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PERSPECTIVES

Consensus statement on the role of fluoroquinolones in the management of urinary tract infections

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A consensus meeting was held aimed at attaining a consensus on the role of fluoroquinolones in the management of complicated urinary tract infections (cUTI), particularly in countries with high rates (>20%) of fluoroquinolone-resistant uropathogens. Pharmacokinetic/pharmacodynamic and limited clinical data support the fact that specific fluoroquinolone breakpoints might be needed for UTI. Resistant isolates causing mild to moderate cUTI with relatively low minimum inhibitory concentrations (MICs $\leq$ 16—32 μg/mL) might clinically respond to fluoroquinolone therapy.

The Taiwan Urinary Tract Infection Consensus Meeting was held on September 18, 2010, in Taipei. A total of 12 infectious-disease specialists from 12 major teaching hospitals located in different parts of Taiwan participated in the meeting. The meeting aimed to attain consensus on the role of fluoroquinolones in the management of UTI,

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particularly in a country with a high rate (>20%) of fluoroquinolone resistance among uropathogens.

Urinary tract infections are the most frequently occurring bacterial infections in the community and in hospitals. Trimethoprim–sulfamethoxazole (SXT) is generally considered to be the drug of choice for the treatment of uncomplicated UTI.[1,2] However, the persistently high rates (>20%) of SXT resistance among urinary *Escherichia coli* isolates have made this agent unsuitable for empirical treatment of UTI (Fig. 1).[1–3] Several international guidelines recommend fluoroquinolones as the drugs of choice for empirical treatment of UTI, including catheter-associated UTI.[2,4–7] Levofloxacin 750 mg once daily for 5 days has been shown to be as effective as ciprofloxacin 400 mg (intravenous) or 500 mg (oral) twice daily for 10 days in the treatment of adults with cUTI and acute pyelonephritis, including patients with concurrent bacteremia.[8,9] However, the rapid emergence of fluoroquinolone-resistant *E coli* (the most commonly encountered uropathogen) suggests that further use would make fluoroquinolones unreliable for treatment within the near future.[10,11] Moreover, the widespread use of fluoroquinolones for cUTI or catheter-associated UTI might result in reduced susceptibility of respiratory pathogens to these agents.[1,10–12]

Increasing resistance of uropathogens to fluoroquinolones is of clinical concern. Rates of levofloxacin susceptibility of clinical isolates of urinary *E coli* obtained from 12 major teaching hospitals located in different parts of Taiwan ranged from 70% to 80% (Fig. 2). In addition, recent studies have found a rapid increase in levofloxacin resistance among *E coli* isolates from patients treated in emergency departments and outpatient clinics.[10,11] Risk factors for infections with levofloxacin-resistant *E coli* include recent hospitalization and prior levofloxacin use.[1,10,11] These risk factors should be considered before initiating empirical treatment with a fluoroquinolone for UTI.

However, the key controversy is that *in vitro* resistance to fluoroquinolones can always translate into clinical failure in patients with UTI, particularly when higher than regular doses of fluoroquinolones (e.g. 750 mg levofloxacin) are administered. Patients with UTI caused by SXT-resistant pathogens have worse clinical outcomes than those infected with susceptible isolates.[1,13] Nevertheless, *in vitro*

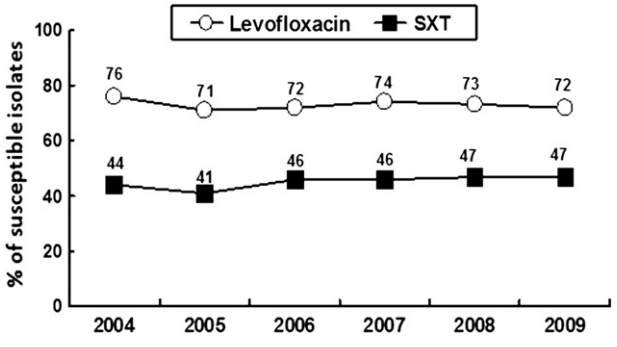

Figure 1. Rates of nonsusceptibility to levofloxacin and trimethoprim-sulfamethoxazole (SXT) among all clinical urinary isolates in patients treated at the National Taiwan University Hospital from 2004 to 2009.

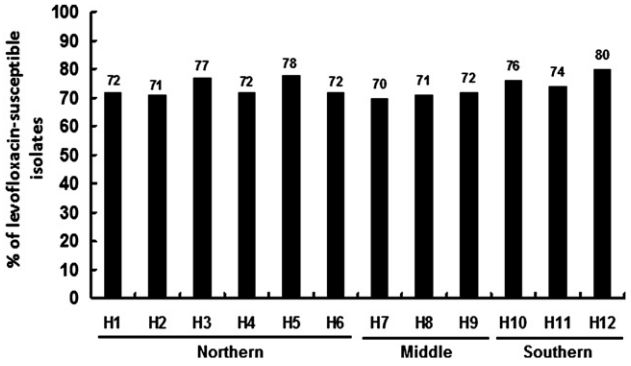

Figure 2. Levofloxacin susceptibility rates among clinical urinary isolates of *Escherichia coli* from 12 major teaching hospitals in Taiwan from January to June 2010.

resistance to SXT translates into clinical failure in approximately 50% of patients with community-acquired UTIs.[1,13] The MIC breakpoints of trimethoprim or SXT for *Enterobacteriaceae* and staphylococci provided by the Clinical and Laboratory Standards Institute were categorized only for treating UTIs.[14] Importantly, the Clinical and Laboratory Standards Institute provides a urine-specific breakpoint for some fluoroquinolones (lomefloxacin, ofloxacin, and norfloxacin) but not for ciprofloxacin or levofloxacin for *Enterobacteriaceae* and *Pseudomonas aeruginosa*.[14] Although most of the clinical microbiology laboratories determine the susceptibilities of urinary isolates of *Enterobacteriaceae* to levofloxacin and ciprofloxacin by applying non-urine-specific MIC breakpoints, it does not mean that levofloxacin and ciprofloxacin are not suitable for the treatment of UTIs caused by pathogens with "*in vitro* resistance" to these two agents.

Previous studies have clearly demonstrated that the mean peak urinary concentrations of levofloxacin (0–1.5 hours) were 347 μg/mL at a dose of 500 mg and 620 μg/mL at a dose of 750 mg.[15–17] High-dose levofloxacin (750 mg) exhibited early and prolonged (8–12 hours) urinary bactericidal activity against levofloxacin-resistant *E coli* isolates (MIC range, 4–32 μg/mL) in virtually all subjects.[15] Previous studies also found that ciprofloxacin at standard doses or ciprofloxacin XR (1,000 mg) once daily had prolonged bactericidal activity in urine.[18]

Some reported clinical cases support those *ex vivo* findings. Miller et al.[19] reported a case in which ciprofloxacin (500 mg twice daily) was an effective treatment for cystitis because of a ciprofloxacin-resistant strain of *E coli* (MICs > 4 μg/mL). In a clinical trial of levofloxacin (750 mg once daily) versus ciprofloxacin (500 mg twice daily) for the treatment of acute pyelonephritis, four patients were infected with fluoroquinolone-resistant *E coli* isolates.[8] Ciprofloxacin was effective at eradicating two of four isolates, and levofloxacin was effective against another isolate. The MIC values of ciprofloxacin were 8 μg/mL and greater than 32 μg/mL, and the MIC value of levofloxacin was 32 μg/mL.[8]

Additional susceptibility breakpoints for uropathogens may be warranted for selected fluoroquinolones.[16,19] The susceptibility concentration (4 μg/mL) in urine for norfloxacin is approximately three times its peak serum level.[14] A similar

ratio for 750 mg of levofloxacin would have a susceptibility breakpoint in urine between 16 μg/mL and 32 μg/mL.[16–18] Based on that assumption, more than 90% of *E coli* (MIC_{90}, 16 μg/mL) causing cUTI in Japan and the *E coli* isolates [MIC_{90}, 16 μg/mL; 29% were categorized as not susceptible to levofloxacin (MIC $\geq$ 4 μg/mL)] recovered in intensive care units in Taiwan were susceptible to levofloxacin.[16,20] Ciprofloxacin exhibited a higher MIC_{90} (64 μg/mL) compared with levofloxacin, indicating a high rate of resistance of *E coli* isolates to ciprofloxacin.[20] The greater effect of the AcrAB, MdfA, and NorE efflux pumps on ciprofloxacin compared with that on levofloxacin in *E coli* might partly contribute to this finding.[21,22]

It is reasonable to consider a 5-day course of levofloxacin or a 10-day course of ciprofloxacin—though other fluoroquinolones may be just as effective but have not been evaluated—for the treatment of cUTI or acute pyelonephritis if the causative uropathogen is susceptible.[23] Moreover, in geographical areas in which more than 20% of urinary *E coli* isolates are nonsusceptible to levofloxacin, a high daily dose (750 mg) of levofloxacin might still be useful for the empirical treatment of cUTI caused by *E coli* isolates with MICs less than 32 μg/mL. The major caveat with this higher susceptibility breakpoint for uropathogens would be in patients who have severe cUTIs or urosepsis with concurrent bacteremia.

In summary, pharmacokinetic/pharmacodynamic data and limited clinical observation indicated that UTI caused by isolates with relatively low MICs (e.g. $\leq$16 μg/mL) might respond to fluoroquinolone therapy, and that specific fluoroquinolone breakpoints would be required for UTI.

List of discussants

A total of 12 infectious-disease specialists from 12 major teaching hospitals located in different parts of Taiwan participated in the meeting. The participants who convened to develop consensus on the role of fluoroquinolones in the management of urinary tract infection in Taiwan were Po-Ren Hsueh, Cheng-Yi Liu, Wen-Chien Ko, Ching-Tai Huang, Muh-Yong Yen, Yung-Ching Liu, Wen-Sen Lee, Chun-Hsing Liao, Ming-Yieh Peng, Yeu-Jun Lau, Chih-Ming Chen, and Yao-Shen Chen.

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