"My Dad Used To Prescribe That!"

DALHOUSIE UNIVERSITY Inspiring Minds

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Sarah's Case

A 35-year-old female professional presents to the ED with complaints of dysuria and frequency and urgency of urination. She has received numerous three-day courses of ciprofloxacin from her family doctor, which resulted in quick resolution of her symptoms. Her most recent prescription for ciprofloxacin does not appear to be working.

A urinalysis and urine culture are sent to the laboratory. Urinalysis shows pyuria, and urine culture shows >100,000 *Escherichia coli*, which is reported to have an extended spectrum β-lactamase (ESBL). The organism is resistant to ciprofloxacin, amoxicillin, trimethoprim/sulphamethoxazole, nitrofurantoin, and amoxicillin/clavulinic acid. It is susceptible to ertapenam and fosfomycin.

The patient takes ibuprofen and oral contraceptives. Upon examination, her temperature is 38.3° Celsius; heart rate is 72 bpm; blood pressure is 125/78; and respiratory rate is 14 breaths per minute.

Read on for more on Sarah.

Questions and Answers

1. What is going on?

Urinary tract infections (UTI) affect millions of people each year; they are the second most common type of community-acquired infections. Women are affected more than men, and one in five women will have a UTI in her lifetime. The most common organism causing UTIs is *Escherichia coli* (*E. coli*) which colonizes the colon.

The usual course of therapy includes urinalysis to confirm infection, followed by treatment with an empiric antibiotic. First-line agents for uncomplicated cystitis include nitrofurantoin 100 mg, b.i.d. for five days, and sulfamethoxazole/trimethoprim 800/160 mg, b.i.d. for three days. Urine cultures are only recommended in specific situations: unclear diagnosis, suspicion of an unusual or resistant organism, if the patient is pregnant, if the episode is a suspected relapse or failure of prior treatment, or if complications to the condition are identified.

2. Why are we worried about ESBLs?

As in any infection, resistant organisms can be seen in UTIs. One of the emerging resistant bacteria is the extended-spectrum ß-lactamase (ESBL) producing *E. coli*.

ESBL-producing bacterias were first seen in the 1980s. The most common organisms, *Klebsiella* species, were thought to cause most hospital-acquired infections. In 2000, more ESBL-producing *E. coli* were recognized, and it became apparent that these infections were community-acquired. ESBL-producing *E. coli* is spreading extensively and quickly in the community setting, and

has become a great concern among healthcare practitioners.

Risk factors for community-acquired ESBL-producing *E. coli* infections include older age (over 65-years-of-age), comorbidities, recent hospitalization, recent antimicrobial use, and residence in long-term care facilities.

ESBL-producing *E. coli* are resistant to penicillins and to cephalosporins; some even have the ability to hydrolyze fourth-generation cephalosporins. They are also frequently resistant to oral agents used to treat UTIs, such as sulfamethoxazole-trimethoprim, nitrofurantoin and ciprofloxacin. The increased incidence of UTIs caused by ESBL-producing *E. coli* is concerning, due to the treatment failure of current empiric antibiotics.

The Infectious Diseases Society of America recently listed ESBL-producing *Klebsiella* species and *E. coli* as some of the six drug-resistant microbes against which new therapies are urgently needed, and have now included fosfomycin as a first-line agent (and ciprofloxacin as second-line) if local epidemiology indicates a high rate of ESBLs in community isolates.

Several studies have looked at ESBL-producing *E. coli* susceptibility. Auer, *et al*, isolated over 6,000 *E. coli* urine specimens, 100 of which were ESBL-producing. Susceptibility to various antibiotics was assessed, and the results showed 100% susceptibility to IV ertapenem, 97% to oral fosfomycin, 94% to oral nitrofurantoin, 27% to oral sulfamethoxazole-trimethoprim, and 22% to oral ciprofloxacin. Hutley, *et al*, found similar results for fosfomycin, which showed 97% susceptibility in community isolates.

Senol, *et al*, compared the current mainstay therapy, carbepenem, administered parenterally, with three doses of fosfomycin, an oral agent. The difference in clinical and microbiologic success was not statistically significant between the two groups.

With all these studies of ESBL-producing *E. coli* showing susceptibility to fosfomycin, this old drug is now of great renewed interest.

3. *What is fosfomycin?**

Fosfomycin is a bactericidal antibiotic that works by inhibiting cell wall synthesis. At a therapeutic dose, it reaches high concentrations in urine, which makes it ideal for UTI therapy. It also works by reducing adherence of bacteria to uroepithelial cells.

Fosfomycin has a broad spectrum of activity against aerobic gram-positive and gram-negative organisms, especially *E. coli*, *Pseudomonas aeruginosa*, and *Proteus*, *Providencia*, *Serratia*, *Klebsiella*, *Citrobacter*, *Enterococcus* and *Enterobacter* species, including multi-drug resistant strains.

There is generally no cross-resistance between fosfomycin and other classes of antibacterial agents, such as ß-lactams and aminoglycosides.

Fosfomycin is given as a single dose in uncomplicated UTIs. It also has off-label indications for both complicated UTIs (3g every two to three days for three

doses) and prostatitis (3g every three days for 21 days).

The most common side effects include diarrhea (9% of patients), vaginitis (5.5%), nausea (4.1%), headache (3.9%), dizziness (1.3%), asthenia (1.1%), and dyspepsia (1.1%).

4. *What do we need to remember when assessing patients for UTI in the ED?*

The recent studies showing ESBL-producing *E. coli* susceptibility with fosfomycin have made it one of the first-line treatment options in the new IDSA guidelines for cystitis. With increasing rates of ESBL-producing *E. coli*, it is important to consider local antibiotic resistance and susceptibilities when choosing empiric treatment, especially in individuals at high risk of community-acquired ESBL-producing *E. coli*.

Back To Sarah

Sarah was prescribed ertapenem for seven days, as fosfomycin was unavailable at the time and no other oral alternatives were available. Because ertapenem is administered intravenously, the patient necessarily had to come to the Medical Day Unit once daily for administration.

Resources

1. Gupta K, Hooton TM, Naber KG, et al. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011;52(5):103-20.
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3. Senol S, Tasbakan M, Pullukcu H, et al. Carbapenem Versus Fosfomycin Tromethanol in the Treatment of Extended-spectrum Beta-lactamase Producing Escherichia coli-related Complicated Lower Urinary Tract Infection. J Chemother. 2010 Oct;22(5): 355-7.
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6. Oteo J, Pérez-Vasquez M, Camos J, et al. Extended-spectrum Beta-lactamase Producing Escherichia coli: Changing Epidemiology and Clinical Impact. Curr Opin Infect Dis 2010;23(4):320–326.
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At the time of publication, fosfomycin is temporarily unavailable from the manufacturer.

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