Extended-spectrum beta-lactamase producing Enterobacteriaceae urinary tract infections

Simon Briggs

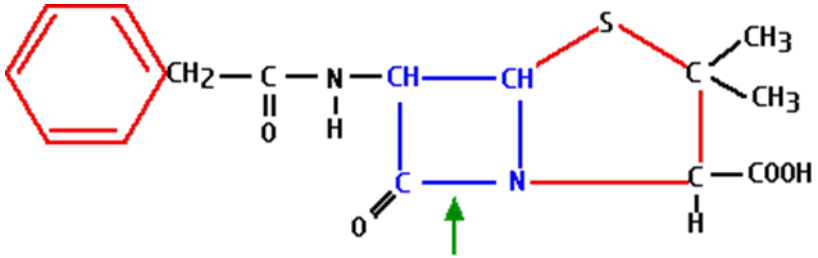
Case

- 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)



Penicillin G

- 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

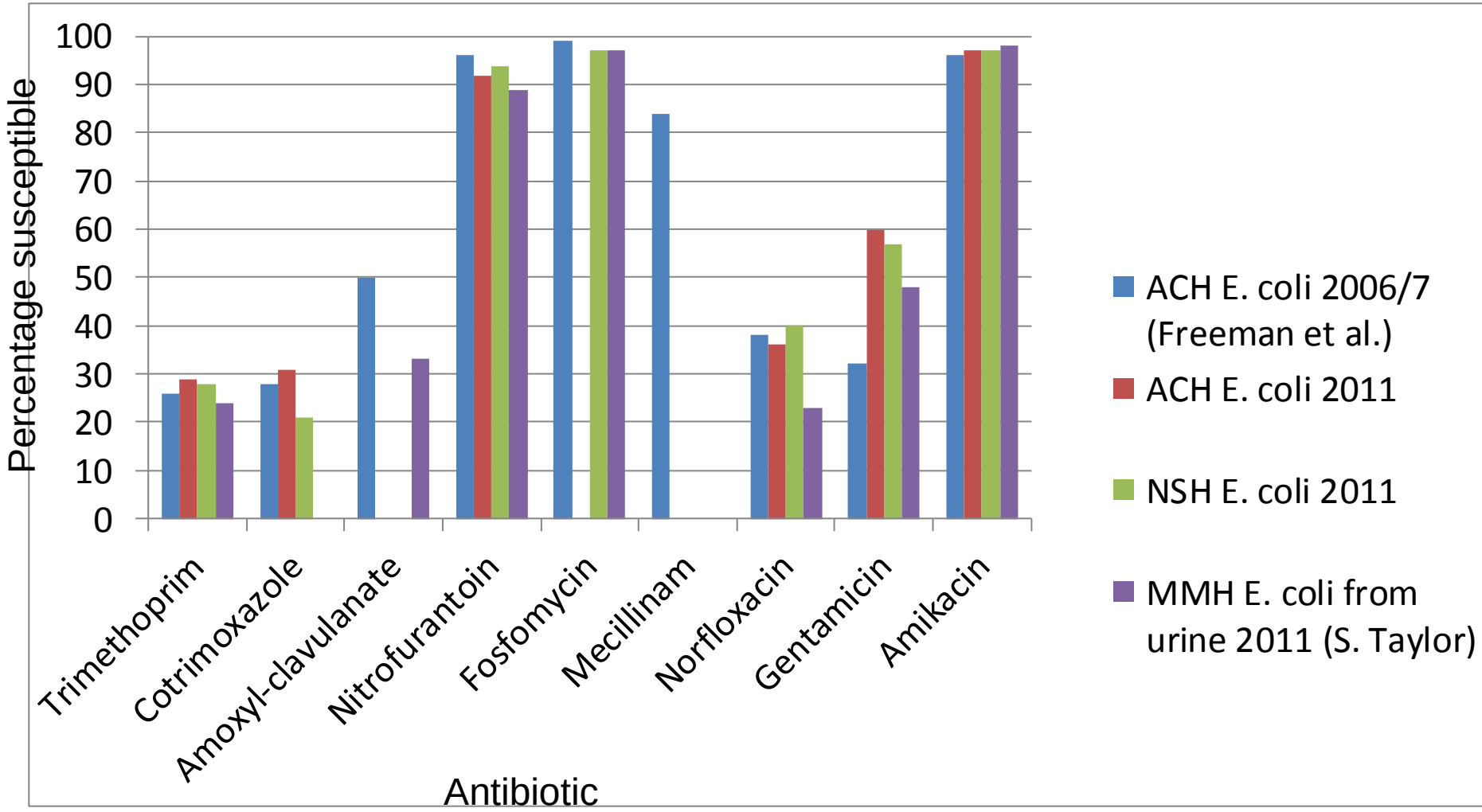
- ESBL-producing *E. coli* are more likely to produce community-onset infections whereas ESBL-producing *K. pneumoniae* are more likely to cause nosocomial-onset infections
- Source of acquisition
  - hospital acquired
  - long-term care facility acquired
  - overseas travel – particularly to the Indian subcontinent Freeman et al. Clin Infect Dis 2008;47: 689
  - community acquired Rodriguez-Bano et al. Clin Infect Dis 2006;42:925

Rates of ESBL-production in Gram-negative bacteria in Auckland 2011

	Number	Percentage urinary isolates	Percentage ESBL-producers
E. coli	39,584	99	2 (≈790)
Klebsiella spp., *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp.	5,291	93	3 (≈150)
Proteus spp. and *Morganella morganii*	1,831	96	0.1 (≈2)

Source: Dragana Drinkovic, Labtests

Susceptibilities of ESBL-producing Enterobacteriaceae in Auckland



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
- Treatment response Endimiani et al. Clin Infect Dis 2004;38:243
  - 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