

## Management of extended spectrum $\beta$ lactamase (ESBL-E) producing enterobacterales

| Pathogens                                                                                                                                                                                                                                                                                                                                                                                                                | Definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Most frequent at PeaceHealth</p> <ul style="list-style-type: none"> <li><i>Escherichia coli</i></li> <li><i>Klebsiella pneumoniae</i></li> <li><i>Klebsiella oxytoca</i></li> </ul> <p>Less common; relevant when present</p> <ul style="list-style-type: none"> <li><i>Proteus mirabilis</i></li> <li><i>Serratia marcescens</i></li> <li><i>Raoultella spp.</i></li> <li>Other non AmpC enterobacterales</li> </ul> | <p><u>Blood isolates</u>: the presence or absence of the CTX-M gene on the blood culture DNA panel (Biofire) is a reliable predictor of ESBL status. <u>All others</u>: non-susceptible (MIC 4 or greater) to ceftriaxone is the most reliable surrogate for ESBL production. Cefpodoxime susceptibility/non-susceptibility is <b>NOT</b> a reliable predictor of the presence or absence ESBLs.</p> <p>AmpC producing enterobacterales (<i>K. aerogenes</i>, <i>E. cloacae</i>, <i>C. freundii</i>, and <i>H. alvei</i>) with non-susceptibility to third generation cephalosporins are not considered ESBL producers.</p> |

- **Meropenem is the formulary agent of choice inpatient for invasive infections with ESBL-E.**
  - Stepdown with susceptibility data as clinically appropriate to
    - SMX-TMP
    - Fluoroquinolones (susceptibility must be demonstrated to **both** agents before use)
    - Ertapenem (not for inpatient use)
- **Nitrofurantoin is the formulary agent of choice for uncomplicated cystitis with ESBL-E**
  - With identification and susceptibility, the following agents may be appropriate
    - SMX-TMP
    - Gentamicin or tobramycin, single dose
    - Fosfomycin (for *E. coli* **only**), single dose

Other  $\beta$ -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  $\beta$ -lactams are used for systemic infections with ESBLs. Non  $\beta$ -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                                        | SMX-TMP, fluoroquinolones (both agents must be S to use either) | Cefepime, tetracyclines, piperacillin/tazobactam*, ampicillin/sulbactam, amoxicillin/clavulanate, cefoxitin, or cefotetan 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<br>nitrofurantoin                                                                                                                                                                                                                                     | Aminoglycoside (gent/tobra) 5 mg/kg x1, meropenem, fluoroquinolones (both agents must be S to use either) or for <i>E. coli</i> only, fosfomycin | Ampicillin/sulbactam, ceftiofur, or cefotetan should not be used, even with susceptibility. Tetracycline derivatives do 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

### 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 (including uncomplicated cystitis), regardless of susceptibility data |
| Amoxicillin/clavulanate         |                                                                                                                   |
| Cephalosporins                  |                                                                                                                   |
| Cefepime                        | Use only in improving cystitis with susceptibility data                                                           |
| Cephameycins                    | 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. Susceptibility must be demonstrated to both agents before use of either. Fluoroquinolones have unreliable CSF penetration. Moxifloxacin does not achieve sufficient concentrations in the urine for use. |
| Tetracyclines    | Tetracycline derivatives do not achieve sufficient concentrations in the urine for use in treating UTI. 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  $\beta$ -lactams for the treatment of extended-spectrum  $\beta$ -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 2026 guidance on the treatment of antimicrobial resistant gram-negative infections. Available at <https://www.idsociety.org/practice-guideline/amr-guidance/> accessed July 2026.