Urinary tract-derived *Escherichia coli* resistant to co-trimoxazole in Japan, where the drug is seldom used for treating acute urinary tract infections

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Sir,

Uropathogens resistant to co-trimoxazole (trimethoprim/sulfamethoxazole) are increasing worldwide and are problematic. Co-trimoxazole is widely used for treatment of urinary tract infections (UTIs) and is one of the current standard drugs for acute uncomplicated bacterial cystitis (AUBC) in women. This drug is seldom used, however, for treatment of AUBC in Japan, where it is more expensive than most oral penicillins and cephems and where authorities have restricted its indications to cases where there is no alternative antibiotic. It is approved for dysentery, typhoid, paratyphoid, respiratory tract infections and chronic, but not acute, UTIs. We were interested in the susceptibilities to co-trimoxazole of urinary tract-derived *Escherichia coli* in Japan, where this drug is prescribed for indications different from those in other countries.

A total of 229 *E. coli* strains, 145 from patients with AUBC and 84 from patients with complicated UTIs (C-UTIs), obtained at 15 institutes in central Japan were examined for antibiotic susceptibilities. AUBC strains were selected using a random number table from our stocks (total number 1457; 295 for AUBC, 1162 for C-UTIs) in 1992 (*n* = 54), 1996 (54) and 2000 (37). UTIs occurring in patients with some underlying urological disease were defined as C-UTI. C-UTI strains were selected in the same manner.

MICs were measured with an agar dilution method using an inoculum of 10⁶ cfu/mL plated on to Mueller–Hinton agar using *E. coli* NIHJ JC-2 and *Enterococcus faecalis* ATCC 29212 as reference strains. For susceptibilities against co-trimoxazole, 7.5% defibrinated horse blood was added to the agar, and the mixing ratio of trimethoprim and sulfamethoxazole was 1:19. In this study, the resistance breakpoint was defined as 50 mg/L of co-trimoxazole.

During our surveillance period, AUBC was diagnosed in 1850 patients, none of whom was treated with co-trimoxazole. The prevalence of co-trimoxazole-resistant strains was 3.4% of AUBC strains. No significant differences occurred in MIC distributions investigated each year. Resistances to other major antibiotics were rarely (<1%) observed except for ampicillin (14%), nalidixic acid (5%) and sultamicillin (5%). Co-resistance between co-trimoxazole and these agents was not observed. The cumulative MIC distribution of co-trimoxazole for AUBC strains was compared with those for strains from C-UTIs (Figure 1), and the latter showed significantly more resistance (*P* = 0.025). No C-UTI patients from whom the isolates were obtained had received co-trimoxazole.

Co-trimoxazole resistance appeared immediately after the start of its clinical use and increased, reflecting its widespread use for urinary and respiratory tract and other infections. For urinary tract-derived *E. coli*, the prevalence of resistance was <1% in the early 1970s. This rate gradually increased worldwide, exceeding 60% in certain situations. Recent epidemiological studies have found the rate of co-trimoxazole-resistant *E. coli* isolated from uncomplicated UTIs to be 15.7% in 16 European countries, including 34.8% in Portugal and Spain,¹ and 18% in the USA.² In contrast, the rate reported in Japanese literature³ was 4.5% in AUBC isolates in a hospital.
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in 1981 and 3.0% in isolates from UTIs in a longitudinal multi-centre study conducted between 1979 and 1988. These results are similar to our figure of 3.4%, indicating that the prevalence of co-trimoxazole-resistant E. coli is consistently low in Japan. Because the major risk factor for co-trimoxazole resistance is current or recent use of co-trimoxazole, an extremely low rate of co-trimoxazole resistance was expected. We were surprised to find co-trimoxazole-resistant strains in 3.4% of our AUBC patients.

Other reported risk factors associated with co-trimoxazole resistance include various types of underlying urological or general disease, and hospital admission. A review of the records indicated that among our AUBC patients with co-trimoxazole-resistant strains, none showed definitive indications of the presence of any of these factors. Other possible factors are that these strains were acquired from family members or from animals. Co-trimoxazole is occasionally prescribed by some paediatric urologists in Japan for prophylaxis of recurrent UTIs in children. In addition, use of sulphonamides and trimethoprim in animals is estimated to exceed that in clinical human use in Japan. Although the prevalence of co-trimoxazole-resistant strains in children and animals has not been fully elucidated in Japan, and no direct evidence indicates infections caused by transferred strains, such a transfer mechanism is feasible.

References


