Guideline/Protocol Title:	*Enterobacterales* Bloodstream Infection Adult IV to PO Step-Down Guideline
Original Author(s):	Ripal Jariwala, PharmD, BCIDP, AAHVIP Sarah Doernberg, MD, MAS, FIDSA
Collaborator(s):	Jennifer Babik, MD, PhD Steve Grapentine, PharmD, BCPS, APP Katherine Gruenberg, PharmD, MAEd, BCPS, BCIDP Conan MacDougall, PharmD, MAS, BCPS, BCIDP Kathy Yang, PharmD, MPH
Approving committee(s):	UCSF Infectious Diseases Management Program (IDMP) (07/2021)
P&T Approval Date:	09/2021
Quick Reference	For preferred antibiotics based on known susceptibilities, click here
Last revision Date:	08/2021

PURPOSE/SCOPE:	To provide guidance on adult patients with certain Gram-negative blood stream 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 an *Enterobacterales* 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

Traditionally, gram-negative (GN) BSIs have been managed with IV antibiotics. However, recent data suggest that IV antibiotics are not necessary for the entirety of the treatment course, especially for uncomplicated episodes. This is an evolving clinical area in ID.

Clinically and hemodynamically stable patients may be appropriate candidates for treatment of BSIs with oral antimicrobial agents. This practice may mitigate additional inpatient length of stay 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
To develop the guidelines, the sources considered include the references below and input from UCSF ID providers and pharmacists. This guideline has been reviewed by all key collaborators and their additional recommendations incorporated.

Reference #	Citation
1	Allison GM, Muldoon EG, Kent DM, et al. Prediction model for 30-day hospital readmissions among patients discharged receiving outpatient parenteral antibiotic therapy. Clin Infect Dis. 2014;58(6):812-19.
2	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. 379 (3): 316-21.
3	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 Oct; 6(10): 1-9.
4	Kutob LF, Justo JA, Bookstaver PB, et al. Effectiveness of oral antibiotics for definitive therapy of Gram-Negative Bloodstream Infections. Int Antimicrobial Agents 48 (2016) 498–503.
5	Yahav D, Francechini 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): 1091-8.
6	Mercuro NJ, Stogdill P, Wungwattana M. Retrospective Analysis Comparing Oral Stepdown for Enterobacteriacea Bloodstream Infections: fluoroquinolones versus ß-lactams. J Antimicrob Agents. 2018 May; 51(5): 687-92.
7	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. 323:2160-9
8	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: 20:8, 903-907.
9	Sutton JS, Stevens VW, Chung N, et al. Oral ß-lactam Antibiotics vs Fluoroquinolones or Trimethoprim-Sulfamethoxazole for Definitive Treatment of Enterobacterales Bacteremia from a Urinary Source. JAMA Netw Open. 2020 Oct; 3(10):1-13.
10	Cyriac JM and E. James. Switch over from intravenous to oral therapy: A concise overview. J Pharmacol Pharmacother. 2014 Apr-Jun; 5(2): 83–87.
11	The Sanford Guide to Antimicrobial Therapy 2020. Sperryville, VA: Antimicrobial Therapy, Inc.,2020.
13	Williams NT. Medication administration through enteral feeding tubes. Am J Health-Syst Pharm. 2008 Dec; 65: 2347-57.

14	Hendrickson JR and DS North. Pharmacoeconomic Benefit of Antibiotic Stepdown Therapy: Converting Patients from Intravenous Ceftriaxone to Oral Cefpodoxime Proxetil. Ann Pharmacother 1995;29: 561-5.
15	Nisly SA, McClain DL, Fillius AG, et al. Oral Antibiotics for the Treatment of Gram-negative Bloodstream Infections: A Retrospective Comparison of Three Antibiotics Classes. J Glob Antimicrob Resist 2020; 20: 74-7.
16	Chotiprasitsakul D 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;66(2):172-7.
17	Tamma PD, Aitken SA, Bonomo RA, et al. Infectious Diseases Society of America Antimicrobial Resistant Treatment Guidance: Gram-Negative Bacterial Infection. Clin Infect Dis 2020 Oct 7; 1-15.
18	Al-Hasan MN and H Rac. Transition from Intravenous to Oral Antimicrobial Therapy in Patients with Uncomplicated and Complicated Bloodstream Infections. Clin Micro and Infect 2020; 26: 299-306.
19	Meije Y, Pigrau C, Fernandez-Hildalgo N, et al. Non-intravenous carbapenem-sparing antibiotics for definitive treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum β-lactamase (ESBL) or AmpC β-lactamase: A propensity score study. Int J Antimicrob. Agents 54: (2019) 189–196.
20	Lung-Lo C, Lee C-C, Li C-W, et al. Fluoroquinolone therapy for bloodstream infections caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae. J Microbiol Immunol (2017) 50, 355-61.

Revision History	
Revision Date	**Update(s)**
August 2021	•

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

Criteria:

Inclusion:

- Controlled source of infection
- Received microbiologically active IV therapy for at least 48 hours
- Clinically stable
    - No vasopressor requirements for at least 48 hours
    - Nomothermia (temperature between 36-38 degrees Celisus) x 48 hours without the administration of anti-pyretic medications
- Able to tolerate and absorb oral medications
- Organism is microbiologically documented as susceptible to oral agent or its tested surrogate
- Eligible organisms:
    - *E. coli*
    - *Klebsiella spp.*
    - *Enterobacter spp.*
    - *Citrobacter spp.*
    - *Proteus spp.*
    - *Serratia spp.*
    - *Morganella spp.*
    - *Providencia spp.*
    - *Hafnia alvei*
    - *Pantoea agglomerans*

Exclusion: For situations below, consideration of oral agents may be considered on a case-by-case basis in consultation with ID but should not be routinely pursued.

- History of IgE-mediated allergy to all susceptible oral agents
- Severe immunocompromise
    - Solid organ transplantation (SOT) within 3 months or recent augmented immunosuppression (for rejection)
    - Current or impending neutropenia defined as absolute neutrophil count (ANC) <500 cells/mm^3
    - History of stem cell transplant in the previous 12 months (assuming immune system not reconstituted) or ongoing therapy for graft versus host disease
    - Other diagnosed chronic condition with equivalent moderate to severe level of immunocompromise
- Retained infected prothesis/foreign materials
- Complex urinary anatomy (may need individual case review)
- Gram-negative BSI due to the following infections:
    - Endocarditis
    - Endovascular infection without a removable focus
    - Necrotizing fasciitis
    - Osteomyelitis or septic arthritis
    - Confirmed prostatitis
    - Undrainable abscess or other unresolved sources requiring surgical intervention
    - Central nervous system infections
    - Empyema
- Polymicrobial infection
- Pregnancy

Recommendations:

When reviewing antibiotic susceptibility data, not every antibiotic is tested. However, certain antibiotics can be inferred or serve as a surrogate marker for susceptibility.

Table I. IV to PO Inferred Susceptibility

Inferred Susceptibility
Ampicillin → amoxicillin
Ampicillin-sulbactam → amoxicillin-clavulanic acid
Cefazolin → cefdinir, cefuroxime axetil, cefpodoxime, cephalexin (cannot infer for cefadroxil)
Ceftriaxone[1] → N/A (cannot always infer susceptibility to oral 3rd generation cephalosporins)

1 For isolates that are resistant to cefazolin but susceptible to ceftriaxone, there may be some isolates that are still susceptible to cefdinir, **cefpodoxime**, and **cefuroxime** (bolded indicates available testing at UCSF). Contact ASP pharmacist if considering these options.

Table II. Tiered Anti-infective Approach*

****If the patient is able to take oral therapy and the bacteria is susceptible, recommend IV-PO transition (the following antibiotics are in order of preferential use top to bottom):**

1st Tier

Ciprofloxacin 750 mg PO twice daily

Levofloxacin 750 mg PO daily

2nd Tier

TMP/SMX 8-10 mg/kg/day (doses divided up into 2-3 doses)

3rd Tier (Avoid use in BSI patients with ESBL or AmpC-producing organisms)

Cefuroxime 500 mg PO twice daily

Amoxicillin 1000 mg PO three times a day

Cephalexin 500 mg PO four times a day

Amoxicillin-clavulanate 875/125 mg PO twice daily

***This table attempts to streamline recommendations, but refer to Table III for details on anti-infective dosing , other anti-infective options (not listed above), and precautions**

****Assumes normal renal function**

If the organism is susceptible to the antibiotic, then dosing as follows. Dosing should be adjusted for renal impairment as clinically appropriate, side effects (e.g QTc prolongation), and *C. difficile* history; in addition, drug interactions should be always evaluated. Lexicomp may provide enhanced details as a reference on side effects and drug interactions. Consult with an ID pharmacist for recommendations if the below does not fit the clinical scenario.

Table III. Oral Antibiotic & Dosing Recommendations

Blood and urine break points may be different – use blood MIC or susceptibility interpretation to guide

Antibiotic	Considerations		
Amoxicillin 1000 mg PO q three times a day[1]	• Does not provide broad anaerobe coverage		
Amoxicillin-clavulanate 875/125 mg PO two times a day[1]	• **Consider using thrice-daily dosing (amoxicillin-clavulanate 875/125 mg po three times a day) at least in class I obesity (BMI ≥ 30 kg/m^2)**		
Cefdinir 300 mg PO twice daily[1,2]			
Cefpodoxime 400 mg PO twice daily[1,2]			
Cefuroxime axetil 500 mg po twice daily[1,2]			
Cephalexin 500 mg PO four times a day[1]	• Alternative dosing: 1000 mg po three times a day		
Ciprofloxacin 750 mg PO twice daily	• Avoid use of ciprofloxacin suspension (brand product) in feeding tubes due to clogging • Various side effects (refer to Lexicomp for details) • Avoid use in patients with prolonged QTc or with myasthenia gravis		
Levofloxacin 750 PO daily	• Various side effects (refer to Lexicomp for details) • Avoid use in patients with prolonged QTc, or with myasthenia gravis		
Moxifloxacin 400 mg PO daily	• Avoid use in urinary source • Various side effects (refer to Lexicomp for details) • Avoid use in patients with prolonged QTc or with myasthenia gravis		
Trimethoprim-sulfamethoxazole (TMP/SMX) 8-10 mg/kg/day (doses divided into 2-3 doses) **Double strength (DS) = 160/800 (TMP/SMX)**	40-59 kg	1 DS PO BID	Avoid use in patients who are on warfarin unless there is close monitoring plan of the INR Dosing based on adjusted body weight (AdjBW)
	60-69 kg	1 DS PO TID	
	70-89 kg	2 DS PO BID	
	90 kg and greater	Consult ASP Pharmacist	

1 Do not use in extended spectrum beta-lactamase (ESBL) producing organisms; Avoid use in HECK-YES organisms – *Hafnia alvei, Enterobacter cloacae, Citrobacter freundii, Enterobacter (Klebsiella) aerogenes, Yersinia enterocolitica*; *Proteus vulgaris* should be avoided in third generation cephalosporins

2 Preferred order for oral cephalosporins: **Cefuroxime** > **cefpodoxime** > cefdinir for urinary sources based upon urinary penetration (bolded indicates available testing at UCSF)

Table IV. Bioavailability

Antibiotic (Do not use oral β-lactams in ESBL-*Enterobacterales* BSI)	Bioavailability (%)	Protein binding (%)	Food Effect on Absorption	Peak Serum Concentration (mg/L)	Half-life (hours)
Amoxicillin	74–92	17-20	Not Significant	3.5–5.0	1-1.2
Amoxicillin- clavulanate	60	18-20	Not Significant	3.7–4.8	1-1.4
Cephalexin	90–100	6–15	Not Significant	15–18	0.6–1.3
Cefdinir	21–25	60–70	Not Significant	1.6–2.3	1.7
Cefpodoxime	29–53	22–33	Increase	3.9–4.5	2.2–2.8
Cefuroxime	30–52	33–50	Increase	7.0	1.0–2.0
Ciprofloxacin	70	20-40	Not significant[1]	4.6	4
Levofloxacin	99	24-38		8.6	7
Moxifloxacin	89	30-50		4.2-4.6	10-14
Trimethoprim/ Sulfamethoxazole (TMP/SMX)	85	44/70	Not significant	1-2/40-60	11/9

1 Fluroquinolones can be taken with or without food. Products that contain magnesium, aluminum, calcium, iron, and/or other minerals may interfere with the absorption of the fluoroquinolone into the bloodstream and reduce its effectiveness.

Extended spectrum β-lactamase- Producing *Enterobacterales* (ESBL-E)

Extended-spectrum beta-lactamases (ESBLs) are enzymes that confer resistance to most beta-lactam antibiotics, including penicillins, cephalosporins, and the monobactam, aztreonam. In general, EBSL-E can remain susceptible to carbapenems, but do not inactivate non-β-lactam agents (e.g., ciprofloxacin, TMP/SMX).

Per the 2020 Infectious Diseases Society of America (IDSA) guidelines on the Treatment of Antimicrobial Resistant Gram-Negative Infections, oral step-down therapy with a fluoroquinolone or TMP/SMX is recognized as a viable option in patients with *Enterobacterales* BSI who meet inclusion criteria. Additionally, other studies have contributed to the ID literature with regards to the use of these agents as a carbapenem sparing strategy.

Amp C organisms

Many organisms have inducible AmpC production, most commonly *E. cloacae*, *E. aerogenes*, *C. freundii*, *S. marcescens*, *Providencia stuartii*, *P. aeruginosa*, *Hafnia alvei*, and *Morganella morganii*, often referred to as the SPACE or SPICE organisms. HECK-YES is also another AmpC acronym and includes *H. alvei, E. cloacae, C. freundii, Enterobacter (Klebsiella) aerogenes, Y. enterocolitica*.

The common phenotypic pattern of these organisms is that they appear to be susceptible to third-generation cephalosporins if AmpC production is not induced, but that resistance can develop upon beta-lactam exposure.

Caution with ceftriaxone and ceftazidime is highly recommended, even if the organism is reported as susceptible to these agents. Prolonged use may select for derepressed AmpC mutants (often ceftriaxone-resistant and cefoxitin-resistant). Do not use oral beta-lactam antibiotics for these organisms, even if susceptible.

Duration

For patients meeting inclusion criteria above, we recommend 7 days of therapy, including the number of days of microbiologically active IV antibiotics received. Repeat blood cultures are not needed to confirm clearance of uncomplicated *Enterobacterales* BSI. If unsure or the patient scenario falls outside of these guidelines, please reach out to ID or ASP pharmacist for guidance.