

Management of extended spectrum β lactamase (ESBL) producing enterobacterales

Pathogens	Definition
<i>Escherichia coli</i> <i>Proteus mirabilis</i> <i>Klebsiella pneumoniae</i> <i>Klebsiella oxytoca</i>	Non-susceptible to third generation cephalosporins. The presence or absence of the CTX-M gene on the blood culture DNA panel (Biofire) is a reliable predictor of ESBL status for blood isolates. AmpC producing enterobacterales (<i>K. aerogenes</i> , <i>E. cloacae</i> , and <i>C. freundii</i> with non-susceptibility to third generation cephalosporins are not considered ESBL producers.

Meropenem is the formulary agent of choice inpatient for systemic infections.

Other β -lactam antibiotics may be reported active against ESBLs. Several good quality studies have demonstrated an increased risk of treatment failure and subsequent mortality when non-carbapenem β -lactams are used for systemic infections with ESBLs. Non β -lactam antibiotics (SMX-TMP, fluoroquinolones, etc.) are not specifically affected by ESBL resistance, however, they should not be used without susceptibility data.

Systemic infections with ESBL should be initially treated with meropenem. Localized infections with ESBL, or stable patients with source control, may be optimally managed by a broader range of antibiotics with sensitivity data. Duration of therapy should not be extended due to ESBL phenotype; duration is the same as for susceptible pathogens at the site. Infectious diseases or clinical pharmacist consultation is encouraged if questions around antibiotic utility, activity, or duration of treatment arise.

Therapy recommendations:

Site of infection	Preferred treatment	Alternate treatments (with susceptibility)	Notes
Bloodstream or other systemic infection	Meropenem, plus infectious diseases consultation	SMX-TMP ciprofloxacin	Cefepime, tetracyclines, piperacillin/tazobactam*, ampicillin/sulbactam, amoxicillin/clavulanate, ceftazidime, or ceftiofur should not be used, regardless of susceptibility data
Central nervous system	Meropenem, plus infectious diseases consultation	SMX-TMP	
Urine: asymptomatic bacteriuria	Supportive care, no antibiotics		Unnecessary antibiotic use promotes further resistance among colonizing flora
Urine: cystitis	SMX-TMP nitrofurantoin	Aminoglycoside (gent/tobra) 5 mg/kg x1, meropenem, ciprofloxacin, or for <i>E. coli</i> only, fosfomycin	Ampicillin/sulbactam, ceftazidime, or ceftiofur should not be used, even with susceptibility. Doxycycline does not achieve reliable urine concentrations. Amoxicillin-clavulanate is linked with recurrent infection – if used due to lack of viable alternatives, patients should be counseled on risk.
	If initiated as initial therapy and clinical improvement occurs, cefepime or piperacillin/tazobactam may be used at standard durations		
Urine: pyelonephritis	See other systemic infection above; alternatively, aminoglycoside (gent/tobra) per pharmacy, if started and clinical improvement occurs, piperacillin/tazobactam* may be continued at standard duration with counseling of potential microbiological failure.		

*updated recommendations acknowledge use may be continued for improving, non-bacteremic pyelonephritis with an understanding of risk of microbiological failure

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Drugs with potential activity against ESBL producers (sensitivity data still important for all):

β-lactams

Carbapenems	
Meropenem	Preferred for systemic infections, avoid for cystitis unless alternatives not available
Ertapenem	Does not achieve central nervous system concentrations
β-lactam/β-lactamase inhibitors	
Piperacillin/tazobactam	Use only in improving cystitis/pyelonephritis* with susceptibility data
Ampicillin/sulbactam	Not recommended for any infection with ESBL, regardless of susceptibility data
Amoxicillin/clavulanate	
Cephalosporins	
Cefepime	Use only in improving cystitis with susceptibility data
Cephamycins	Not recommended for any infection with ESBL, regardless of susceptibility data

*updated recommendations acknowledge use may be continued for improving, non-bacteremic pyelonephritis with an understanding of risk of microbiological failure

Non β-lactams

SMX-TMP	Recommended for use in all sites of infection, with susceptibility data
Aminoglycosides	Alternative recommendation for UTI with susceptibility data, not recommended for infections outside of the urinary tract.
Fluoroquinolones	Ciprofloxacin may be used for oral stepdown therapy with susceptibility for systemic infections, and as an alternative for cystitis. Levofloxacin is acceptable if gram positive activity is also needed and with susceptibility. Non susceptibility to one fluoroquinolone precludes use of any others. Fluoroquinolones have unreliable CSF penetration. Moxifloxacin does not achieve sufficient concentrations in the urine for use.
Tetracyclines	Tetracycline achieves sufficient concentrations in the urine to treat cystitis, minocycline and doxycycline do not. Tetracyclines should not be used for systemic infections.
Nitrofurantoin	Preferred agent for ESBL cystitis with susceptibility data. Should not be used for systemic infections. Limited utility for eCrCl less than 30 mL/min.
Fosfomycin	Use as an alternative for cystitis with ESBL <i>E. coli</i> only (not for ESBL <i>Klebsiella</i> or <i>Proteus</i> spp., or for systemic infections with any pathogen).

1. Tamma PD et al. The use of non-carbapenem β-lactams for the treatment of extended-spectrum β-lactamase infections. Clin Infect Dis 2017;64(7):972-80.
2. Tamma PD et al. Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with stented spectrum beta lactamase bacteremia. Clin Infect Dis. 2015;60(9):1319-25.
3. Harris P et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients With *E. coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance: a randomized clinical trial. JAMA 2018; 320(10):984-994.
4. Tamma PD et al. IDSA 2024 guidance on the treatment of antimicrobial resistant gram-negative infections: Version 4.0. Available at <https://www.idsociety.org/practice-guideline/amr-guidance/> accessed July 2024.