Management of extended spectrum β lactamase (ESBL) producing enterobacterales

Pathogens	Definition
Escherichia coli *Proteus mirabilis* *Klebsiella pneumoniae* *Klebsiella oxytoca*	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 (*K. aerogenes, E. cloaceae,* and *C. freundii* with non-susceptibility to third generation cephalosporins are not considered to be ESBL producers unless the cefepime MIC is 4 or greater.

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

Other β-lactam antibiotics may be reported as active against ESBL-producing pathogens. 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, depending on the clinical scenario. 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:

<table>
<tr><th>Site of infection</th><th>Preferred treatment</th><th>Alternate treatments (with susceptibility)</th><th>Notes</th></tr>
<tr><td>Bloodstream or other systemic infection</td><td>Meropenem, plus infectious diseases consultation</td><td>SMX-TMP
ciprofloxacin</td><td rowspan="2">Cefepime, tetracyclines, piperacillin/tazobactam, ampicillin/sulbactam, amoxicillin/clavulanate, cefoxitin, or cefotetan should not be used, regardless of susceptibility data</td></tr>
<tr><td>Central nervous system</td><td>Meropenem, plus infectious diseases consultation</td><td>SMX-TMP</td></tr>
<tr><td>Urine: asymptomatic bacteriuria</td><td>No treatment</td><td></td><td>Avoiding antibiotics for ESBL asymptomatic bacteriuria is especially important, to prevent further resistance among colonizing flora</td></tr>
<tr><td rowspan="2">Urine: cystitis</td><td>SMX-TMP
nitrofurantoin</td><td>Aminoglycoside (gent/tobra) 5 mg/kg x1, meropenem, ciprofloxacin, or for E. coli only, fosfomycin</td><td rowspan="2">Tetracycline achieves sufficient concentrations in the urine to treat cystitis; minocycline and doxycycline do not. Ampicillin/sulbactam, amoxicillin/clavulanate, cefoxitin, or cefotetan should not be used, regardless of susceptibility data.</td></tr>
<tr><td colspan="2">If initiated as initial therapy and clinical improvement occurs, cefepime or piperacillin/ tazobactam may be used at standard durations</td></tr>
<tr><td>Urine: pyelonephritis</td><td colspan="3">See other systemic infection above</td></tr>
</table>

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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 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

Non β-lactams

SMX-TMP	Recommended for use in all sites of infection, with susceptibility data
Aminoglycosides	Most suitable 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 *E. coli* only (not for ESBL K*lebsiella* or *Proteus* 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 P et al. Infectious Diseases Society of America guidance on the treatment of extended-spectrum β-lactamase producing enterobacterales (ESBL-E), carbapenem-resistant enterobacterales (CRE), and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*). Clin Infect Dis 2023; 10.1093/cid/ciad428

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