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Continuous Medical Education Forum (CME from EB)

Continuous medical education activities; Answers to Case No. 4

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A 19-years-old female patient was admitted to the outpatient clinic. She gave a history of urinary tract infection (UTI) 4 months preceding admission for which she was treated with oral ampicillin without complications. Five days prior to this admission, she began to complain nausea without vomiting. One day later, she developed left flank pain, fever, and chills, and increased micturition frequency. She was admitted to a general hospital. She noted foul-smelling urine on the day before admission. She was presented with a temperature of 38.8°C.

1. Interpret the urinalysis report?

Urine from normal individuals usually has <10 white blood cells per high-power field. Pyuria (the presence of >10 white blood cells per high-power field in urine) and hematuria (the presence of red blood cells in urine), as seen in this patient, are reasonably sensitive but not always specific indicators of UTI. The presence of bacteriuria (bacteria in urine) in this patient further supports this diagnosis. However, the presence of bacteriuria on urinalysis should always be interpreted with caution. Clean-catch urine, which is obtained by having the patient cleanse her external genitalia begin a flow of urine, and then “catch” the flow of urine in “midstream,” is rarely sterile because the distal urethra is colonized with bacteria. Urine is an excellent growth medium. Therefore, if urine is not analyzed quickly (within 1 hour), the organisms colonizing the urethra can divide (two to three generations per hour) if the urine specimen is left at room temperature rather than refrigerated or immediately planted on culture media. Organisms colonizing the urethra may be present in sufficient numbers to be visualized during urinalysis even when the patient is not infected [1].

2. Why were the numbers of organisms in her urine quantitated on culture? How would you interpret the culture results in this case?

In a normal individual, urine within the bladder is sterile. As it passes through the urethra, which has a resident microflora, it almost always becomes contaminated with a small number (<103 CFU/ml) of organisms. As a result of urethral contamination, essentially all clean-catch urine samples will contain a small number of organisms, so culturing urine non-quantitatively will not allow differentiation between colonization of the urethra and infection of the bladder. It should be noted that only a small number of clinical specimens other than urine are cultured quantitatively.

Patients in whom the bladder is infected tend to have very large numbers of bacteria in their urine. These organisms usually, but not always, are of a single species. Studies have shown that most individuals with true UTIs have >105 CFU/ml in clean-catch urine specimens.

There are exceptions to this generalization. In a woman with symptoms consistent with UTIs, bacterial counts as low as 102 CFU/ml of a uropathogen e.g., *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp., *Proteus* spp., or *Staphylococcus saprophyticus* may indicate that she has a UTI. Colony counts of 102 CFU/ml of a uropathogen are highly sensitive for diagnosing UTIs but are of low specificity; colony counts of >105 CFU/ml are highly

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specific, but the sensitivity in the setting of acute, uncomplicated cystitis in women is only ~50% [2].

3. What is the name of this organism?

The lactose-fermenting, Gram-negative bacilli that are most isolated from urine are the “KEE” organisms (*Klebsiella* spp., *E. coli*, and *Enterobacter* spp.). *Escherichia coli* is recovered from ~80 to 85% of outpatients and ~40 to 50% of inpatients with UTI. The observation that the organism is beta-hemolytic indicates that, likely, the organism is *E. coli*. Approximately 55% of *E. coli* isolates recovered from urine of patients with pyelonephritis are beta-hemolytic, whereas *K. pneumoniae* and *Enterobacter* spp. are rarely, if ever, beta-hemolytic. Another common Gram-negative rod that is frequently beta-hemolytic is *Pseudomonas aeruginosa*, which is very unlikely to be the cause of community-acquired cystitis or pyelonephritis in an otherwise healthy woman. This organism is incapable of fermenting carbohydrates and should not be confused with lactose-fermenting isolates of *E. coli*. A spot indole test was done on the patient’s isolate and was positive, confirming the identity of this organism as *E. coli* [3].

4. This bacterium was resistant to ampicillin. What in this patient’s history might explain this observation? Multidrug-resistant strains of this organism are beginning to be seen as an important cause of UTI. Describe the mechanism of resistance that these organisms most likely will have.

The patient had a previous UTI, at which time she received oral ampicillin. One of the deleterious effects associated with the use of antimicrobial agents is the selection of antibiotic-resistant bacteria. This occurs with some degree of frequency in gut flora, where plasmids coding for resistance may be mobilized in response to antimicrobial pressure, leading to the transfer of resistance to previously susceptible organisms, such as in this *E. coli* isolate. Not only may resistance to the agent supplying the selective pressure result, but also the plasmid may contain genes that code for resistance to other antimicrobial agents, the result being a multidrug-resistant organism.

During the past 10 years, the emergence of multidrug-resistant *E. coli* causing both community-acquired as well as health care-associated UTIs has made the selection of empiric antimicrobial therapy much more difficult. Globally, ~20% of *E. coli* strains causing UTIs produce extended-spectrum β -lactamases (ESBLs). Mutations in the active site of the β -lactam “extend” the activity of the β -lactamases so that they are active against all penicillins and

cephalosporins. Extended-spectrum β -lactamases are carried on plasmids that frequently also encode resistance to trimethoprim-sulfamethoxazole, fluoroquinolones, and aminoglycosides. Both fluoroquinolones and trimethoprim-sulfamethoxazole are widely used as empiric therapy for cystitis in women. The increasing resistance being seen in *E. coli*, due in part to ESBL-producing strains, greatly limits the choice of oral agents to treat uncomplicated cases of UTI. For now, ESBL-producing *E. coli* isolates remain susceptible to the oral agents fosfomycin and to a lesser degree nitrofurantoin, but how long this will continue to be true is difficult to predict. ESBL-producing organisms remain susceptible to carbapenems such as ertapenem and imipenem. These parenterally administered antimicrobials are widely used to treat systemic infections such as pyelonephritis due to ESBL-producing organisms. However, carbapenemases have also emerged and can be encoded on plasmids that carry resistance genes like those found on ESBL-encoding plasmids. These carbapenemase-encoding plasmids have been found in *E. coli*. Nitrofurantoin is not active against carbapenemase-producing strains, while fosfomycin has some degree of activity and may be useful in treating cystitis. However, fosfomycin is poorly absorbed systemically and should not be used to treat patients with pyelonephritis, such as the patient in this case, or urosepsis [4].

5. Why UTIs are more frequent in women than men?

In adults, 90% of uncomplicated UTIs occur in women. It is one of the most common reasons why adolescent and adult women seek health care, resulting in ~10 million physician visits annually in the United States. The simplistic view of why women have more UTIs than do men is that the shorter urethra in women results in a greater like that organisms will ascend the urethra and enter the bladder. Sexual activity is thought to play a significant role in the introduction of uropathogens into the urethra. In addition, the use of spermicides, with both diaphragms and coated condoms, has been shown to predispose women to UTIs. However, other factors that may play a role in this gender difference have been identified. It has been observed that prostatic fluid inhibits the growth of common urinary tract pathogens in urine, providing a unique defense mechanism for men. It has also been observed that specific uropathogens bind to vaginal and periurethral epithelial cells. Binding in the periurethral region by these organisms is often seen in women prior to the development of UTI, as well as in women who have recurrent UTIs. Binding of uropathogens

to the periurethral epithelium is highest when estrogen levels reach their peak during the menstrual cycle. These observations may further explain why a preponderance of UTIs are seen in women [5].

6. Did this woman have cystitis or pyelonephritis? Why is it important to differentiate between the two?

The clinical presentation in this patient is consistent with acute pyelonephritis. Pyelonephritis is an infection of the kidney, whereas cystitis is an infection of the bladder. The findings of fever, chills, and left flank pain, with corresponding costovertebral angle tenderness, are all consistent with pyelonephritis. If white blood cell casts were seen in the patient's urinalysis, that finding would further support the diagnosis of pyelonephritis. Culture results would not be useful in differentiating between the two types of infections. Radiographic or cystoscopic studies would be necessary to make a definitive diagnosis of pyelonephritis, but clinical judgment is usually sufficient. The reason it is important to distinguish between pyelonephritis and cystitis is that antimicrobial treatment strategies differ. Cystitis therapy is usually brief, typically a 3-day course of trimethoprim-sulfamethoxazole unless there is a high rate of resistance to this agent in the community, while pyelonephritis therapy may be more prolonged, typically lasting 7 days to 2 weeks. The outcome of antimicrobial therapy is dependent in great part on the susceptibility of the *E. coli* strain. If patients are treated empirically with an antimicrobial agent to which their isolate is resistant, their outcome will be less likely to be favorable than in those patients who receive an antimicrobial agent to which their isolate is susceptible [6].

7. Briefly explain the evolution of the organism causing this infection in terms of its ability to infect the urinary tract. What virulence factors have been shown to play a pathogenic role in this infection?

Pathogenicity islands" are an exciting recent concept for understanding the evolution of human microbial pathogens. They are relatively large segments of DNA that encode virulence factors that have been inserted by recombination into chromosomal regions that appear to allow "foreign" DNA more readily. What that means practically is that organisms such as *E. coli* can quickly evolve from harmless gastrointestinal tract commensals to agents capable of causing UTI by incorporating DNA that encodes virulence factors. Acquisition of virulence factors by gene transfer is a common theme in *E. coli* pathogenicity, not only in strains causing UTI but also in strains that cause diarrheal disease.

Two virulence factors known to be important in the pathogenesis of *E. coli* pyelonephritis, P fimbriae and hemolysin, have been found on pathogenicity islands.

Pathogenicity islands are found much more frequently in *E. coli* strains that cause cystitis and pyelonephritis than in fecal isolates. The fimbriae are the major means of adhesion of uropathogenic *E. coli*, allowing them to bind to the various types of epithelial cells that line the urinary tract. Two different fimbriae found on the surface of uropathogenic *E. coli*, types P and 1, have been well studied. The P fimbriae are so designated because they agglutinate red blood cells possessing the P blood group antigen. They bind to uroepithelial cells and are resistant to phagocytosis. More than 80% of *E. coli* isolates causing pyelonephritis have pathogenicity islands that encode these fimbriae. Type 1 fimbriae are distinct from the P fimbriae. Both agglutination of red blood cells and binding to uroepithelial cells by *E. coli* possessing type 1 fimbriae can be blocked by preincubating the organism with mannose, while binding of type P-fimbriated *E. coli* is not blocked by mannose. Type 1-fimbriated *E. coli* strains are thus said to be mannose sensitive, while type P strains are said to be mannose insensitive. Type 1 fimbriae are found more frequently in patients with cystitis and less frequently in patients with pyelonephritis. Our patient likely had a P-fimbriated *E. coli* strain because she had pyelonephritis.

Another important virulence factor of uropathogenic *E. coli* is hemolysin. Hemolysin production is detected in ~55% of *E. coli* recovered from patients with pyelonephritis. Studies with renal tubular cells in primary culture have shown them to be quite sensitive to the cytotoxic activity of this virulence factor. Aerobactin is a third virulence factor, found in ~75% of *E. coli* strains causing pyelonephritis. Aerobactin is a siderophore. Siderophores are molecules produced by bacteria and scavenge iron, an essential nutrient for bacteria, from the host. Strains of *E. coli* that produce aerobactins have been shown to grow faster in urine than nonproducing strains, although how important this is in the pathogenesis of UTI is unclear [7].

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