Extended-spectrum beta-lactamase producing Enterobacteriaceae urinary tract infections

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Case

- A 74 year old man presents with urosepsis
- He is found to have left hydronephrosis with multiple calculi in the left kidney, ureter and bladder
- Antibiotics are started, some calculi are removed and a JJ stent is inserted
- His urine grows an ESBL-producing *Klebsiella pneumoniae*
  - resistant – amoxyl, amoxyl-clavulanate, nitrofurantoin, gentamicin, norfloxacin, trimethoprim, ceftriaxone
  - susceptible – ertapenem, amikacin, fosfomycin
Case continued

• Following initial treatment he has a left percutaneous nephrolithotomy and removal of JJ stent (all calculi are removed)
• Two months later he presents with occasional symptoms of urinary frequency and urgency
• The ESBL-producing *K. pneumoniae* is again grown from his urine
• Fosfomycin 3g on days 1 and 4 is trialled
Extended-spectrum beta-lactamases (ESBL)

- Mainly occur in *E. coli* and *Klebsiella* spp.
- Confer resistance to penicillins, cephalosporins and monobactams.
- Genes coding for ESBLs are carried on plasmids that also carry genes coding for resistance to other antibiotics such as gentamicin, trimethoprim / cotrimoxazole and fluoroquinolones.
• ESBL-producing *E. coli* are more likely to produce community-onset infections whereas ESBL-producing *K. pneumoniae* are more likely to cause nosocomial-onset infections

• Source of acquisition
  – hospital acquired
  – long-term care facility acquired
  – overseas travel – particularly to the Indian subcontinent  
  – community acquired  
## Rates of ESBL-production in Gram-negative bacteria in Auckland 2011

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Percentage urinary isolates</th>
<th>Percentage ESBL-producers</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>39,584</td>
<td>99</td>
<td>2 (≈790)</td>
</tr>
<tr>
<td><em>Klebsiella</em> spp., <em>Enterobacter</em> spp., <em>Citrobacter</em> spp., <em>Serratia</em> spp.</td>
<td>5,291</td>
<td>93</td>
<td>3 (≈150)</td>
</tr>
<tr>
<td><em>Proteus</em> spp. and <em>Morganella morganii</em></td>
<td>1,831</td>
<td>96</td>
<td>0.1 (≈2)</td>
</tr>
</tbody>
</table>

Source: Dragana Drinkovic, Labtests
Susceptibilities of ESBL-producing Enterobacteriaceae in Auckland

![Bar chart showing the percentage susceptibility of different antibiotics against various strains of Enterobacteriaceae. The chart includes data from ACH E. coli 2006/7 (Freeman et al.), ACH E. coli 2011, NSH E. coli 2011, MMH E. coli from urine 2011 (S. Taylor).]
Amoxyl-clavulanate

- ESBLs are inhibited by beta-lactamase inhibitors Pitout et al. Lancet Infect Dis 2008
- Beta-lactam/beta-lactamase inhibitors are active against a proportion of ESBL-producing Enterobacteriaceae particularly *E. coli*
- 31 of 37 (84%) patients with ESBL-producing *E. coli* cystitis treated with amoxyl-clavulanate for 5 to 7 days were “clinically cured” Rodriguez-Bano et al. Arch Intern Med 2008
Fosfomycin

• Used in some European countries for over 20 years
• Unique mechanism of action - inhibits UDP-N-acetylglucosamine enolpyruvate transferase (enzyme involved in peptidoglycan synthesis)
• Active against Gram-positive and Gram-negative bacteria
• Bactericidal
• Section 29
Fosfomycin cont.

- A single dose of fosfomycin is usually effective for the treatment of uncomplicated urinary tract infections
- Usual dose
  - 3g on day 1 +/- a further dose on day 4
  - each sachet of fosfomycin granules is dissolved in half a glass of water
- Usually well tolerated with minimal side effects
Fosfomycin for lower UTI with ESBL-producing *E. coli*

- 49 of 52 (94%) patients treated with fosfomycin (3 doses of 3g every second day) had resolution of symptoms Pullukcu et al. Int J Antimicrob Agents 2007;29:62
  - 32 (69%) had a “complicating factor”
    - indwelling urinary catheter, hemiplegia, malignancy, diabetes, renal transplant, renal calculi, recent urological intervention
- 26 of 28 (93%) patients with cystitis treated with a single dose of fosfomycin were “clinically cured” Rodriguez-Bano Arch Intern Med 2008
Fosfomycin POAC

- Patient presents to GP with ESBL-producing Enterobacteriaceae/multi-resistant UTI
- GP contacts ID physician/microbiologist
- Fosfomycin is recommended
- GP generates POAC claim
- GP writes a script with POAC number and name of ID physician/microbiologist
- GP directs patient to one of the inpatient pharmacies at ACH, MMH or NSH
Nitrofurantoin

• Many studies report that most urinary ESBL-producing *E. coli* / *Klebsiella* spp. isolates are nitrofurantoin susceptible

• Despite this there are no trial data as to the efficacy of nitrofurantoin treatment of these infections
Quinolones

• ESBL-producing *K. pneumoniae* bacteraemia

  – imipenem treatment
    • complete response (8), non response (2)
  – ciprofloxacin treatment
    • partial response (2), non response (5) \( (p=0.03) \)

• **14 day mortality** Paterson et al. Clin Infect Dis 2004;39:31
  – carbapenem treatment 1/27 (3.7%)
  – ciprofloxacin treatment 4/11 (36.3%) \( (p=0.02) \)
What Labtests report

• Report fosfomycin susceptibility for all ESBL-producing Enterobacteriaceae

• If amoxyl-clavulanate tests as susceptible then the following comment is added
  – "The isolate is susceptible to amoxycillin-clavulanic acid. Limited clinical data suggests that its efficacy for treatment of simple UTI is approximately 85 – 90%"
What antibiotic to use?

- Trimethoprim or amoxyl-clavulanate if susceptible
- Nitrofurantoin
- Norfloxacin
- Fosfomycin
Case cont.

• Three weeks after fosfomycin, the same ESBL-producing *K. pneumoniae* was again cultured from his urine

• It was now fosfomycin resistant

• As he was asymptomatic no further treatment was given

• Will need admission to hospital for consideration of amikacin or a carbapenem if he presents with significant urinary symptoms