Carolina Antimicrobial Stewardship Program | UNC Hospitals

Gram-negative Bacteremia Treatment Pathway

This treatment pathway is intended for patients with uncomplicated Gram-negative bacteremia with a known pathogen and pending microbiological susceptibility testing results. For treatment recommendations based on results from the LIAISON PLEX® rapid blood culture assay, including resistance genes, see **Appendix A**.

DEFINITION

We define **uncomplicated** bacteremia as follows:[1–7]

1. Monomicrobial (excluding *Brucella* or *Salmonella*)
2. Bloodstream infection secondary to urinary tract infection, indwelling intravascular catheter, intra-abdominal or biliary infection, pneumonia (without structural lung disease, empyema, abscess, or cystic fibrosis), or skin and soft tissue infection.
3. No evidence of endocarditis, endovascular disease, central nervous system infection or bone/joint infection.
4. Source control achieved (e.g., abscess drained, infected catheter(s) removed, biliary obstruction resolved)
5. Clinical improvement observed within 72 hours of initiating effective antibiotic treatment (e.g., fevers resolved, hemodynamically stable without need for vasopressor support)
6. Occurring in an immunocompetent host (excludes absolute neutrophil count (ANC) < 500 cells/mL, CD4 < 200 cells/mL, recent solid organ transplantation, recent hematopoietic stem cell transplantation, taking chronic corticosteroids (≥5 mg/day prednisolone-equivalent for ≥30 days) and/or immunomodulator therapy (those on stable immunomodulatory therapy may be considered on a case-by-case basis))

FIGURE 1: INCORPORATION OF RAPID DIAGNOSTICS AND TREATMENT DECISIONS

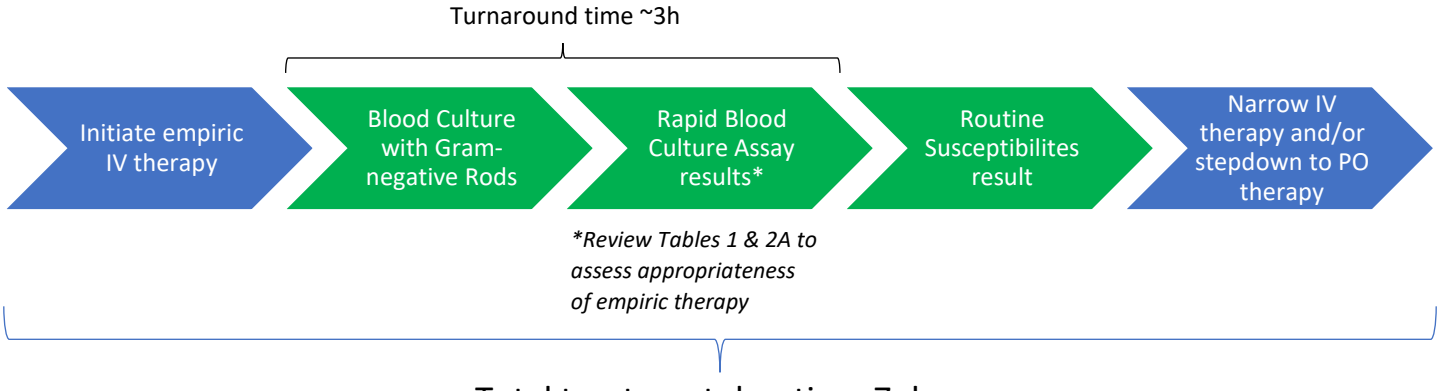

TABLE 1: EMPIRIC ANTIBIOTIC TREATMENT RECOMMENDATIONS BY ORGANISM

Organism	Recommended Empiric Treatment Listed in order of preference *(Dosing recommendations for normal renal function)*
Escherichia coli *Klebsiella* spp. (not *aerogenes*) *Proteus* spp. *Citrobacter koseri* *Serratia marcescens* *Morganella morganii* *Providencia* spp. For organisms with resistance genes detected, see **Table 2A**	• Ceftriaxone 2 g IV every 24 hours • Cefepime 2 g IV every 8 hours • Piperacillin-tazobactam 3.375 g IV every 6 hours±
	Following Susceptibility Results
	If susceptible to empiric treatment: • Preferred: Targeted IV therapy OR change to highly bioavailable oral antibiotics (see Table 2) • Alternative: Continue current therapy If resistant to ceftriaxone (suspect extended spectrum ß-lactamase (ESBL)-production):[5] • Ertapenem 1 g IV every 24 hours ¥ • Meropenem 1 g IV every 8 hours ± • Change to highly bioavailable oral antibiotics If resistant to carbapenems, **consult Infectious Diseases**
Hafnia alvei *Enterobacter cloacae* *Citrobacter freundii* *Klebsiella aerogenes* *Yersinia enterocolitica* For organisms with resistance genes detected, see **Table 2A**	**Recommended Empiric Treatment**
	These organisms are at moderate to high risk for AmpC production, conferring ceftriaxone resistance. Avoid use of ß-lactams (except cefepime) as these can induce AmpC production or hydrolysis by AmpC.[5] • Cefepime 2 g IV every 8 hours • Ertapenem 1 g IV every 24 hours¥ • Meropenem 1 g IV every 8 hours ±
	Following Susceptibility Results
	If susceptible to empiric treatment: • Preferred: Targeted IV therapy (still avoid 3rd generation cephalosporins) OR change to highly bioavailable oral antibiotics • Alternative: Continue current therapy
Pseudomonas aeruginosa	**Recommended Empiric Treatment**
	Consider Infectious Diseases consult • Ceftazidime 2 g IV every 8 hours • Cefepime 2 g IV every 8 hours (extended infusion) • Piperacillin-tazobactam 4.5 g IV every 6 hours ± • Meropenem 1 g IV every 8 hours ±
	Following Susceptibility Results
	If susceptible to empiric treatment:

	• Preferred: Targeted IV therapy OR change to highly bioavailable oral antibiotics • Alternative: Continue current therapy If multi-drug resistant, **consult Infectious Diseases**
Stenotrophomonas maltophilia	**Recommended Empiric Treatment**
	Consider Infectious Diseases consult Combination therapy with two of the following: • TMP/SMX 10-15 mg/kg/day divided in 2 or 3 doses • Levofloxacin 750 mg IV/PO every 24 hours • Minocycline 200 mg PO every 12 hours[Σ]
	Following Susceptibility Results
	If susceptible to empiric treatment: • Continue current combination therapy • If multi-drug resistant, **consult Infectious Diseases**
Acinetobacter baumanii	**Recommended Empiric Treatment**
	Consider ID consult • Ampicillin-sulbactam 3 g IV every 4 hours • Ceftazidime 2 g IV every 8 hours • Cefepime 2 g IV every 8 hours • Piperacillin-tazobactam 4.5 g IV every 8 hours • Meropenem 2 g IV every 8 hours
	Following Susceptibility Results
	If multi-drug resistant, **consult Infectious Diseases**
IV to PO policy: https://unchealthcare-uncmc.policystat.com/policy/15916641/latest [±] If ICU-status, severely ill, utilize extended-infusion regimen [¥] Preference for ertapenem over meropenem due to narrower spectrum. Avoid use of ertapenem if hypoalbuminemia (serum albumin < 2 g/dL). [Σ] Minocycline achieves poor serum concentrations; recommend other agents for dual-treatment of *S. maltophilia* bacteremia when possible	

TABLE 2: ORAL ANTIBIOTIC DOSING RECOMMENDATIONS

Oral Antibiotic Dosing Recommendations	
Levofloxacin	750 mg PO every 24 hours
Ciprofloxacin	500 mg PO every 12 hours If *Pseudomonas*: 750 mg PO every 12 hours
TMP/SMX (use adjusted body weight if BMI ≥30 kg/m^2)	8-10 TMP/kg/day in 2-3 divided doses If *Stenotrophomonas:* 10-15 TMP/kg/day in 2-3 divided doses
Consult Infectious Diseases if considering oral beta-lactams as susceptibility may be incorrectly conferred, high doses are needed for target attainment, and some agents have inferior bioavailability	

APPENDIX A. Treatment Recommendations for Organisms with Resistance Genes Present

The University of North Carolina Medical Center's McLendon Clinical Laboratories utilizes the **LIAISON PLEX® Gram-negative Blood Culture Assay** to detect and identify common Gram-negative organisms and resistance genes directly from positive blood culture bottles that demonstrate Gram-negative organisms on Gram stain. This platform detects 19 bacterial targets and 8 resistance genes (Table 1A) in as little as three hours from notification of positive Gram stain.

How to use this appendix: This appendix provides standardized interpretation of results from this diagnostic platform to support rapid optimization of empiric treatment in patients with Gram-negative bacteremia. Prior to changing treatment upon the basis of these test results in patients with Gram-negative bacteremia, it is important to note several limitations:

- This test does not detect all Gram-negative organisms and potential resistance mechanisms.
- The absence of a resistance gene **does not** confirm susceptibility to antimicrobials usually affected by that resistance gene as multiple non-enzymatic resistance mechanisms exist for commonly used antimicrobials (e.g., porin mutations, target site modification, etc.).
- The presence of a resistance gene generally indicates resistance but does not prove phenotypic expression or that the gene is carried by the detected organism. In some patients experiencing clinical improvement, broadening antimicrobial therapy based on these results might not be indicated.

Table 1A. Gram-negative Organisms and Resistance Genes Detected by LIAISON PLEX®

Genus or Genus Species	Resistance Genes (Type)
Acinetobacter baumannii	CTX-M (*bla*$_{CTX-M}$) (ESBL)
*Acinetobacter spp.**	KPC (*bla*$_{KPC}$) (Carbapenemase)
Citrobacter spp.	OXA (*bla*$_{OXA}$) (Carbapenemase)
Enterobacter spp.	SME (*bla*$_{SME}$) (Carbapenemase)
*Enterobacteriaceae**	IMP (*bla*$_{IMP}$) (Metallo-beta-lactamase)
Escherichia coli	NDM (*bla*$_{NDM}$) (Metallo-beta-lactamase)
Haemophilus influenzae	VIM (*bla*$_{VIM}$) (Metallo-beta-lactamase)
Klebsiella oxytoca	MCR (Other, only affects colistin)
Klebsiella pneumoniae	
Klebsiella variicola	
Morganella morganii	
Neisseria meningitidis	
Proteus spp.	
Pseudomonas aeruginosa	
Pseudomonas spp.	
Salmonella spp.	
Serratia marcescens	
Stenotrophomonas maltophilia	

*Indicates family name. For many Gram-negative organisms, the family (e.g., Enterobacteriaceae) will be identified in addition to the genus/species (e.g., *Escherichia coli*). Both names will result as "detected' in Epic. These results do not suggest polymicrobial bacteremia.

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Table 2A. Empiric Treatment Recommendations for Organisms with Resistance Gene(s) Detected

Resistance Gene	Enzyme Type	Key Resistance Profile	Common Organisms	First-line Empiric Treatment	Alternative Empiric Treatment Options	Comments
CTX-M (*bla*$_{CTX-M}$)	ESBL	All penicillins and cephalosporins	*E. coli* *K. pneumoniae*	Meropenem	Ertapenem Imipenem/Cilastatin	
KPC (*bla*$_{KPC}$)	Carbapenemase	Nearly all beta-lactams including carbapenems and aztreonam	*K. pneumoniae* *E. coli* *P. aeruginosa*	Ceftazidime/Avibactam	Meropenem/Vaborbactam Imipenem/Relebactam Cefiderocol	Consult ID or CASP to approve restricted agent
OXA (*bla*$_{OXA}$)	Carbapenemase	Nearly all beta-lactams including carbapenems with or without beta-lactamase inhibitor	*K. pneumoniae* *E. coli* *A. baumannii*	Ceftazidime-avibactam	Cefiderocol	Consult ID or CASP to approve restricted agent
SME (*bla*$_{SME}$)	Carbapenemase (non-traditional)	Nearly all beta-lactams; spares 3rd and 4th generation cephalosporins	*S. marcescens*	Ceftriaxone Ceftazidime Cefepime	N/A	Consult ID
IMP (*bla*$_{IMP}$)	Metallo-beta-lactamase	All penicillins, cephalosporins, and carbapenems; spares aztreonam	Enterobacteriaceae *P. aeruginosa* *A. baumannii*	Aztreonam/Avibactam	Cefiderocol	Consult ID
NDM (*bla*$_{NDM}$)	Metallo-beta-lactamase	All penicillins, cephalosporins, and carbapenems; spares aztreonam	*E. coli* *K. pneumoniae* *E. cloacae*	Aztreonam/Avibactam	Cefiderocol	Consult ID
VIM (*bla*$_{VIM}$)	Metallo-beta-lactamase	All penicillins, cephalosporins, and carbapenems; spares aztreonam	Enterobacteriaceae *P. aeruginosa*	Aztreonam/Avibactam	Cefiderocol	Consult ID
MCR	N/A	Colistin / Polymyxin B	Enterobacteriaceae	N/A	N/A	The presence of this resistance gene does not affect therapy

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