# Stanford De-escalation Guide for Gram-negative Bacteremia

## Antibiotic Selection

| Pathogens | Preferred therapeutic options IF SUSCEPTIBLE<br>*Switch to PO when clinically stable, able to take orals, no concern for absorption issues* |
|---|---|
| *E.coli*<br>*Klebsiella* spp.<br>*Proteus* spp.<br>*Citrobacter koseri* | Preferred:<br>• Ceftriaxone 2g IV q24h<br>• Ciprofloxacin 500-750mg* PO BID<br>• Levofloxacin 500-750mg* PO daily<br>• Cefazolin 2g IV q8h†<br><br>2nd line oral alternatives:<br>• TMP-SMX 2DS PO BID or 8-10mg TMP/kg/day PO divided in 2 or 3 doses<br><br>3rd line oral alternatives: *Data supports stepdown to oral beta-lactams in uncomplicated bacteremia.[13, 21] Higher than usual doses are recommended to achieve target attainment, especially if organism has a higher or unknown MIC and/or oral stepdown occurs before ~5 days of active IV therapy [13,22] Consult ASP or ID with any concerns or questions.*<br>• Amoxicillin 1g PO q8h if ampicillin MIC ≤ 2<br>• Amoxicillin/clavulanate 875/125mg PO q8h‡ or 2g XR BID (if covered by insurance) if ampicillin MIC ≤ 2<br>• Cephalexin 1g PO q6h†<br>• Call ASP if considering cefpodoxime† or cefadroxil: low likelihood of target attainment.<br>• Avoid cefdinir- poor clinical outcomes observed.[21]<br><br>† At SHC, cefazolin susceptibility testing not routinely performed on blood. Caution with inferring from urine culture, as blood cultures have different cefazolin breakpoints than urine cultures. Mechanistically, may infer cefazolin-S from ampicillin-S. If ampicillin-R, call micro lab to add on cefazolin testing in blood. *K.pneumoniae* is intrinsically ampicillin-R.<br>‡ Alternative if GI upset: with appropriate counseling 875/125mg PO BID (qAM and qPM) + amoxicillin 1000mg q noon. |
| | **ESBL-producers**<br>Often ceftriaxone resistant + cefoxitin susceptible. At SHC, micro comments state these isolates "possibly harboring a cephalosporinase"<br>• Ertapenem 1g IV q24h<br>• Ciprofloxacin 500-750mg* PO BID<br>• Levofloxacin 500-750mg* PO daily<br>• TMP-SMX 8-10mg/kg/day PO divided in 2 or 3 doses<br>*Note: Avoid most beta-lactams (including piperacillin-tazobactam and amoxicillin-clavulanate). May report as susceptible, but treatment failure may occur. MERINO trial: higher mortality in those treated with piperacillin-tazobactam vs meropenem.* |
| *Enterobacter cloacae, Klebsiella aerogenes, Hafnia alvei, Citrobacter freundii*<br><br>(moderate-high risk AmpC production) [18,19**] | • Cefepime 2g IV q8h extended infusion<br>  • At SHC, susceptibility is inferred if ceftriaxone and ceftazidime susceptible. Contact micro lab for testing if cefepime is considered for therapy. Ceftriaxone-R + ceftazidime-R + cefoxitin-R isolates are highly consistent with ampC and rarely, ESBL co-production.<br>• Ertapenem 1g IV q24h<br>• Ciprofloxacin 500-750mg* PO BID<br>• Levofloxacin 500-750mg* PO daily<br>• TMP-SMX 8-10mg/kg/day PO divided in 2 or 3 doses<br>*Note: Avoid ceftriaxone and piperacillin-tazobactam, even if reported as susceptible. Prolonged use may result in emergence of ceftriaxone resistance via selection of derepressed AmpC mutants (often ceftriaxone resistant + cefoxitin resistant).* |

| | |
|---|---|
| *Serratia marcescens, Morganella morganii, Providencia spp* (low risk AmpC production).[18,19**] | • Same as above with additional options in uncomplicated bacteremia as follows:<br>• Ceftriaxone 2g IV q24h<br>• Piperacillin-tazobactam 3.375-4.5g* IV q8h extended infusion |
| *Pseudomonas aeruginosa* | **Consider ID consult**<br>• Cefepime 2g IV q8h extended infusion<br>• Ceftazidime 2g IV q8h<br>• Piperacillin-tazobactam 4.5g* IV q8h extended infusion<br>• Meropenem 1g IV q8h extended infusion<br>• Ciprofloxacin 750mg PO BID<br>• Levofloxacin 750mg IV/PO daily<br>• Consult ID for multi-drug resistant strains and/or unable to take the above agents |
| *Stenotrophomonas maltophilia* | **ID consult recommended** |
| *Acinetobacter baumanii* | **ID consult recommended**. Commonly resistant to many antibiotics. Ampicillin-sulbactam is usually active. |

* Lower doses listed are for typical 70kg, normal renal function, tailored for the organism causing bacteremia. Higher dose may be considered for deep seated infections, obese (BMI ≥ 30), high CrCl > 100 ml/min. Use clinical judgement.
**Clinical reports of emergence of resistance has been reported mainly in *Enterobacter spp*[19] Higher mutation rates reported in experimental model of *E. cloacae complex, E, aerogenes, C. freundii, H. alvei* than *Providencia spp, Serratia spp. M. morganii*.[18]
Abbreviations: TMP-SMX= trimethoprim/sulfamethoxazole, DS = double strength, FQ= fluoroquinolone, PK/PD = pharmacokinetic/pharmacodynamic, MIC= minimum inhibitory concentration

**Duration (excludes neutropenia-** see FN pathway, consult ID**)**

| Type | Duration of therapy | Notes |
|---|---|---|
| Uncomplicated bacteremia<br><br>(See below definition†) | 7 days[2, 7, 8]<br><br>Count day 1 from the 1st day of active therapy†<br><br>ID consult if:<br>• Patient is severely immunocompromised<br>• Considering a longer course of therapy | • Inclusion criteria:<br>  ○ Must have clinically improved<br>  ○ Must have source control if applicable<br>• Excludes neutropenic patients: see FN pathway; ID consult.<br>• *P.aeruginosa*: 8-10 days may be considered in select patients.[3]<br>• **Reminder**: Rule out infections involving long term catheters, ports, or hardware: longer treatment may be warranted if prosthesis/foreign materials are infected. Consider ID or ASP consult. |
| Complicated bacteremia. E.g.<br>Endovascular (e.g. infective endocarditis, VAD, ICD/pacemaker)<br>Osteomyelitis<br>Complicated abdominal<br>Meningitis/ventriculitis | Varies depending on source control and other co-morbid conditions | Consult ID |

†Repeat blood cultures are generally not necessary to confirm clearance of uncomplicated Gram-negative bacteremia and are not necessary to determine day 1 of treatment.[10, 12] For clinically improved patients with source control, count day 1 from the 1st day of active therapy. Consult ID or ASP with additional questions or concerns.

†**Definition**:
Uncomplicated gram-negative bloodstream infections are defined as the following (suggest all 4 conditions must be met):[22]

a. Bloodstream infection confirmed to be secondary to 1 of the following sources:
   i. Urinary tract infection
   ii. Intra-abdominal or biliary infections
   iii. Catheter-related bloodstream infection
   iv. Pneumonia (without structural lung disease, empyema/abscess, cystic fibrosis)
   v. Skin and soft tissue infection
b. Source control (ie, removal of any infected hardware, catheters, or devices and near complete drainage of infected fluid collections, as well as imaging assurance [as needed] of no residual or metastatic sites of infection)
c. Patients without immunocompromise and risk for opportunistic infections (eg, recent solid organ transplant recipients; expected prolonged neutropenia with ANC <500 cells/mL during the GN-BSI treatment course; recent CD4 cell count <200 cells/mL; chronic corticosteroids and/or immunomodulator therapy); select immunocompromised patients such as those on stable immunomodulatory therapy may be considered on a case-by-case basis
d. Clinical improvement within 72 hours of effective antibiotic treatment—at a minimum includes defervescence and hemodynamic stability

**References:**

1. Tamma et al, JAMA Int'l Med 2019 PMID: 30667477
2. Yahav et al, CID 2018 PMID: 30535100
3. Fabre et al, CID 2019 PMID: 30882137
4. Mercuro et al, IJAA 2018 PMID: 29284155
5. Eliakim-Raz et al, JAC 2013 PMID: 23696620
6. Kutob et al, IJAA 2016 PMID: 27590704
7. Canzoneri et al, CID 2017 PMID 29020307
8. Chotiprasitsakul et al, CID 2019 PMID: 29190320
9. Tansarli et al, AAC 2019 PMID: 30803971
10. Wu et al, BMC 2018 PMID 29902981
11. MERINO Trial JAMA 2018 PMID: 30208454
12. Wiggers et al, BMC ID 2016 PMID: 27296858
13. Punjabi C et al, OFID 2019 PMID: 31412127
14. Wang AAC 2014 PMID: 24145530
15. Ko CMI 2019 DOI: 10.1016/j.cmi.2018.11.008
16. Cho BMCID 2015 PMID: 25887489
17. Lai et al, ID week 2017
18. Kohlmann et al, J Antimicrob Chemother. 2018 Jun 1;73(6):1530-1536. doi: 10.1093/jac/dky084.
19. Tamma et al, CID 2019;69(8):1446–55 DOI: 10.1093/cid/ciz173
20. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the Treatment of AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. Clin Infect Dis. 2021 Dec 5:ciab1013. doi: 10.1093/cid/ciab1013. Epub ahead of print. PMID: 34864936. [accessed 3/14/2022]
21. Mack et al 2022 PMID: 35758168
22. Heil et al 2021 PMID: 34738022

**Authors:** Lina Meng, PharmD, Emily Mui, PharmD, Stan Deresinski, MD, Samaneh Pourali, PharmD, Cassie Kwok, PharmD, Noah Fang, PharmD, Alycia Hatashima, PharmD, 7/19/2019.

**Original Date:** 7/15/2019 **ABX Subcommittee approved:** 7/25/2019, 3/25/2022, pending 3/2024
**Revisions**: 9/9/2020 ASP team, David Epstein, MD, 3/16/2022 ASP team, 2/8/2024 ASP team