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SHORT COMMUNICATION

Ciprofloxacin Treatment of Urinary Infections Results in Increased Resistance of Urinary *E. coli* to Ciprofloxacin and Co-trimoxazole

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Abstract

Between 2000 and 2006 the sum of ciprofloxacin and folic acid antagonists prescriptions to Bavarian (South-eastern Germany) outpatients stayed constant. However, prescription numbers of ciprofloxacin increased while those of folic acid antagonists decreased suggesting an apparent shift in the treatment of urinary infections toward ciprofloxacin. During the observation period the proportion of *E. coli* resistant against ciprofloxacin increased from 5% to 10% while that against co-trimoxazole increased from 21% to 27%. The proportion of *E. coli* simultaneously exhibiting resistance to ciprofloxacin and co-trimoxazole increased from 3.9% to 8.5%. A leading influence of ciprofloxacin application for these developments is discussed.

Key words: *E. coli*, antibiotic prescription, ciprofloxacin, co-trimoxazole, urinary infection

E. coli is the most common pathogen of urinary tract infections of outpatients. Ciprofloxacin and co-trimoxazole (trimethoprim and sulfamethoxazole) are often used for the treatment of these infections. It is common knowledge that increased use of antibiotics results in increased resistances of bacterial pathogens. This study focuses on alterations in the strategies for the antibiotic treatment of urinary infections in Bavaria (South-East Germany) and their effect on antibiotic resistance patterns. Our laboratory performs microbiological diagnostic services for more than 2000 ambulatory physicians, covering more than 10% of Bavaria. Also, the composition of physicians defined by their respective fields of specialisation throughout Bavaria is well reflected by our customers (Borgmann *et al.*, 2009). Here we use this platform for assessing microbiological trends in the treatment of urinary infections caused by *E. coli.*

From 2000 to 2006 the number of urinary *E. coli* findings increased by 22.7% (5,136 to 6,300). Seasonal variations indicated by the number of *E. coli* isolated per month were not observed (data not shown). As demonstrated in Fig. 1A prescription numbers of folic acid antagonists decreased while those of ciprofloxacin markedly increased between 2000 and 2006. On the other hand, the sum of these antibiotics remained rather constant suggesting ciprofloxacin replaced folic acid antagonists for the treatment of urinary infections as described earlier (Huang and Stafford 2002).

As shown in Fig. 1B the percentage of ciprofloxacin resistant *E. coli* increased from 5% to 10% within the observation period. However, these numbers of ciprofloxacin resistances were still lower than the average for Germany (Kresken and Straube 2008). Apparently, the low percentage of resistance development parallels the low antibiotic prescription numbers in Bavaria compared to other German regions (Kern and Schröder 2008). On the other hand, a strong positive correlation between ciprofloxacin usage and resistance resulted comparing annual ciprofloxacin prescriptions to relative proportions of ciprofloxacin resistant *E. coli* (Bravais-Pearson's product moment correlation coefficient $r = 0.97$, $p < 0.01$). A likewise association of co-trimoxazole consumption and formation of resistance has been described earlier (Livermore *et al.*, 2000). Surprisingly, in the present study the proportion

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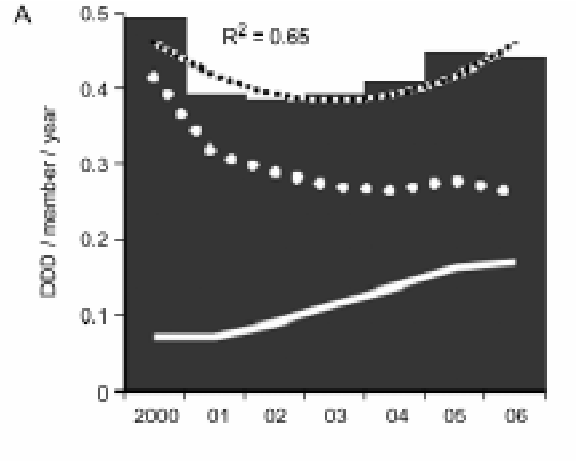

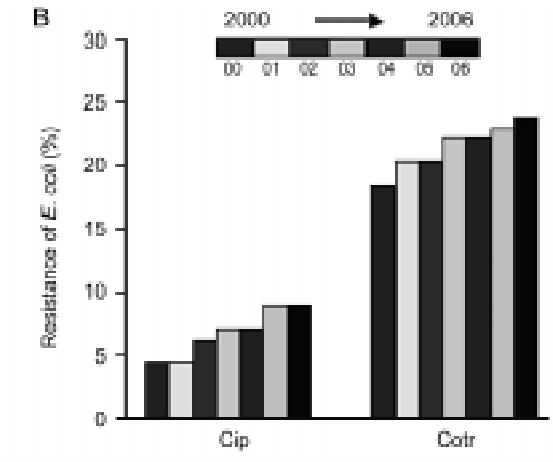

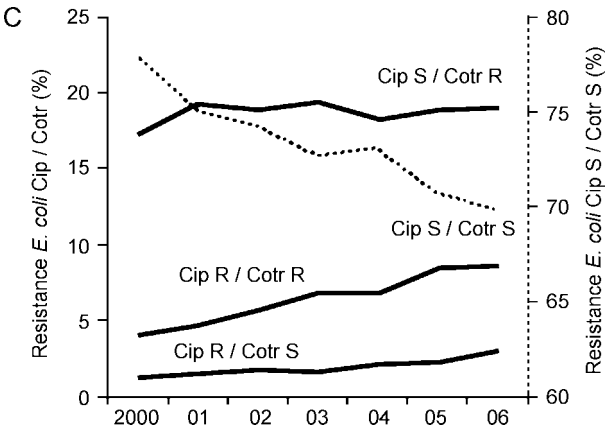

Fig. 1. Antibiotic prescriptions and resistances of urinary *E. coli*.

A: Defined daily dosages of prescribed ciprofloxacin (ATC code J01MA02) and of combinations of sulfonamides and trimethoprim including derivatives (folic acid antagonists; J01EE). Given are prescription numbers per year. Dark grey bars: Sum of folic acid antagonists and ciprofloxacin. White line: Ciprofloxacin. Dotted white line: Folic acid antagonists. Dotted black line: Best fit of the course of the sum of both. Prescription numbers in Bavaria were obtained as described recently (Borgmann et al. 2009).

B: Percentage of *E. coli* exhibiting resistance to ciprofloxacin and co-trimoxazole per year. Antibiotic resistance data of *E. coli* were obtained from the results of routine examinations of urinary samples from outpatients. Numbers of *E. coli* in urinary samples and proportions of antibiotic resistant *E. coli* were calculated as described recently (Borgmann et al. 2009). Antibiotic susceptibility tests were performed according to CLSI standard.

C: Percentage of *E. coli* exhibiting cross-resistance to ciprofloxacin and co-trimoxazole per year. Cip = ciprofloxacin, Cotr = co-trimoxazole, S = susceptible, R = resistant.

of co-trimoxazole resistant *E. coli* increased although prescription numbers of folic acid antagonists indeed decreased resulting in a negative correlation of folic acid antagonist consumption and co-trimoxazole resistance per year ($r = -0.84$, $p = 0.01$). Moreover, a strong positive correlation was noticed when comparing ciprofloxacin usage to the proportion of co-trimoxazole resistant *E. coli* per year ($r = 0.94$, $p < 0.01$) suggesting that resistance to co-trimoxazole might have been induced by ciprofloxacin treatment. Interestingly, a similar association has previously been observed in *E. coli* isolated from patients in Swedish hospitals (Farra *et al.*, 2002).

Based on this surprising result we took a step further and examined the cross-resistances of both antibiotics. Almost consequently we noticed a prominent increase of *E. coli* showing resistance to both antibiotics (Fig. 1C). Again, this leads to the conclusion that increased usage of ciprofloxacin resulted in the formation of *E. coli* simultaneously exhibiting cross-resistance to ciprofloxacin and folic acids antagonists. Similar developments have been described for North America (Karlowsky *et al.*, 2006) and various European countries (Kahlmeter and Menday 2003).

As a direct result in 2006 only 68.9% of co-trimoxazole resistant urinary *E. coli* were susceptible to ciprofloxacin while in 2000 there were 81.4%. On the other hand, in 2000 only 21.8% of ciprofloxacin resistant *E. coli* were susceptible to co-trimoxazole and this proportion remained low in 2006 (25.3%). Since more than 97% of *E. coli* isolates were susceptible to cefaclor (data not shown) treatment with cephalosporins gives hope for an effective alternative treatment.

In summary we show that in Bavaria ciprofloxacin is increasingly used for treatment of urinary infections of outpatients. This development resulted in a marked increase of *E. coli* exhibiting resistances to co-trimoxazole and to a combination of ciprofloxacin plus co-trimoxazole altogether.

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