

Stanford De-escalation Guide for Gram-negative Bacteremia

Antibiotic Selection

Pathogens	Preferred therapeutic options IF SUSCEPTIBLE <i>Switch to PO when clinically stable, able to take orals, no concern for absorption issues</i>
<i>E.coli</i> <i>Klebsiella</i> spp. <i>Proteus</i> spp. <i>Citrobacter koseri</i>	<p><u>Preferred:</u></p> <ul style="list-style-type: none"> • Ceftriaxone 2g IV q24h • Ciprofloxacin 500mg PO BID • Levofloxacin 500-750mg* PO daily • Cefazolin 2g IV q8h† <p><u>2nd line oral alternatives:</u></p> <ul style="list-style-type: none"> • TMP-SMX 2DS PO BID or 8-10mg TMP/kg/day PO divided in 2 or 3 doses <p><u>3rd line oral alternatives:</u> 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.</p> <ul style="list-style-type: none"> • Amoxicillin 1g PO q8h if ampicillin MIC ≤ 2 • Amoxicillin/clavulanate 875/125mg PO q8h‡ or 2g XR BID (if covered by insurance) if ampicillin MIC ≤ 2 • Cephalexin 1g PO q6h† • Call ASP if considering cefpodoxime† or cefadroxil: low likelihood of target attainment. • Avoid cefdinir- poor clinical outcomes observed.²¹ <p>† 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. <i>K.pneumoniae</i> is intrinsically ampicillin-R. ‡ Alternative if GI upset: with appropriate counseling 875/125mg PO BID (qAM and qPM) + amoxicillin 1000mg q noon.</p> <p>ESBL-producers Often ceftriaxone resistant + cefoxitin susceptible. At SHC, micro comments state these isolates "possibly harboring a cephalosporinase"</p> <ul style="list-style-type: none"> • Ertapenem 1g IV q24h • Ciprofloxacin 500-750mg* PO BID • Levofloxacin 500-750mg* PO daily • TMP-SMX 8-10mg/kg/day PO divided in 2 or 3 doses <p><i>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.</i></p>
<i>Enterobacter cloacae</i> , <i>Klebsiella aerogenes</i> , <i>Hafnia alvei</i> , <i>Citrobacter freundii</i> (moderate-high risk AmpC production) ^{18,19**}	<ul style="list-style-type: none"> • Cefepime 2g IV q8h extended infusion <ul style="list-style-type: none"> • 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. • Ertapenem 1g IV q24h • Ciprofloxacin 500-750mg* PO BID • Levofloxacin 500-750mg* PO daily • TMP-SMX 8-10mg/kg/day PO divided in 2 or 3 doses <p><i>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).</i></p>

<i>Serratia marcescens</i> , <i>Morganella morganii</i> , <i>Providencia spp</i> (low risk AmpC production). ^{18,19**}	<ul style="list-style-type: none"> Same as above with additional options in uncomplicated bacteremia as follows: Ceftriaxone 2g IV q24h Piperacillin-tazobactam 3.375-4.5g* IV q8h extended infusion
<i>Pseudomonas aeruginosa</i>	Consider ID consult <ul style="list-style-type: none"> Cefepime 2g IV q8h extended infusion Ceftazidime 2g IV q8h Piperacillin-tazobactam 4.5g* IV q8h extended infusion Meropenem 1g IV q8h extended infusion Ciprofloxacin 750mg PO BID Levofloxacin 750mg IV/PO daily Consult ID for multi-drug resistant strains and/or unable to take the above agents
<i>Stenotrophomonas maltophilia</i>	ID consult recommended
<i>Acinetobacter baumanii</i>	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 (See below definition†)	7 days ^{2, 7, 8} Count day 1 from the 1st day of active therapy [†] ID consult if: <ul style="list-style-type: none"> Patient is severely immunocompromised Considering a longer course of therapy 	<ul style="list-style-type: none"> Inclusion criteria: <ul style="list-style-type: none"> Must have clinically improved Must have source control if applicable Excludes neutropenic patients: see FN pathway; ID consult. <i>P.aeruginosa</i>: 8-10 days may be considered in select patients.³ 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. Endovascular (e.g. infective endocarditis, VAD, ICD/pacemaker) Osteomyelitis Complicated abdominal 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

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