

The Susceptibility of Urinary Pathogens in Complicated Urinary Tract Infections

Richard D. David, MD, FACS

Urology Specialists of Southern California,
Board Certified Adult & Pediatric Urology,
Associate Clinical Professor of Urology at UCLA,
Los Angeles, California, USA



The bacterial etiology and antimicrobial susceptibilities of genitourinary infections continue to evolve as patient populations and treatment strategies change. To enable adequate pathogen coverage against both Gram-positive and Gram-negative bacteria, and antimicrobial penetration into target tissues at required concentrations, antimicrobial treatment should be tailored to individual patient variables. Differences in pathogen susceptibilities must be accounted for. Continued monitoring of changes in etiological patterns and uropathogen susceptibility will ensure appropriate and effective treatment.

Different classes of antibiotics work by affecting different bacterial structure components or processes and the susceptibility patterns are examined. Continuous monitoring of the changing patterns of resistance is critical to the choice of an antibiotic and the current schemes are discussed, particularly as they apply to the United States and Canada. In general, resistance rates are lower for fluoroquinolones than for antibiotics such as ampicillin and trimethoprim-sulfamethoxazole (TMP-SMX).

The susceptibility patterns of fluoroquinolones against genitourinary pathogens is examined in detail. There have been no reports of a pathogen that is levofloxacin-resistant but ciprofloxacin-susceptible although the converse is not true. Ampicillin and TMP-SMX have limited efficacy for the treatment of genitourinary infections and fluoroquinolones like levofloxacin are a recommended option in the empiric treatment of complicated urinary tract infections. In cases where quinolone resistance has been confirmed, it is most likely due to multidrug resistant bacteria. These bacteria are usually also resistant to ampicillin and TMP-SMX and thus we must practice good infection control measures.

Introduction

Urinary tract infections (UTIs) are extremely common, resulting in more than 8 million physician visits per year in the United States, and accounting for 15% of all community-prescribed antibiotics at an estimated annual cost of more than \$1 billion (1). Estimated direct and indirect costs of community-acquired infections exceed \$1.6 billion. UTIs account for nearly 100,000 hospital admissions per year.

The rising prevalence of antimicrobial resistance continues to plague physicians when choosing an effective agent. Resistance can have a significant impact on clinical outcomes as one study showed that resistance to trimethoprim-sulfamethoxazole (TMP-SMX) was associated with higher rates of clinical and microbiologic failure (2). In addition, *Escherichia coli* resistance to ampicillin has approached 40% across the United States

(and above 50% in some regions) (2, 3).

Challenges associated with current treatment strategies: high rates of resistance

The apparent cause of increasing antibiotic resistance is selective pressure by antimicrobial substances in various environmental settings causing emergence of antibiotic-resistant bacterial clones, followed by the widespread geographic distribution of such clones. The epidemiology of antibiotic-resistant bacteria varies with the sites of infection, with the medical specialty, with the region, and with time.

Increased bacterial resistance to antibiotics is a major concern in the treatment of a variety of infections and requires careful attention. As resistance increases, new strategies need to be employed to combat the pathogens in order to treat the patient successfully and protect the community from

Address for correspondence

Richard D. David, MD, FACS
Urology Specialists of Southern
California,
4955 Van Nuys Blvd., Suite 704
Sherman Oaks, California
91403-1888, USA
Phone: 818-990-5020
Fax: 818-990-8549
E-mail: rdd@earthlink.net

resistance. Physicians need to be aware of the patterns of resistance in their region and of strategies targeted towards both Gram-positive and Gram-negative pathogens in order to appropriately treat the bacterial infection.

Microbiology: pathophysiology of common and resistant pathogens causing cUTI and AP, and mechanisms of resistance

The distribution of organisms in complicated urinary tract infection (cUTI) is influenced by factors such as whether the infection is initial or recurrent, prior antimicrobial therapy, presence of genitourinary instrumentation, and whether it is acquired by community or nosocomial exposure (4). The course of untreated bacterial infection is determined by bacterial virulence factors as well as the integrity of host defense mechanisms (1). cUTIs occur by an ascending route, with failure of complete voiding, resulting in persistence of infecting organisms within the genitourinary tract (4). In catheterized patients, specific organism virulence factors are not necessary to promote infection; host abnormalities are sufficient. In fact, *E. coli* isolated from patients with cUTIs have consistently shown a lower prevalence of virulence genes and phenotypic expression of virulence factors compared with strains isolated from uncomplicated infection or pyelonephritis. The virulence impact of the organisms in establishing infection is less in cUTIs than uncomplicated UTIs, but organism variables are likely relevant in determining whether the infection is symptomatic and whether it will persist (5). It is probable that the infection is maintained due to significant polymicrobial resistance to antibiotics, especially to ampicillin and TMP-SMX.

Bacterial resistance results from selective pressure in the presence of antibiotics (1). Rapid doubling times facilitate the random occurrence of mutations. Mutant bacteria that have the ability to overcome the inhibitory action of an antibiotic have a selective advantage. Long-term exposure to the antibiotic facilitates the emergence of more strains exhibiting resistance to a given drug or multiple drugs. The effects can be seen in terms of increasing treatment failures and reemergence of infectious disease as a serious health problem.

Different antibiotics classes target different components of bacterial structure and metabolism (1). For example, β -lactam antibiotics (including penicillins and cephalosporins) target the synthesis of bacterial cell walls while trimethoprim and sulfonamides target folic acid synthesis by inhibiting dihydrofolate reductase. Some classes of antibiotics target the ribosomes, affecting protein synthesis. The fluoroquinolones, as a class, interfere with

bacterial metabolism by inhibiting crucial enzymes such as DNA gyrase and topoisomerase IV (1, 5).

Fluoroquinolone resistance can occur through multiple mechanisms, with the most common attributed to multiple mutations to the quinolone-resistant determining regions (QRDR) of the topoisomerase and gyrase genes. However, efflux mechanisms can play a significant role in conferring resistance to certain fluoroquinolones, and may explain some differences in susceptibility between levofloxacin and ciprofloxacin (6). In *E. coli*, one study showed that ciprofloxacin was susceptible to two of the three efflux pumps analyzed, while levofloxacin was not a substrate for this mechanism of resistance (7). Bacterial cells are able to pump the ciprofloxacin out of the cell thereby reducing the intracellular concentration. This efflux can reduce the susceptibility of an organism to the antimicrobial, and increase the potential for resistance development. Active efflux alone has been shown in one report to account for resistance to ciprofloxacin in a clinical situation (8).

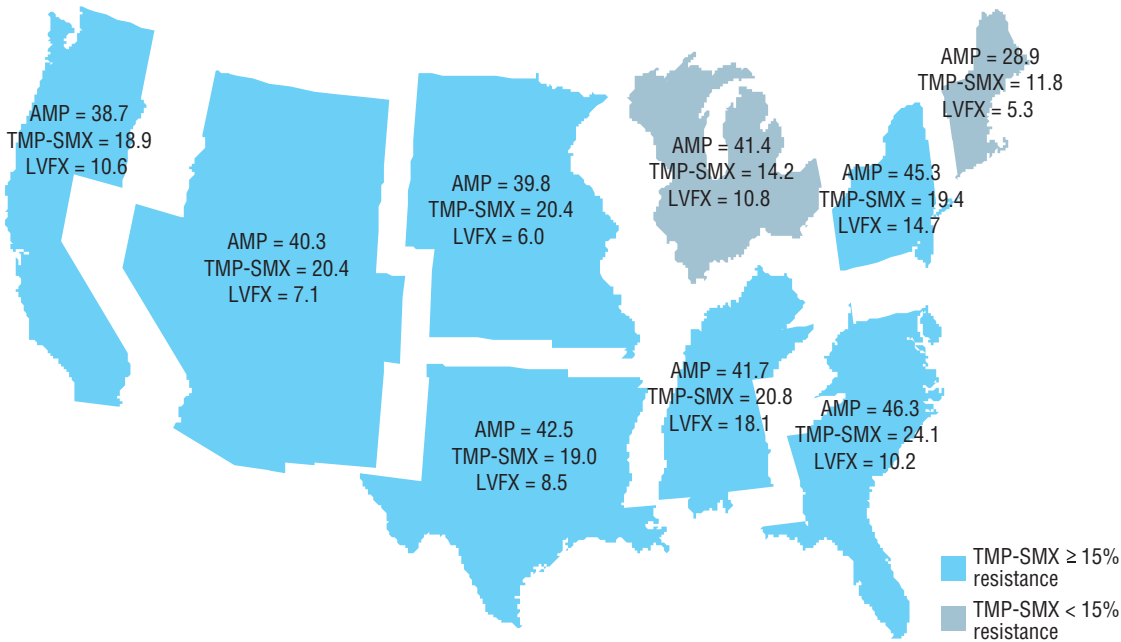
Tracking bacterial resistance trends: TRUST surveillance, TSN, NAUTICA, and clinical trials

A number of studies have tracked the emerging patterns of bacterial resistance to antibiotics in the United States, Canada, and throughout the world. These studies are vital for clinicians to understand the appropriateness of use of antimicrobial therapies in a specific community, for the development for empirical antimicrobial therapy recommendations and to guide the design of interventions to control or minimize antimicrobial resistance (9).

The percentage of resistant *E. coli* from UTI isolates obtained from outpatients has been described in various studies. A study using The Surveillance Network (TSN) database showed *E. coli* resistance to ampicillin approaching or exceeding 35% in all regions of the United States, while resistance to TMP-SMX was approximately 16% (10). A more recent study showed *E. coli* resistance in the United States at 39.3% for ampicillin, and 22.6% for TMP-SMX (11). The TSN database looked at regional variations in susceptibilities in the United States (Figure 1). Most of the country shows resistance $\geq 15\%$ to TMP-SMX and even greater resistance to ampicillin. Of interest, the level of resistance seen to the fluoroquinolone levofloxacin in each area is less than for β -lactams and TMP-SMX.

The Tracking Resistance in the United States Today (TRUST) surveillance studies have been conducted from 2003 to 2007. These studies have tracked a variety of Gram-negative pathogens in 45 sites, in 9 regions and reviewed fluoroquino-

Figure 1. The percentage resistance of *Escherichia coli* UTI isolates collected from outpatients, 2006



In vitro activity does not necessarily correlate with clinical results.

Abbreviations: AMP = ampicillin, TMP-SMX = trimethoprim-sulfamethoxazole, LVFX = levofloxacin.

Adapted from reference (12).

lones and other agents. The trend towards increased resistance is seen across a spectrum of antibiotic classes over a span of 5 years (Table 1). Increased resistance correlates to a drug being less efficacious in controlling an infection, potentially resulting in complications, increased morbidity, and even mortality. *E. coli* shows significantly less resistance to both levofloxacin and ciprofloxacin than to ampicillin and TMP-SMX but, since 2005, the rate of resistance to ciprofloxacin has been rising faster than that to levofloxacin.

The North American Urinary Tract Infection Collaborative Alliance (NAUTICA) was designed to determine antibiotic susceptibility to commonly used agents for UTIs and involved outpatient urinary isolates obtained in various geographic regions in the United States and Canada (11).

Of the 1990 bacteria isolated in this study, the most common organism was *E. coli* 57.5%. Other Gram-negatives included: *Klebsiella pneumoniae* (12.4%), *Proteus mirabilis* (5.4%), *Pseudomonas aeruginosa* (2.9%), *Citrobacter* spp. (2.7%), and Gram-positives such as *Enterococcus* spp. (6.6%) and *Staphylococcus aureus* (2.2%) (11). This surveillance study from women in the United States and Canada showed greater TMP-SMX resistance in women from 51 to 64 years of age (21% resistant) compared with from 15 to 50 years of age (15% resistant) (11, 13, 14). Among the isolates collected, resistance to TMP-SMX was > 20% in 5 of 7 US Bureau of the Census geographic regions. Among

Table 1. Susceptibility of Gram-negative pathogens to levofloxacin and ciprofloxacin (TRUST 10, 2005–2006)

Organism	No. of isolates	% S	
		Levofloxacin	Ciprofloxacin
<i>Escherichia coli</i>	2,607	87.8	87.5
<i>Klebsiella pneumoniae</i>	1,293	95.7	94.4
<i>Proteus mirabilis</i>	778	85.5	77.6
<i>Enterobacter cloacae</i>	572	93.5	92.3
<i>Serratia marcescens</i>	427	95.6	92.3
<i>Citrobacter</i> spp.	549	95.3	94.4
<i>Pseudomonas aeruginosa</i>	1,219	69.1	70.4

Abbreviation: %S = percent susceptible.

Adapted from reference (10).

the 1,990 isolates, 45.9% were resistant to ampicillin, 20.4% to TMP-SMX, 9.7% to ciprofloxacin, and 8.1% to levofloxacin. Fluoroquinolone resistance was highest in patients older than 65 years. Overall resistance rates were higher in the United States than in Canada. Results demonstrate a continuing evolution of resistance to antimicrobial agents (11).

The fluoroquinolones continue to be effective against most genitourinary pathogens. In the NAUTICA study, among all outpatient urinary isolates in the United States (including Gram-positive and Gram-negative pathogens), resistance rates were 10.6% for ciprofloxacin and 8.8% for levofloxacin (11). Resistance rates by *E. coli* isolates were below 7% for each agent, suggesting that both

agents can be used effectively for these types of infections. However, surveillance data from the TRUST program illustrate that there are some differences in susceptibility to levofloxacin and ciprofloxacin for Gram-negative pathogens (Table 1). Additionally, for several of these pathogens, isolates have been identified that were ciprofloxacin-resistant and levofloxacin-susceptible, but no isolate was found to be levofloxacin-resistant and ciprofloxacin-susceptible (15).

Peterson et al.

A recent study by Peterson et al. looked at patients between 2004 and 2006 and described a post hoc analysis of a multicenter study looking at a new treatment for cUTI primarily community acquired (99.4%) (16). A total of 650 patients were recruited of which 68.2% had cUTIs. Pre-therapy microbiology and fluoroquinolone susceptibility of pathogens from these 650 patients with cUTI or acute pyelonephritis (AP) were assessed. Susceptibility to nonstudy drugs (ampicillin and TMP-SMX) was compared with study drugs (levofloxacin and ciprofloxacin) and were categorized as susceptible, intermediate, or resistant. It was found that 99.4% of the infections were community-acquired. The most common pathogen identified was *E. coli* in 65.6% of patients and 12.2% of patients had Gram-positive pathogens. In addition, 79% of patients with cUTI had complicating factors (e.g., obstruction, catheter, retention). Of all the Gram-negative pathogens, 50.1% were resistant to ampicillin; 22.1% were resistant to TMP-SMX. However, 91.9% of isolates were susceptible to levofloxacin and ciprofloxacin, with 6.5% resistant or intermediately resistant to levofloxacin, and 9.7% resistant or intermediately resistant to cipro-

floxacin. All isolates resistant to levofloxacin were also resistant to ciprofloxacin, but 6 isolates fully susceptible to levofloxacin were fully resistant to ciprofloxacin. Breaking this down further, 42 isolates or 6.2% were resistant to both levofloxacin and ciprofloxacin at study entry; 18 isolates or 2.6% were sensitive to levofloxacin but intermediate to ciprofloxacin; 6 isolates were resistant to ciprofloxacin and fully sensitive to levofloxacin. The organisms involved were *E. coli*, *S. aureus*, *S. saprophyticus*, and *Alcaligenes xylosoxidans* (16).

The data from this study supports the concept that the level of fluoroquinolone susceptibility of urinary pathogens remains high and ampicillin and TMP-SMX resistance is high. Where bacteria were fluoroquinolone-resistant, cross-resistance to ampicillin or TMP-SMX was common.

What is the significance of levofloxacin-sensitive and ciprofloxacin-resistant strains?

A number of clinical trials have shown that quinolone bacterial resistance may not be a class effect but differs within the quinolones for certain organisms. In addition to Peterson et al. where 3% of organisms were resistant or intermediate to ciprofloxacin but sensitive to levofloxacin, other studies have shown similar findings. Data from the TRUST database over the period from 2003 to 2007 showed that 12% of *P. mirabilis*, 7.3% of *Serratia marcescens* and 5% of *K. pneumoniae* were all resistant to ciprofloxacin and sensitive to levofloxacin. The converse was not seen: no isolates were sensitive to ciprofloxacin and resistant to levofloxacin. This information should be important in the selection of antibiotics for cUTIs.

REFERENCES

- 1 Wagenlehner FM, Naber KG. Treatment of bacterial urinary tract infections: presence and future. *Eur Urol* 2006; 49: 235–44.
- 2 Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). *Clin Infect Dis* 1999; 29: 745–58.
- 3 Cornia PB, Takahashi TA, Lipsky BA. The microbiology of bacteriuria in men: a 5-year study at a Veterans' Affairs hospital. *Diagn Microbiol Infect Dis* 2006; 56: 25–30.
- 4 Nicolle LE. Urinary tract pathogens in complicated infection and in elderly individuals. *J Infect Dis* 2001; 183 (Suppl 1): S5–8.
- 5 Newquist M. Advances in the treatment of genitourinary infections. *Forum on Urology: Practical Discussions of Genitourinary Tract Infections and Other Clinical Challenges in Urology 2007*; (Suppl to Cortlandt Forum): 7–10.
- 6 Zhanel GG, Hoban DJ, Schurek K, Karlowsky JA. Role of efflux mechanisms on fluoroquinolone resistance in *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*. *Int J Antimicrob Agents* 2004; 24: 529–35.
- 7 Yang S, Clayton SR, Zechiedrich EL. Relative contributions of the AcrAB, MdfA and NorE efflux pumps to quinolone resistance in *Escherichia coli*. *J Antimicrob Chemother* 2003; 51: 545–56.
- 8 Giraud E, Cloeckaert A, Kerboeuf D, Chaslus-Dancla E. Evidence for active efflux as the primary mechanism of resistance to ciprofloxacin in *Salmonella enterica* serovar Typhimurium. *Antimicrob Agents Chemother* 2000; 44: 1223–8.
- 9 Sader HS, Fritsche TR, Jones RN. Potency and spectrum trends for cefepime tested against 65746 clinical bacterial isolates collected in North American medical centers: results from the SENTRY Antimicrobial Surveillance Program (1998–2003). *Diagn Microbiol Infect Dis* 2005; 52: 265–73.
- 10 Data from TRUST 10 surveillance study (2005–2006). Ortho-McNeil Pharmaceutical, Inc., December 2006.
- 11 Zhanel GG, Hisanaga TL, Laing NM, DeCorby MR, Nichol KA, Palatnik LP, Johnson J, Noreddin

A, Harding GK, Nicolle LE, Hoban DJ; The NAUTICA Group. Antibiotic resistance in outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). *Int J Antimicrob Agents* 2005; 26: 380–8.

12

The Surveillance Network (TSN) database, 2006, Eurofins Medinet.

13

Gupta K, Stamm WE. Outcomes

associated with trimethoprim/sulphamethoxazole (TMP/SMX) therapy in TMP/SMX resistant community-acquired UTI. *Int J Antimicrob Agents* 2002; 19: 554–6.

14

Gupta K, Sahn DF, Mayfield D, Stamm WE. Antimicrobial resistance among uropathogens that cause community-acquired urinary tract infections in women: a nationwide analysis. *Clin Infect Dis* 2001; 33: 89–94.

15

Yee YC, Evangelista AT, Brown NP, Sahn DF, Thornsberry C. Analysis of levofloxacin and comparator antibiograms against urinary tract infection (UTI) isolates of *E. coli* and other Enterobacteriaceae across the United States, [abstract No. 507: 155–6]. 45th Annual Meeting of the Infectious Diseases Society of America; October 4–7, 2007; San Diego, California.

16

Peterson J, Kaul S, Khashab M, Fisher A, Kahn JB. Identification and pretherapy susceptibility of pathogens in patients with complicated urinary tract infection or acute pyelonephritis enrolled in a clinical study in the United States from November 2004 through April 2006. *Clin Ther* 2007; 29: 2215–21.