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Five-Year Survey of Changing Patterns of Susceptibility of Bacterial Uropathogens to Trimethoprim-Sulfamethoxazole and Other Antimicrobial Agents

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We analyzed the antibiotic susceptibility of 5,348 urinary isolates of *Escherichia coli*, "*Klebsiella aerogenes*," and *Proteus mirabilis* grown in three laboratories from 1980 to 1985. A continuous rise in resistance to trimethoprim-sulfamethoxazole was observed; 63% of the strains from inpatients in 1984 and 51% of those from outpatients in 1985 were resistant to this drug. Isolates from outpatients in 1985 were mostly susceptible to nitrofurantoin (mean susceptibility, 92%) and to oral cephalosporins (mean susceptibility, 84%). As for isolates from inpatients, none of the antimicrobial agents now used was satisfactory for initial chemotherapy, indicating a need for new antibacterial strategies.

With the introduction of trimethoprim-sulfamethoxazole (TMP-SMX), which acts synergistically on bacterial folic acid synthesis (2, 7), it was believed that the development of resistance among bacterial species susceptible to the combination was highly unlikely, because it would require two independent mutational events (14). The same speculation also applied to the acquisition of plasmid-mediated resistance (13). During the last 15 years, TMP-SMX has been regarded as the first-line drug for the curative and prophylactic management of patients with urinary tract infection (UTI; 6, 15, 18, 19), and indeed it has been the initial therapeutic agent in over 91% of our patients. However, by 1972 Lacey et al. (9) had already found a 2.5% incidence of resistance to TMP among urinary bacterial isolates, and later Freuensgaard and Korner (5) and Huovinen and Toivanen (8) reported increasing resistance, up to 30.1%, to TMP or TMP-SMX. In 1982, Murray et al. (14) reported a high incidence of resistance to TMP-SMX among fecal enterobacteria, particularly *Escherichia coli* strains isolated during a diarrhea prevention study.

In view of these data and with our clinical impression that the rate of urinary bacterial isolates resistant to TMP-SMX is gradually increasing, this study was conducted to try to answer the following questions. (i) What changes have occurred over the last 5 years in bacterial susceptibility to antimicrobial agents routinely used for the treatment of UTI, and (ii) what is the current drug(s) of choice for the treatment of patients with UTI?

Data were collected from three bacteriological laboratories in the city of Haifa: Ezra Central Laboratory (laboratory A), which serves exclusively outpatient clinics; Haifa Medical Center (Rothschild) (laboratory B), which provides services almost only to hospitalized patients, including two departments of geriatric rehabilitation; and Rambam Medical Center (laboratory C), which serves both inpatients and outpatients and the Military Medical Corps.

E. coli, "*Klebsiella aerogenes*," and *Proteus mirabilis* strains constituted 88% of urinary isolates in laboratory A and 76 and 69% of isolates in laboratories B and C, respectively. The organisms were tested for susceptibility to TMP-SMX, ampicillin, cephalosporins, and nitrofurantoin during the whole period and were also tested for susceptibility to gentamicin in 1984. *Pseudomonas aeruginosa* and other bacteria isolated mainly in laboratories B and C from hospitalized patients with complicated UTI were examined for susceptibility to gentamicin, in view of their already well-recognized high resistance to TMP-SMX, ampicillin, and nitrofurantoin (4, 6, 8, 18).

Antimicrobial susceptibility was assessed by the disk diffusion technique with commercially obtained disks according to National Committee for Clinical Laboratory Standards performance standards (14a). The recommended media and standard control strains were used by all three laboratories. Quality control test results remained within a similar zone diameter range throughout the study. The zone diameter interpretative standards for resistance to TMP-SMX, ampicillin, cephalothin, nitrofurantoin, and gentamicin were, respectively, ≤10, ≤11, ≤14, ≤14, and ≤12 mm. Otherwise, the organism was designated as being susceptible to the antimicrobial agent tested.

The bacteriological findings and the rates of bacterial susceptibility to antimicrobial agents are shown in Tables 1 and 2.

A total of 5,348 *E. coli*, "*K. aerogenes*," and *P. mirabilis* isolates were examined. In all three laboratories, a gradual increase in bacterial resistance to TMP-SMX was observed. The trend toward development of *E. coli* resistance to TMP-SMX in the outpatient laboratory (laboratory A) lagged behind that of the two medical centers (laboratories B and C) by about 1 year; the incidence of resistant *E. coli* was 56 and 48% in laboratories B and C in 1984 and 52% in laboratory A in 1985.

Bacterial resistance to ampicillin in laboratories B and C was already high for all three bacteria in 1980 and remained more or less the same during 1982 and 1984. In laboratory A, the rates of ampicillin resistance observed in 1985 were similar to those observed among inpatients.

No significant changes in bacterial susceptibility to cephalosporins and nitrofurantoin were noted over the period studied. For cephalosporins, susceptibility rates were better

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TABLE 1. Number and distribution of 5,348 urinary isolates

Organism	No. (%) of isolates from the following laboratory in the indicated year:								
	A (Ezra Central)			B (Haifa Medical Center)			C (Rambam Medical Center)		
	1981	1984	1985	1980	1982	1984	1980	1982	1984
Escherichia coli	461 (82.2)	671 (84.2)	453 (82.2)	231 (49.1)	211 (51.1)	195 (50.3)	355 (51.8)	440 (53.5)	404 (60.6)
"*Klebsiella aerogenes*"	41 (7.3)	58 (7.3)	66 (12.0)	148 (31.5)	134 (32.4)	122 (31.4)	193 (28.2)	223 (27.1)	153 (22.9)
Proteus mirabilis	59 (10.5)	68 (8.5)	32 (5.8)	91 (19.4)	68 (16.5)	71 (18.3)	137 (20.0)	160 (19.4)	110 (16.5)

in strains from outpatients than in strains from inpatients: 86% of *E. coli* isolates from outpatients in 1985 versus 66 and 75% from inpatient isolates in 1984. For nitrofurantoin, the susceptibility rates of *E. coli* were similar in all three laboratories over the whole period (89 to 99%). For "*K. aerogenes*" and *P. mirabilis*, susceptibility to nitrofurantoin was found to be satisfactory in laboratories A and C but low in laboratory B.

Bacterial susceptibility to gentamicin was studied in 1984 in laboratories B and C. The susceptibility rates of *E. coli* were 90.5 and 91%, the susceptibility rates of *P. mirabilis* were 81 and 83%, and the susceptibility rates of "*K. aerogenes*" were 86 and 85%; for all three organisms combined, the susceptibility rates were 85 and 84% in laboratories B and C, respectively. In 1984, susceptibilities to gentamicin were also examined in 244 isolates of *P. aeruginosa*, *Enterobacter aerogenes*, *Staphylococcus epidermidis*, *Streptococcus faecalis*, and others at laboratories B and C and were found to be 68 and 61%, respectively.

Our study showed a progressive increase in the incidence of resistance of the common bacterial uropathogens to TMP-SMX, from 46% (in 1980) to 63% (in 1984) in isolates obtained from inpatients and from 27% (in 1981) to 51% (in 1985) in those obtained from outpatients (Table 2). This trend can also be discerned from reports published during the last 15 years showing a 2.5% incidence of resistance to TMP in urine bacterial isolates, in 1972 (9), 13.2%, in 1977 (11), and 20.3 to 39.8%, in 1980 (8). Such rates of resistance toward TMP-SMX were also found (8). As observed also by others (1, 4, 8), we found that bacteria isolated from inpatients generally showed a higher incidence of resistance as compared with those isolated at the same time from outpatients. In our series, it sometimes took only 1 year for *E. coli* strains isolated from outpatients to gain the same degree of resistance to TMP-SMX as isolates from inpatients (Table 2). Such a rapid decline in bacterial susceptibility to TMP-SMX might be partly the result of the popularity and promiscuous use of the medication (4, 11, 16, 18).

The choice of antimicrobial agent for the initial treatment of uncomplicated UTIs in outpatients should be derived from knowledge of the antimicrobial susceptibility status of *E. coli*, "*K. aerogenes*," and *P. mirabilis*, which are responsible for most of the infections in this population (8, 20). Practically, it can rely on the antibiotic susceptibility of *E. coli* alone, because this organism constitutes 82.2 to 84.2% of the common uropathogens isolated from outpatients (Table 1), and the combined mean antimicrobial susceptibility of all three common uropathogens thus mostly conforms with that of *E. coli* alone (Table 2). According to our data, among the commonly administered antimicrobial agents, nitrofurantoin appears to be the best choice, with 92% of *E. coli* strains being susceptible to this drug. Second best would be oral cephalosporins, to which 84% of the *E. coli* strains were susceptible (Table 2). On the other hand, susceptibility to

TABLE 2. Susceptibility rates of 5,348 urinary isolates

Organism(s) and antimicrobial agent	Susceptibility rate (%) for isolates from the following laboratory in the indicated year:								
	A (Ezra Central)			B (Haifa Medical Center)			C (Rambam Medical Center)		
	1981	1984	1985	1980	1982	1984	1980	1982	1984
Escherichia coli									
TMP-SMX	75	55	48	75	67	44	79	67	52
Ampicillin	51	43	28	42	45	38	39	48	36
Cephalosporins			86	68	65	66	87	83	75
Nitrofurantoin	99	93	93			89	97	99	96
"*Klebsiella aerogenes*"									
TMP-SMX	62	69	50	31	28	24	68	45	31
Ampicillin	38	36	50	15	13	5	10	26	5
Cephalosporins			100	37	48	41	75	67	60
Nitrofurantoin	87	91	100			62	96	93	96
Proteus mirabilis									
TMP-SMX	60	44	50	38	35	40	60	58	47
Ampicillin	37	26	22	26	38	29	30	34	30
Cephalosporins			64	22	27	31	60	56	57
Nitrofurantoin	88	70	77			21	93	93	93
All									
TMP-SMX	73	55	49	54	49	37	72	61	46
Ampicillin	50	41	29	30	33	26	29	34	28
Cephalosporins			84	49	53	52	78	73	68
Nitrofurantoin	98	91	92			69	95	96	96

cephalosporins was low among the isolates from inpatients, and a further decrease in susceptibility to these drugs is also soon to be expected among isolates from outpatients.

With regard to isolates from inpatients, all three organisms exhibited high or moderate resistance to all four antimicrobial agents tested; only *E. coli* showed good susceptibility to nitrofurantoin. The combined susceptibility of *E. coli*, "*K. aerogenes*," and *P. mirabilis* to gentamicin was 84 to 85%. However, in hospitalized patients with complicated urinary conditions, infections are frequently caused by other bacteria, such as *P. aeruginosa*, *E. aerogenes*, *S. epidermidis*, and *S. faecalis*, whose susceptibility to gentamicin in our series was only 61 to 68%. Gentamicin alone thus would not be sufficient as the initial treatment for inpatients with UTI, and a combination of drugs is necessary. According to our data, the best such combination is gentamicin and cephalosporins, although a continuous and unrestricted use of these medications would increase the incidence of resistant strains, whereas a temporary reduction in the use of gentamicin may reduce the rate of bacterial resistance to the drug (10, 17). There appears to be a need to introduce new modes of therapy for UTIs, e.g., amoxicillin-clavulanic acid in outpatients (3, 12) and broad-spectrum cephalosporins, new aminoglycosides, and extended-spectrum ureido penicillins in inpatients and subjects with complicated infections (10, 15, 17).

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