Antimicrobial Stewardship Programme:
Innovation, Research, Education, and Safety
Quality and Patient Safety, Vancouver Coastal Health
Vancouver General Hospital
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BETA (β)-LACTAMASES IN GRAM-NEGATIVE ORGANISMS:
An Overview of Extended-spectrum β-lactamases (ESBL) and AmpC β-lactamases

Penicillin and cephalosporin resistance due to β-lactamases

- Organisms can exhibit resistance to antibiotics through a variety of mechanisms, including the production of β-lactamases (see Figure 1)
- β-lactamases are enzymes which inactivate penicillins, cephalosporins and, in some cases, carbapenems, by breaking down their molecular structures. Examples of these enzymes in enteric Gram-negative organisms:

  i) Extended spectrum β-lactamases (ESBLs)
  ii) AmpC β-lactamases
  iii) Carbapenemases (in carbapenemase-producing organisms, or CPOs)
  Note: This article will focus on ESBLs and AmpC resistance, since carbapenemases are relatively uncommon in the Coastal Community of Care

- Duration of therapy is similar for treatment of both antibiotic resistant (ESBL and AmpC) and non-resistant organisms

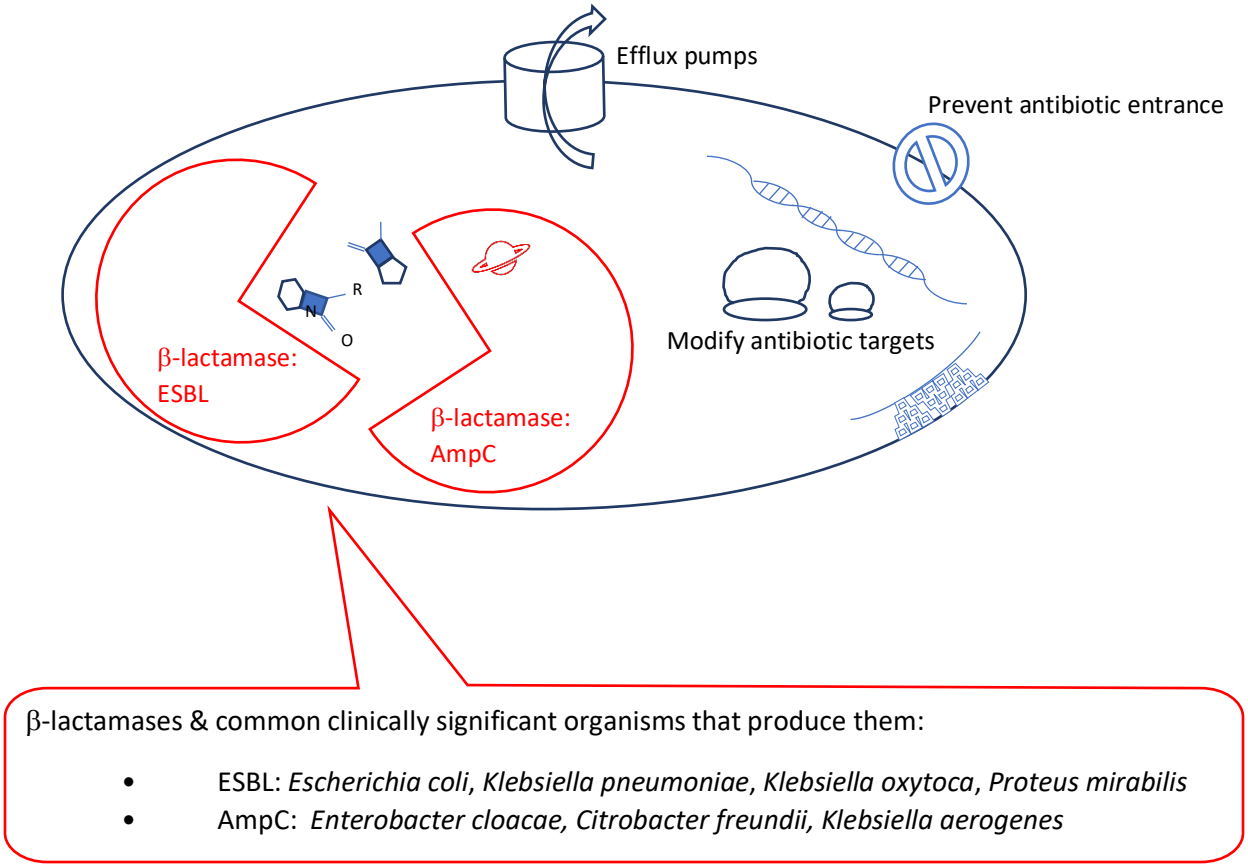

Figure 1. Antibiotic resistance mechanisms

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Extended spectrum β-lactamases (ESBLs)

- Common organisms which may produce ESBLs: *E. coli, K. pneumoniae, K. oxytoca, P. mirabilis*
- ESBLs inactivate most penicillins and cephalosporins, but are generally susceptible to carbapenems
- Since ESBL enzymes do NOT usually affect non-β-lactam antibiotics, these can be used to treat infections when susceptible
- ESBL organisms often test susceptible to beta-lactam/lactamase combinations (e.g. piperacillin-tazobactam), their clinical use depends on location of infection and disease severity. Beta-lactam/lactamase combinations are generally not advised for severe infections (e.g. sepsis).
- It remains controversial whether piperacillin-tazobactam can be used to treat ESBL bacteremias. It is generally not used during the acute bacteremia episode but may be considered a step-down agent (when the bacteremia clears), or if the patient has already substantially improved on therapy by the time the ESBL is recognized.

Table 1. Extended spectrum β-lactamase enzyme (ESBL) treatment

Common organisms producing ESBLs	**Not recommended**	**Recommended antibiotics for ESBLs**
E. coli *K. pneumoniae* *K. oxytoca* *P. mirabilis*	Penicillins Ampicillin Amoxicillin Cephalosporins	**Urinary infection** Cystitis: • nitrofurantoin 100mg po bid • co-trimoxazole DS 1 tab po bid • amoxicillin-clavulanate 875/125mg po bid (if susceptible) • fosfomycin 3g po x 1 dose (for *E. coli*) Complicated UTI, pyelonephritis: *mild to moderate* • co-trimoxazole DS 1 tab po bid • ciprofloxacin 500mg po bid • piperacillin-tazobactam 3.375g IV q6h *severely ill/septic/bacteremic* • co-trimoxazole TMP 10mg/kg/day IV/PO ÷ BID to QID • ciprofloxacin 500mg po bid • meropenem 500mg IV q6h **Non-urinary infection** • co-trimoxazole TMP 5-20mg/kg/day IV/PO ÷ BID to QID • ciprofloxacin 500mg po bid or 400mg IV q12h • meropenem 500mg IV q6h • ertapenem 1g IV q24h (outpatient only) **Step-down** • co-trimoxazole DS 1-2 tab(s) po bid • ciprofloxacin 500mg po bid • amoxicillin-clavulanate 875/125mg po bid **Duration of therapy** • similar to non-ESBL organisms

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AmpC β-lactamases

- AmpC genes are present in some enteric Gram-negative organisms, but they are not always expressed
- Some AmpC genes are inducible – in the presence of cephalosporins, the gene can be expressed resulting in penicillin and cephalosporin resistance
- Initially, organisms with inducible AmpC genes may test susceptible to cephalosporins, but once exposed to cephalosporins they can develop resistance within 24 hours to 2-3 weeks
- Inducible AmpC genes are usually found in "SPACE", "SPICE", "ESKAPE", "SPECKHEM", "HECK Yes" organisms. However, many organisms traditionally included in these acronyms may be of lesser concern in selected situations (discuss with ID). Organisms that are generally of lesser concern include *Serratia marcescens*, *Providencia spp.*, *Proteus spp.*, *Hafnia alvei*, *Edwardsiella spp.*, *Morganella morganii*.
- **The organisms of highest concern are *Enterobacter cloacae*, *Citrobacter freundii*, and *Klebsiella aerogenes***
- Penicillins and 1st & 2nd generation cephalosporins are resistant to these organisms, β-lactamase inhibitors do not have activity against these enzymes
- 3rd generation cephalosporins (ceftriaxone)
    - Avoid use in these situations: resistance to 3rd generation cephalosporins, poor source control, severe disease, or high bacterial load
- Piperacillin-tazobactam and ceftazidime
    - May be considered in these situations: susceptible to ceftriaxone *and* the treatment is likely to be short-lived *with* a low bacterial burden (e.g. urinary infection, biliary tract) and/or good source control. Piperacillin-tazobactam or ceftazidime may be considered in this context because they are less likely to induce AmpC.
    - There is uncertainty on the clinical impact of using antibiotics that are hydrolyzed by AmpC (e.g. piperacillin, ceftazidime) in the absence of induction. Some experts recommend alternative agents (cotrimoxazole, fluoroquinolones). Carbapenems should only be used when their broad-spectrum of coverage is required.

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Table 2. AmpC β-lactamase treatment

Enterobacterales at moderate to high-risk for clinically significant AmpC production	**Not recommended**	**Recommended antibiotics for AmpCs**
Enterobacter cloaceae ***Citrobacter freundii****†*** ***Klebsiella aerogenes*** (formerly *Enterobacter aerogenes*)	Penicillins Ampicillin Amoxicillin Cephalosporins (However piperacillin-tazobactam & ceftazidime may work in selected cases – consult ID).	**Urinary infection** Cystitis: • nitrofurantoin 100mg po bid • co-trimoxazole DS 1 tab po bid • ciprofloxacin 500mg po bid • cefixime 400mg po od (if susceptible, uncomplicated cystitis, improving clinically, and ≤7 days) Complicated UTI, pyelonephritis: *mild to moderate* • co-trimoxazole DS 1 tab po bid • ciprofloxacin 500mg po bid *severely ill/septic/bacteremic* • co-trimoxazole TMP 10mg/kg/day IV/PO ÷ BID to QID • ciprofloxacin 500mg po bid • meropenem 500mg IV q6h **Non-urinary infection** • co-trimoxazole TMP 5-20mg/kg/day ÷ BID to QID • ciprofloxacin 500mg po bid or 400mg IV q12h • piperacillin-tazobactam 3.375g IV q6h (if 3rd generation cephalosporin susceptible, ***and*** not septic, ***and*** with good source control) (consult ID) • meropenem 500mg IV q6h • ertapenem 1g IV q24h (outpatient only) • aminoglycosides (consult ID) • ceftazidime (consult ID) **Step-down** • co-trimoxazole DS 1-2 tab(s) po bid • ciprofloxacin 500mg po bid **Duration of therapy** • similar to non-AmpC expressed organisms

*not *Citrobacter koseri*

† *Citrobacter freundii* complex includes numerous species and may be reported as a complex or individual species *(C. braakii, C. gillenii, C. murliniae, C. werkmanii, C. youngae)*

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AmpC β-lactamase

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