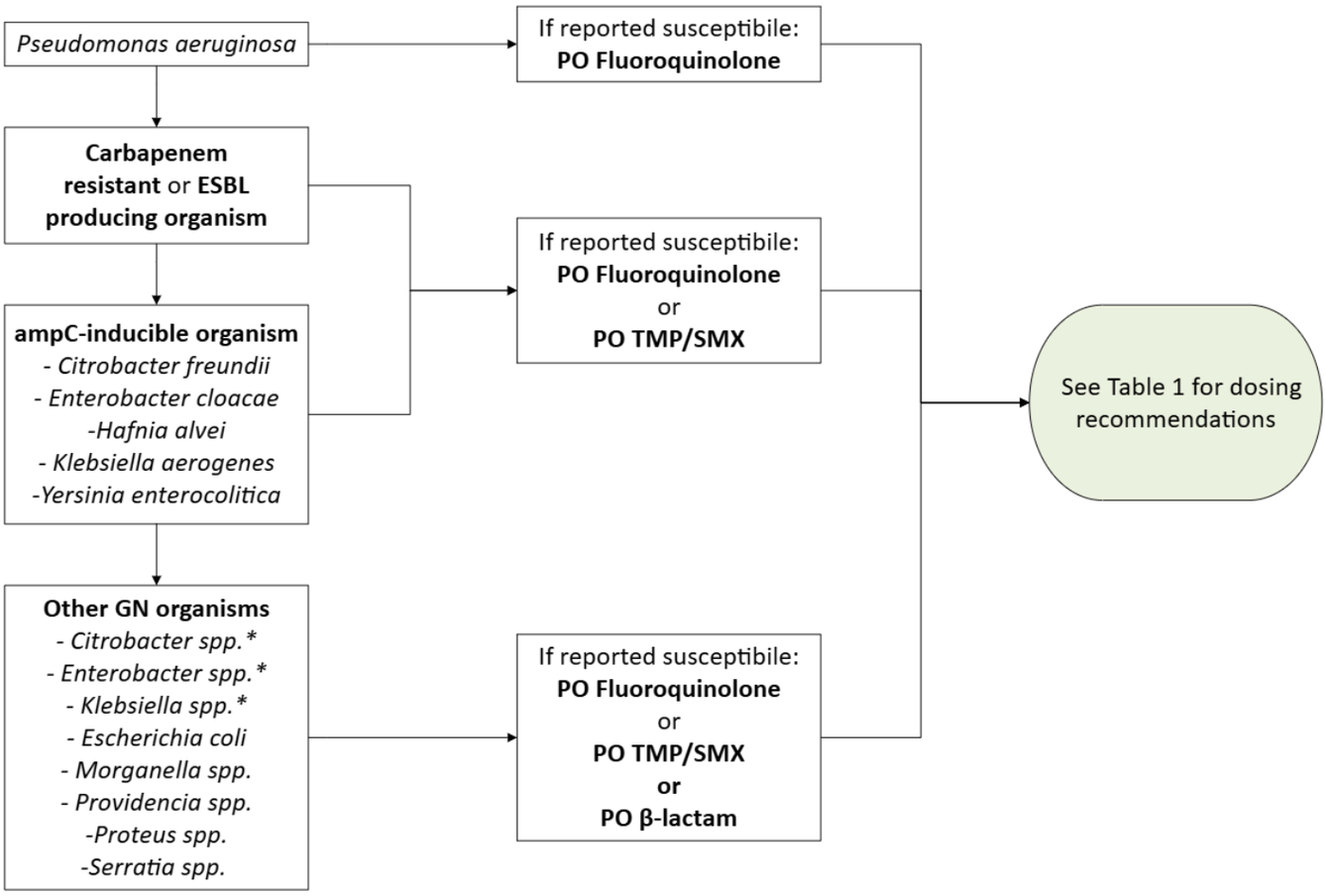
Part 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria

<u>Must meet ALL of the following:</u>
 	
☐ Received **≥ 48 hours** of microbiologically **active IV therapy**
 	
☐ **Clinically stable ≥ 48 hours**, i.e., no vasopressor requirement and normothermic without antipyretic medications
 	
☐ Able to **tolerate and absorb oral medications**
	• Polymicrobial BSI with **non-GN organisms**
	
	• **Uncontrolled source:**
	  ○ Endovascular infection without a removable focus
	  ○ Necrotizing fasciitis requiring further debridement
	  ○ Retained infected line, hardware, device, or prosthesis
	  ○ Undrained/undrainable abscess
	
	• **Metastatic site of infection:**
	  ○ CNS infections
	  ○ Empyema
	  ○ Endocarditis
	  ○ Osteomyelitis
	  ○ Septic arthritis

Part 2: PO Antibiotic Options by Organism

For more information on GN resistance mechanisms, see **Part 4: Resistance**.



*Non-*C. freundii, E. cloacae* or *K. aerogenes*

Table 1: PO Antibiotic Dosing Recommendations

Antibiotic	**Recommended Dose** (for normal renal function)
Fluoroquinolone	
Ciprofloxacin	750 mg PO twice daily
Levofloxacin	750 mg PO daily
TMP/SMX	
Trimethoprim/Sulfamethoxazole	2 DS tablets PO twice daily*
β-lactams	
Amoxicillin - infer susceptibility from ampicillin	1,000 mg PO three times daily
Amoxicillin/Clavulanate - infer susceptibility from ampicillin/sulbactam	875/125 mg PO three times daily
Cephalexin - infer susceptibility from cefazolin in **blood culture**	1,000 mg PO four times daily

***Target 8 - 10 mg TMP/kg/day. May require dose adjustment for BW < 40 kg or > 85 kg. Contact ID/ASP pharmacy to assist if needed.

Part 3: Duration of Therapy
For most patients meeting inclusion criteria above, we recommend a 7 day duration therapy (DOT), where day 1 of therapy is counted from the first day of microbiologically active therapy. Repeat blood cultures are not needed to confirm clearance of uncomplicated GN BSI. If unsure or the patient scenario falls outside of these guidelines, please reach out to ID or ASP for guidance.

Immunocompromised Patients:
Among immunocompromised patients, clinical judgement should always be exercised. A 7 day duration of therapy may be reasonable EXCEPT for the following populations:

- Solid organ transplant recipients within 1 year from transplant or augmented immunosuppression
- Stem cell transplant recipients or hematologic malignancy with severe neutropenia (ANC < 500 cells/mL)

For other populations, literature is limited but growing (see Appendix A, below). Clinicians should continue to align practice with established society guidelines for specific syndromes (e.g. renal allograft pyelonephritis).

Part 4: Resistance
Always confirm reported susceptibility before selecting a PO antibiotic option. Not all gram-negative organisms will have a susceptible PO options available.

Carbapenem resistant organisms: resistant to at least one carbapenem antibiotic (i.e., ertapenem, meropenem, or imipenem-cilastatin). This may be due to carbapenemase enzyme production or other resistance mechanisms. Gene testing is reported for carbapenemase genes in the comments section of culture results. Carbapenem resistant organisms often have resistance to non β-lactam antibiotics (e.g., fluoroquinolones, TMP/SMX). **Do not use oral beta-lactam antibiotics for carbapenem resistant organisms.**

Extended spectrum β-lactamase (ESBL): enzymes that confer resistance to most β-lactam antibiotics, including penicillins, cephalosporins, and aztreonam. ESBL producing organisms generally remain susceptible to carbapenems. While ESBL enzymes do not inactivate non-β-lactam antibiotics, they may carry other genes that can confer resistance to non β-lactam antibiotics, but non-beta lactams can be used if they test susceptible. **Do not use oral beta-lactam antibiotics for ESBL producing organisms.**

Amp-C inducible organisms: include *Enterobacter cloacae*, *Klebsiella aerogenes*, and *Citrobacter freundii*, as well as the more rarely seen *Hafnia alvei* and *Yersinia enterocolitica*. While these organisms may be reported to be susceptible to third-generation cephalosporins, exposure to even a few doses of β-lactams can induce ampC production and development of resistance to many β-lactams, including ceftriaxone, ceftazidime, cefotaxime, ampicillin-sulbactam, and piperacillin-tazobactam. AmpC enzymes do not inactive non-β-lactam antibiotics, including fluoroquinolones and TMP/SMX. **Do not use oral beta-lactam antibiotics for ampC inducible organisms, even if reported susceptible.**

Part 5: Common Questions

Which agent should be chosen when multiple are reported susceptible?
We recommend that any option reported susceptible may be chosen based on patient-specific considerations such as allergies, renal function, side-effects profile, etc.

Fluoroquinolones and TMP/SMX have high oral bioavailability, but have less desirable side effect profiles when compared to oral β-lactams. While there were previously concerns due to the lower oral bioavailability of β-lactams, the higher doses recommended in this guideline are expected to reach pharmacokinetic targets.[39] While the most data are available in the literature for oral fluoroquinolones, followed by TMP/SMX, multiple studies have shown that there is no significant difference in recurrence of bacteremia or mortality between oral fluoroquinolones, TMP/SMX and high-dose β-lactams.[31-38]

Why are cefuroxime and cefpodoxime not listed as options in Table 1?
The oral cephalosporins cefuroxime and cefpodoxime are excluded from the recommended options in Table 1 due to the limited data on the optimal dosing for pharmacokinetic target attainment for *Enterobacterales*. Use may be considered on a case-by-case basis in discussion with ID pharmacy.

Cefuroxime and cefpodoxime have lower bioavailability compared to the oral β-lactams recommended in Table 1, and lack robust pharmacokinetic studies to inform at what dose pharmacokinetic target attainment for *Enterobacterales* would be expected.[39] While retrospective studies including patients transitioned to oral cefuroxime and cefpodoxime in the oral β-lactam group have found no difference in recurrence of bacteremia or mortality, it is unclear what dosing regimens, durations of IV therapy prior to transitioning, and strategies of inferring susceptibility from IV cephalosporins were used.[32-33, 35-38] Based on the lack of sufficient evidence at this time, no recommendation is made in this guidance on the use of cefuroxime and cefpodoxime. Please contact ID/ASP pharmacy if considering either of these agents for IV to PO step down in GN BSI.

Appendix A: Literature on Patients with Immunocompromising Conditions:

While studies on long versus short DOTs have historically excluded patients with immunocompromising conditions, there is increasing data which includes patients with malignancy, SOT, SCT, or receiving chemotherapy/immunosuppressive medications, as well as some patients with neutropenia. These studies have found no difference in mortality, BSI recurrence, or hospital readmission and are summarized in the table below, though are at times limited by small numbers of patients.

Study	Population	Immunocompromised Population	DOT	Outcomes
Molina et al., 2022 Open-label non-inferiority RCT (10% margin)	Adults w/ *Enterobacterales* BSI and source control n = 231	Malignancy: n = 64 SOT: n = 11 Immunosuppression: n = 31 Excluded pts on chemotherapy and expected to have ANC < 500 cells/µL for > 7 days	7 vs 14d	- Non-inferior: clinical cure, BSI relapse, or death - Not non-inferior: fever relapse - DOOR/RADAR score: 77.7% probability of achieving better results w/7d DOT
Yahav et al., 2019 Open-label non-inferiority RCT (10% margin)	Adults w/aerobic GN BSI and source control if HDS and afebrile ≥ 48h n = 604	Malignancy: n = 159 SOT: n = 51 SCT: n = 5 Immunosuppression (any immunosuppressive drug, including prednisone ≥20 mg/day or equivalent): n = 150 Excluded pts with neutropenia at time of randomization, HIV infection, allogeneic SCT w/in 1 mo and at any time before engraftment.	7 vs 14 d	-Noninferior: 90 d all-cause mortality, clinical failure, readmission or extended (> 14d) hospitalization
BALANCE trial, 2024 Open-label non-inferiority RCT (4% margin)	Adults w/BSI excluding *S. aureus, S.lugdunensis,* and fungal BSI n = 3,608	Solid-organ cancer: n = 782 Leukemia/lymphoma: n = 101 Immunosuppression (including chemotherapy and prednisone ≥15 mg/day or equivalent) n = 440 Excluded pts with ANC < 500 cells/µL or receiving immunosuppressive treatment for SOT or SCT	7 vs 14 d	-Noninferior: 90 d all-cause mortality
Herrera et al., 2023 Prospective observational study	Adults w/GN BSI who also have 1 of the following: - Solid tumor or hematologic malignancy w/chemotherapy w/in 1 mo OR biologic agents 6 mo prior to admission - Allogeneic SCT in the 1st 2 years ± graft versus host disease (GVHD) - Autologous HSCT in the 1st year post-transplant Total n = 74 ANC < 500 cells/µL: n = 54 (59.5%)		7 vs 14 d (median DOTs)	-30 d Mortality: 2.8% vs. 7.9% (7 vs 14d, p = 0.61) -30 d BSI relapse: 2.8% vs 0% (7 vs 14d, p = 0.30)
Ranganath et al., 2023 Retrospective cohort study	Adults w/GN BSI and ANC ≤ 1,000 cells/µL Total n = 205 SCT: n = 99 Hematologic malignancy: n = 73 Solid organ malignancy: n = 20 SOT: n = 9		≤ 10 vs 11-14 vs ≥ 15 d	-90 d mortality and BSI relapse: 16.5% vs 21.3% vs 28.0% (≤ 10 vs 11-14 vs ≥ 15 d) -Propensity score adjusted HR 0.89 (11-14 vs ≤ 10 d) and 1.22 (≥ 15 vs ≤ 10 d); p = 0.722
McAteer et al., 2023 Retrospective cohort study	Adults w GN BSI w/a urinary source n = 1,099	SCT w/in 12 mo or active GVHD treatment, active chemotherapy w/in 6 mo, previous SOT, HIV infection w/CD4 < 200 cells/mm^3, ANC < 500 cells/µL at or w/in 7d after diagnosis, or prednisone ≥10 mg/day or equivalent for ≥ 14 days or other immunosuppressive therapy: n = 160	7 vs 14 d	-Immunocompromised pts more likely to receive longer DOT: 16% vs 26% (7 vs 14 d, p = 0.004) - ↑ risk of BSI recurrence w/7 days vs 14 days, but no difference in pts receiving IV or highly bioavailable oral β-lactam at doses recommended for GN BSI.

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Quick Reference	
Last revision Date:	06/2025

PURPOSE/SCOPE:	To provide guidance on adult patients with certain Gram-negative bloodstream infections who meet criteria for early oral antibiotic therapy step-down.

EXECUTIVE SUMMARY

This is an adult guideline that provides the criteria for select patients with a gram-negative (GN) bloodstream infection (BSI) who are eligible to receive oral antibiotics, an evolving practice that may decrease length of stay and avoid complications from intravenous (IV) therapy. Patients must have clinically stabilized and meet criteria below:

- Source control is imperative.
- Metastatic infections secondary from BSI are excluded.
- Duration should typically be 7 days total, including days of microbiologically active IV therapy.
- Consult Infectious Diseases (ID) or contact Adult Antimicrobial Stewardship Program (ASP) if you have questions.

BACKGROUND / INTRODUCTION
GN BSIs have traditionally been managed with IV antibiotics. However, data suggest that IV antibiotics are not always necessary for the entirety of the treatment course. This is an evolving clinical area in infectious diseases. Clinically and hemodynamically stable patients may be appropriate candidates for treatment of BSIs with oral antimicrobials. This practice may mitigate additional inpatient length of stay and/or the need for outpatient IV therapy. This guideline focuses on early IV to PO transition in uncomplicated GN BSI in patients who meet criteria.
SUPPORTING EVIDENCE
The references below and input from UCSF ID providers and pharmacists were utilized in developing this guideline. This guideline has been reviewed by all key collaborators and their additional recommendations incorporated.

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Revision History	
Revision Date	**Update(s)**
June 2025	- Simplified inclusion/exclusion criteria - Added flow chart to guide antibiotic selection - Updated dosing table and recommended antibiotic options to reflect newer data - Added section on duration of therapy in patients with immunocompromise to support decision-making in these situations - Enhanced section on select resistance mechanisms for clarity - Added section on commonly asked questions for clarity and completeness - Removed tables on bioavailability, inferred susceptibility, and other considerations to focus guideline recommendations and streamline decision making