N^7-guanine levels in urine as a biomarker in experimental rat models and humans. *Environ Health Perspect* (in press).
10. Groopman JD, Trudel LJ, Donahue PR, Marshak-Rothstein A, Wogan GN. High-affinity monoclonal antibodies for aflatoxins and their application to solid phase immunoassays. *Proc Natl Acad Sci USA* 1984; **81:** 7728–31.
11. Groopman JD, Donahue PR, Zhu J, Chen J, Wogan GN. Aflatoxin metabolism in humans: detection of metabolites and nucleic acid adducts in urine by affinity chromatography. *Proc Natl Acad Sci USA* 1985; **82:** 6492–96.
12. Li J, Liu B, Li G, et al, eds. Atlas of cancer mortality in People's Republic of China. Shanghai: China Map Press, 1979: 39–46.
13. Parkin DM, Stjernsward J, Muir CS. Estimates of the worldwide frequency of twelve major cancers. *Bull WHO* 1984; **62:** 163–82.
14. Muir C, Waterhouse J, Mack T, Powell J, Whelan S, eds. Cancer in five continents, vol 5. Lyon: International Agency for Research on Cancer, 1987.
15. Breslow NE, Day NE. Statistical methods in cancer research, vol 1. Lyon: International Agency for Research on Cancer, 1980.
16. International Agency for Research on Cancer. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: aflatoxins (suppl 7). Lyon: International Agency for Research on Cancer, 1987: 83–87.
17. Campbell TC, Chen J, Liu C, Li J, Parpia B. Nonassociation of aflatoxin with primary liver cancer in a cross-sectional ecological survey in the People's Republic of China. *Cancer Res* 1990; **50:** 6882–93.
18. Campbell TC, Parpia B, Chen J, Liu C, Li J. Letter to the editor. *Cancer Res* 1991; **51:** 3826–27.
19. Yeh F-S, Yu MC, Mo C-C, Luo S, Tong MJ, Henderson BE. Hepatitis B virus, aflatoxins, and hepatocellular carcinoma in southern Guangxi, China. *Cancer Res* 1989; **49:** 2506–09.
20. Alpert ME, Hutt MSR, Wogan GN, Davidson CS. Association between aflatoxin content of food and hepatoma frequency in Uganda. *Cancer* 1971; **28:** 253–60.
21. Bulatao-Jayme J, Almero EM, Castro MCA, Jardeleza MTR, Salamat LA. A case-control dietary study of primary liver cancer risk from aflatoxin exposure. *Int J Epidemiol* 1982; **11:** 112–19.
22. Lam KC, Yu MC, Leung JWC, Henderson BE. Hepatitis B virus and cigarette smoking—risk factors for hepatocellular carcinoma in Hong Kong. *Cancer Res* 1982; **42:** 5246–48.
23. World Health Organisation Scientific Group. Prevention of primary liver cancer. *Lancet* 1983; i: 463.
24. Yu MC, Tong MJ, Govindarajan S, Henderson BE. Nonviral risk factors for hepatocellular carcinoma in a low-risk population, the non-Asians of Los Angeles County, California. *J Natl Cancer Inst* 1991; **83:** 1820–26.
25. Groopman JD, Sabbioni G, Wild CP. Molecular dosimetry of human aflatoxin exposures. In: Groopman JD, Skipper PL, eds. Molecular dosimetry in human cancer: epidemiological analytical and social considerations. Boca Raton: CRC Press, 1991: 303–24.

Prophylactic ciprofloxacin for catheter-associated urinary-tract infection

ELSKEN VAN DER WALL ROEL P. VERKOOYEN
JOKE MINTJES-DE GROOT JOKE OOSTINGA
ARIE VAN DIJK WILLEM N. M. HUSTINX HENRI A. VERBRUGH

Patients receiving antibiotics during bladder drainage have a lower incidence of urinary-tract infections compared with similar patients not on antibiotics. However, antibiotic prophylaxis in patients with a urinary catheter is opposed because of the fear of inducing resistant bacterial strains. We have done a double-blind, placebo-controlled trial of prophylactic ciprofloxacin in selected groups of surgical patients who had postoperative bladder drainage scheduled to last for 3 to 14 days. Patients were randomly assigned to receive placebo (n = 61), 250 mg ciprofloxacin per day (n = 59), or 500 mg ciprofloxacin twice daily (n = 64) from postoperative day 2 until catheter removal.

75% of placebo patients were bacteriuric at catheter removal compared with 16% of ciprofloxacin-treated patients (relative risk [RR] [95% CI] 4·7 [3·0–7·4]). The prevalence of pyuria among placebo patients increased from 11% to 42% while the catheter was in place; by contrast, the rate of pyuria was 11% or less in patients receiving ciprofloxacin (RR 4·0 [2·1–7·3]). 20% of placebo patients had symptomatic urinary-tract infections, including 3 with septicaemia, compared with 5% of the ciprofloxacin groups (RR 4·0 [1·6–10·2]). Bacteria isolated from urines of placebo patients at catheter removal were mostly species of enterobacteriaceae (37%), staphylococci (26%), and *Entercoccus faecalis* (20%), whereas species isolated from urines of ciprofloxacin patients were virtually all gram-positive. Ciprofloxacin-resistant mutants of normally sensitive gram-negative bacteria were not observed.

Ciprofloxacin prophylaxis is effective and safe in the prevention of catheter-associated urinary tract infection and related morbidity in selected groups of patients requiring 3 to 14 days of bladder drainage.

Lancet 1992; **339:** 946–51.

Introduction

Urinary-tract infection is the most common type of hospital-acquired infection, accounting for more than 30% of all cases.[1] Presence of a urinary catheter is an important risk factor for acquisition of nosocomial urinary-tract infection.[2-6] Of the measures that have been proposed to reduce the incidence of catheter-associated urinary-tract infection only the sterile closed drainage system has gained wide acceptance.[7,8] Even with a closed drainage system the risk of urinary-tract infection remains high at an estimated 5–10% for each day the catheter is in place.[2,9]

ADDRESSES: **Departments of Medical Microbiology** (H. A Verbrugh, MD, R. P. Verkooyen Bsc), **Medicine** (E van der Wall, MD, W N. M. Hustinx MD), **and Hospital Pharmacy** (J. Oostinga, Pharm D), **Diakonessen Hospital, Utrecht; and Departments of Hospital Hygiene** (J. Mintjes-De Groot, RN, H. A. Verbrugh) **and Hospital Pharmacy** (A. van Dijk, Pharm D), **Oudenrijn Hospital, Utrecht, Netherlands.** Correspondence to Dr H. A. Verbrugh, Department of Medical Microbiology, Diakonessen Hospital, 1 Bosboomstraat, 3182 KE, Utrecht, Netherlands

Patients taking antibiotics while they have a catheter in place have a much lower incidence of urinary-tract infection compared with similar patients not receiving antimicrobial agents.[6,7,10-12] However, the prophylactic use of antibiotics during bladder drainage remains controversial. Antibiotic prophylaxis is opposed because of the fear of induction and subsequent spread of resistant bacterial strains that may cause serious infections.[2,3,13,14] This objection must be carefully balanced against the potential benefits of prophylaxis. We have therefore done a prospective study that compares the benefits and hazards of prophylactic ciprofloxacin versus placebo in patients requiring temporary bladder drainage following surgery.

Patients and methods

Study design

Patients were enrolled from those admitted to two acute-care general hospitals (Diakonessen Hospital and Oudenrijn Hospital) in Utrecht, Netherlands, for vaginal repair, total hip replacement, or colorectal surgery (in Oudenrijn Hospital, only patients admitted for vaginal repair participated). In these patients, bladder drainage for more than 2 days but less than 14 days was planned. The pattern of use of indwelling urinary catheters in the two hospitals was known from an earlier survey.[11]

Patients were eligible for enrolment if they were at least 18 years old and had given informed consent. Exclusion criteria were pregnancy, impaired renal or hepatic function (serum creatinine >150 mmol/l, serum transaminases >75 IU/l, respectively), symptomatic urinary-tract infection, fever, or antibiotic use. If antibiotics had been stopped at least 48 h before the study drug was given patients were not excluded. Similarly, 24 h perioperative antibiotic prophylaxis with cefotetan (single preoperative intravenous dose of 2 g), amoxycillin/clavulanic acid (single preoperative intravenous dose of 1·2 g), lincomycin (three doses of 600 mg starting preoperatively), or cephalothin (1 g every 6 h starting preoperatively) did not lead to exclusion. Patients were randomly assigned to receive either placebo or 250 mg once daily or 500 mg twice daily of ciprofloxacin. Medication was given from the second postoperative day until catheter removal. Randomisation was achieved with separate lists with permuted blocks of 12 random numbers for each of the two hospitals and for each hospital service (gynaecology, surgery, orthopaedics) participating in the study. Assignment to one of the study groups was done with these lists by the hospital pharmacy at the time of drug delivery to the wards. Patients and the doctors and nurses involved in their care were all unaware of the nature of the medication being given. All tablets were identical and contained either 250 mg ciprofloxacin or no active drug. Patients received two doses of two tablets per day; thus, patients assigned to the lower dose of ciprofloxacin received one tablet of drug and three of placebo per day. Ciprofloxacin and placebo tablets were provided by Bayer AG (Leverkusen, Germany) and were individually wrapped in identical blister packs by an independent pharmacy.

Clinical and laboratory assessments

The past medical history, Apache II score, and any drugs being taken were recorded for each patient at enrolment. Patients were visited daily by an investigator to record the occurrence of infectious morbidity and adverse events. Hospital-acquired infections were defined according to recognised criteria.[15] Febrile illness was defined as two successive episodes at least 6 h apart during which the patient's temperature exceeded 38°C, excluding episodes within 48 h of surgery. Adverse events were assessed by interview and, if present, classified as possibly study drug-related or not. Daily visits continued until the patient was discharged from hospital.

Specimens of urine were taken for quantitative culture within 24 h of insertion of the catheter, just before its removal, and if requested by the treating physicians. A clean-catch urine sample was obtained at six-weeks' follow-up. Significant bacteriuria was defined as $\geq 10^3$ colony-forming units (cfu)/ml of catheter urine or $\geq 10^5$ cfu/ml clean-catch urine.[16] All microorganisms were identified to at least the genus level. All coagulase-negative staphylococci were considered to be *Staphylococcus epidermidis*. A minimum inhibitory concentration (MIC) of ≤ 2 mg/l ciprofloxacin denoted sensitivity of a bacterial strain. Multiple resistance was defined as resistance to at least ampicillin, cefamandole, and one of the aminoglycoside antibiotics. Urine containing more than 8 leucocytes/μl by a standardised sedimentation technique was considered pyuric. To monitor the effects of study drug on aerobic faecal flora, faecal specimens for quantitative culture were obtained at the same time as urine specimens from 41 consecutively randomised patients admitted for gynaecological or orthopaedic procedures to the Diakonessen Hospital. Quantitative culture of faeces was done by serial dilutions. Only the predominant isolates—ie, those present at the highest dilution—were speciated and counted.

Blood samples were taken before surgery and on the day of catheter removal for measurement of total and differential leucocyte count, haemoglobin, packed cell volume, erythrocyte sedimentation rate, bilirubin, liver transaminases, and creatinine. If abnormal values were found, a third blood sample was obtained at six-weeks' follow-up.

About six weeks after discharge, patients were seen in the outpatient clinic and checked for symptoms of urinary-tract

TABLE I—INTENTION-TO-TREAT ANALYSIS OF RANDOMISED PATIENTS ACCORDING TO PROPHYLACTIC REGIMEN

Characteristic	Prophylaxis with: Placebo (n=68)	Ciprofloxacin 250 mg/day (n=66)	Ciprofloxacin 1000 mg/day (n=68)
Age (yr)			
Median (range)	65 (31–90)	68 (31–91)	64 (39–90)
Female/male	64/4	60/6	64/4
No (%) with surgical procedure:			
Burch or MMK*	28 (41·1)	21 (31·8)	23 (33·8)
Anterior colporraphy	17 (25·0)	20 (30·3)	22 (32·4)
Total hip replacement	18 (26 5)	17 (25·8)	17 (25·0)
Colorectal surgery	4 (5·9)	7 (10·6)	6 (8·8)
No surgery	1 (1·5)	1 (1·5)	0
Bladder drainage			
Suprapubic/urethral	17/51	16/50	12/56
Median no days	7·5	7·0	7 0
No (%) with adverse outcome:			
Infectious morbidity	16 (23·5)†	5 (7·6)	5 (7·4)
Side-effects	2 (2 9)	1 (1·6)	2 (2·9)

*Burch or Marshall-Marchetti-Krantz retropubic urethral suspension
†RR (95% CI) *vs* 250 mg ciprofloxacin group=3·1 (1 2–8 0), *vs* 1000 mg ciprofloxacin group=3 2 (1 2–8 2)

TABLE II—CHARACTERISTICS OF 184 EVALUABLE PATIENTS ACCORDING TO PROPHYLACTIC REGIMEN

Characteristic	Prophylaxis with: Placebo (n=61)	Ciprofloxacin 250 mg/day (n=59)	Ciprofloxacin 1000 mg/day (n=64)
Age (yr)			
Median (range)	63 (31–90)	67 (31–91)	65 (39–90)
Female/male	58/3	54/5	60/4
No (%) with surgical procedure:			
Burch or MMK*	28 (45·9)	21 (35·6)	21 (32·8)
Anterior colporraphy	15 (24·6)	19 32·2)	21 (32·8)
Total hip replacement	14 (22·9)	12 (20·3)	16 (25·0)
Colorectal surgery	4 (6·6)	7 (11·9)	6 (9·4)
Bladder drainage			
Suprapubic/urethral	17/44	16/43	11/53
Median (range) days	8·0 (3–16)	7·0 (3–18)	7·0 (3–15)
Follow-up days			
Median (range)	46·0 (18–70)	45·5 (19–102)	45·0 (13–80)

*Burch or Marshall-Marchetti-Krantz retropubic urethral suspension.

infection. They were asked to bring a clean-catch midstream urine specimen and complete a questionnaire dealing with the post-discharge frequency of urination, dysuria, fever, and use of antibiotics. An investigator visited patients who were unable to come to the outpatient clinic at home and collected specimens.

Surveillance of nosocomial infections

The incidence of hospital-acquired infections in the two hospitals has been under constant surveillance since January, 1984. Surveillance is done by methods modified from those of Wenzel et al[17] through weekly visits to each ward by the infection-control nurse.

Statistical analysis

Statistical analysis of numerical data was done with SPSS software (version 3.1, SPSS Inc, Chicago, USA). Variables such as age, number of days catheter in place, number of ciprofloxacin doses, Apache II score, and follow-up days were compared with median tests. The mean and range were also determined for these variables. Univariate analysis by the chi-squared test was used to assess differences in the occurrence of bacteriuria, pyuria, infectious morbidity, and adverse events. The magnitude of differences was estimated by relative risk (RR) with 95% confidence intervals (CI). Fisher's test and Student's *t* test were used to determine the influence of the study medication on laboratory variables. The influence on infectious outcome of age, sex, hospital, type of surgery, type of catheter, and duration of catheter insertion was assessed by stepwise logistical regression analysis.

Results

Between December 1, 1988, and June 1, 1990, 142 patients in Diakonessen Hospital and 60 patients in Oudenrijn Hospital were enrolled in the study. Table I shows the characteristics of all randomised patients and an intention-to-treat analysis of infectious morbidity and side-effects in each of the three study groups. Patients given placebo had a threefold increased risk of infectious morbidity, but were in their other characteristics comparable to patients given active drug. 18 patients were excluded from further analysis because of protocol errors (16) or because they refused further participation (2). These patients were evenly distributed over the three study arms. Characteristics of the 184 evaluable patients are shown in table II. The placebo and two treatment groups were comparable in terms of age, gender, type of surgery, type of bladder drainage, duration catheter in place, and the number of follow-up days. The median Apache II score of all patients was 5 (range 0–9).

14 patients (4 placebo, 5 receiving 250 mg per day ciprofloxacin, and 5 receiving 1000 mg per day) were not evaluable for occurrence of bacteriuria and pyuria because a second specimen of catheter urine was not obtained at the time of catheter removal, usually because the patient had accidentally removed the catheter. Of the 170 patients evaluated, 11% or less in each group were bacteriuric at the time of catheter insertion. However, at catheter removal, 75% of placebo patients were bacteriuric ($\geq 10^3$ cfu/ml) compared with 19% of patients who received 250 mg per day ciprofloxacin and 14% who received 1000 mg per day (RR [95% CI] *vs* 250 mg = 4·1 [2·3–7·3] and *vs* 1000 mg = 5·6 [2·9–10·8]). Furthermore, a striking difference in urine colony count was seen at catheter removal: in 70% of patients receiving placebo the colony count was at least 10^5 cfu/ml, but only 7% of the group receiving 250 mg ciprofloxacin and 3% of those on 1000 mg had the same level of bacteriuria. Patients receiving placebo had a fourfold to fivefold greater risk of pyuria or bacteriuria at the time of catheter removal compared with all those receiving ciprofloxacin (table III).

TABLE III—EFFECT OF CIPROFLOXACIN ON PYURIA AND BACTERIURIA

Analysis of urine at catheter removal	Placebo (n = 57)	Ciprofloxacin (n = 113)	Relative risk (95% CI)
Pyuria			
No	33	101	4·0
Yes	24	12	(2·1–7·3)
Bacteriuria $\geq 10^3$ *cfu/ml*			
No	14	95	4·7
Yes	43	18	(3·0–7·4)
Bacteriuria $\geq 10^5$ *cfu/ml*			
No	17	107	13·2
Yes	40	6	(6·0–29·3)

14 patients were not evaluable at the time of catheter removal (see text)

Symptomatic infections or fever developed in 16 (26%) patients in the placebo group but in only 10 (8%) of those receiving ciprofloxacin. Urinary-tract infection accounted for 67% (12/18) of the episodes of infectious morbidity in the placebo group and surgical wound infections for 22% (4/18) of episodes. 2 patients in the placebo group had two separate infectious episodes. Therapeutic courses of antibiotics were given to placebo-group patients for surgical wound infections (2 patients), pneumonia (two courses in 1 patient), and for urinary-tract infection (8 patients of whom 3 were septicaemic). 4 patients receiving 250 mg ciprofloxacin had febrile episodes (1 urinary-tract infection, 2 wound infections, 1 fever of unknown origin), and 1 had a urinary-tract infection without fever. Only 2 patients on 250 mg ciprofloxacin received therapeutic antibiotics, both because of urinary-tract infection, of whom 1 had septicaemia that was associated with ciprofloxacin-resistant *S epidermidis* bacteriuria. No patients in the group given 1000 mg per day ciprofloxacin had febrile episodes ($p \leq 0{\cdot}023$ compared with placebo and 250 mg groups), although a phlebitis was seen in 1 patient and 4 had urinary-tract infection for which antibiotics were prescribed.

There was no relation between the onset of febrile morbidity and either the time of insertion or of removal of the bladder catheter; however, non-febrile morbidity usually occurred a few days before or within 1–4 days after catheter removal (data not shown). Patients receiving ciprofloxacin prophylaxis (both doses) had a fourfold lower risk of symptomatic urinary-tract infection compared with those on placebo (table IV), giving an absolute risk reduction of 15%. Clinically, this suggests that only 7 patients need to be given prophylaxis to prevent 1 from having infectious morbidity. The difference in infectious morbidity remained

TABLE IV—EFFECT OF CIPROFLOXACIN PROPHYLAXIS ON SYMPTOMATIC URINARY-TRACT INFECTIONS

Prophylaxis	Patients with symptomatic urinary-tract infection	Patients without symptomatic urinary-tract infection
Placebo (n = 61)	12	49
250 mg/day ciprofloxacin (n = 59)	2	57
1000 mg/day ciprofloxacin (n = 64)	4	60
250 mg or 1000 mg/day ciprofloxacin (n = 123)	6	117

RR (95% CI) for placebo *vs* 250 mg/day ciprofloxacin = 5·8 (1·4–24·8), *vs* 1000 mg/day ciprofloxacin = 3·2 (1·1–9·2), and *vs* 250 or 1000 mg/day ciprofloxacin = 4·0 (1·6–10·2)

TABLE V—NUMBER OF ISOLATES OF MICROORGANISMS IN URINE SPECIMENS ACCORDING TO PROPHYLACTIC REGIMEN

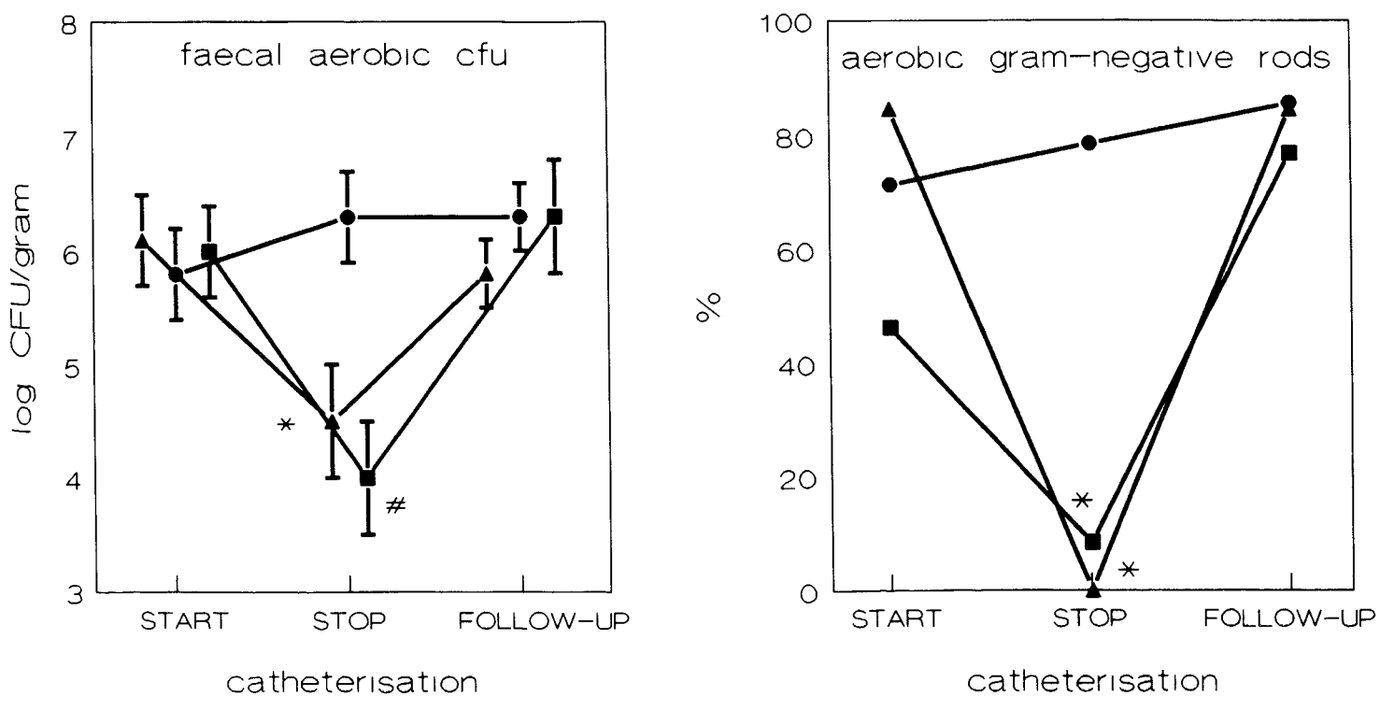
Microorganisms	Prophylaxis with:								
	Placebo			250 mg/day ciprofloxacin			1000 mg/day ciprofloxacin		
	After catheter insertion (n=57)	Before catheter removal (n=57)	Six-weeks' follow-up (n=54)	After catheter insertion (n=54)	Before catheter removal (n=54)	Six-weeks' follow-up (n=53)	After catheter insertion (n=59)	Before catheter removal (n=59)	Six-weeks' follow-up (n=58)
Enterobacteriaceae									
E coli	4	20	14	10	0	3	9	0	5
Other	0	6	6	0	0	1	2	0	6
Glucose-non-fermenting									
Pseudomonas sp	0	2	4	0	0	0	0	0	2
Other	0	1	3	0	0	3	0	0	4
Gram-positive bacteria									
Diphtheroids	1	1	7 (1)	0	1 (1)	9 (1)	0	0	10 (5)
S aureus	0	2	0	0	0	0	0	0	2
S epidermidis	0	16	8	3 (1)	6 (5)	14 (6)	2	5 (5)	22 (7)
E faecalis	1	14 (1)	4	2	2	6 (1)	1	0	9 (1)
Beta streptococcus	0	3 (2)	1	1	1	7 (2)	0	0	9
Other streptococci	0	1	1	0	0	4	0	0	6 (2)
Lactobacillus sp	0	2 (2)	0	0	0	1 (1)	0	0	2
Micrococcus luteus	0	0	0	0	0	1	0	0	0
Candida sp	1 (1)	2 (2)	3 (3)	1 (1)	3 (3)	0	1	5 (5)	0
Total isolates	7 (1)	70 (7)	51 (4)	17 (2)	13 (9)	49 (11)	15	10 (10)	77 (15)

Figures in parentheses are the number of isolates resistant to ciprofloxacin

highly significant when data were adjusted for age, sex, hospital, type of surgery, type of catheter, and duration catheter in place by stepwise logistical regression analysis. Placebo patients were more likely to need therapeutic antibiotics for symptomatic urinary-tract infection (RR 2·7, 95% CI 1·0–7·4).

3 patients on ciprofloxacin experienced moderate gastrointestinal symptoms, including nausea and vomiting, on the second day of prophylaxis, and medication was discontinued. These complaints resolved without further treatment. No other laboratory values were remarkable.

The effect of prophylaxis with ciprofloxacin on the distribution of bacterial species in patients' urine is shown in table V. At the time of catheter insertion, the number of isolates and their species distribution were comparable between the three study groups. The predominant species of bacteria found in urine samples from placebo patients at cather removal were *Escherichia coli* and other enterobacteriaceae (37% of all isolates), staphylococci (26%), and *Enterococcus faecalis* (20%); the total number of isolates increased tenfold during catheter insertion. By contrast, in patients taking ciprofloxacin the number of isolates from urines did not increase during catheter insertion and aerobic gram-negative rods were not found. The few culture-positive urines from ciprofloxacin-treated patients yielded, predominantly, *S epidermidis* and *Candida*



Effect of ciprofloxacin prophylaxis on aerobic faecal flora.

The total number of aerobic organisms per g faeces was transiently reduced by ciprofloxacin prophylaxis (left panel) Ciprofloxacin virtually eradicated aerobic gram-negative rods (right panel), an effect that was fully reversed at six-weeks' follow-up (% on y-axis = % of faecal samples with predominance of gram-negative rods). Patients received placebo (●), 250 mg ciprofloxacin (▲), or 1000 mg ciprofloxacin (■) daily while a catheter was in place.
*$p<0·0001$ and # $p<0·001$ compared with placebo.

species. At six-weeks' follow-up, gram-positive bacteria predominated in the urine of patients who had received ciprofloxacin, but ciprofloxacin-sensitive gram-negative bacteria were again cultured from the urine of these patients. Resistance to ciprofloxacin was not found among aerobic gram-negative bacteria cultured from urine. The aerobic gram-positive microorganisms cultured from urine samples at the end of ciprofloxacin prophylaxis were largely resistant to ciprofloxacin (table v). However, at six-weeks' follow-up, nearly 75% of isolates of gram-positive bacteria were sensitive to ciprofloxacin, indicating repopulation of the urinary tract with ciprofloxacin-sensitive organisms.

The effect of ciprofloxacin prophylaxis on the aerobic faecal flora manifested itself as a transient reduction in the number of all aerobic organisms, and as almost complete eradication of aerobic gram-negative rods (figure). Before prophylaxis, enterobacteriaceae or glucose-non-fermenting species were usually the predominant aerobic bacteria in faeces from all three groups of patients (between 59 and 82% of patients' samples). At the end of prophylaxis, no enterobacteriaceae and only a single ciprofloxacin-sensitive pseudomonas were isolated from the faeces of ciprofloxacin-treated patients. By contrast, at the same time, enterobacteriaceae species and aerobic glucose-non-fermenting gram-negative bacilli predominated in 79% and 5%, respectively, of faecal samples from placebo patients. Streptococci (usually α-haemolytic) were the predominant aerobic organisms in 63% or faecal samples from patients given 250 mg per day ciprofloxacin and in 54% of faecal samples from patients given 1000 mg per day ciprofloxacin. Yeasts predominated in the faeces of 13% of patients on 250 mg per day ciprofloxacin and 31% of those on 1000 mg per day, but were not found in faecal samples from placebo patients.

No ciprofloxacin-resistant enterobacteriaceae species emerged in the faecal flora as a consequence of antibiotic prophylaxis. At the time of catheter insertion, a ciprofloxacin-resistant *E faecalis* was found in the faeces of 1 patient in the ciprofloxacin-treated groups. After prophylaxis, 8 of 23 (35%) faecal isolates of aerobic gram-positive bacteria from ciprofloxacin-treated patients were resistant to ciprofloxacin. 1 ciprofloxacin-resistant strain of a β-haemolytic streptococcus (group D) was isolated from the faeces of a placebo patient after prophylaxis. The effect of ciprofloxacin on the aerobic faecal flora was fully reversed at six-weeks' follow-up: 1 ciprofloxacin-resistant *E faecalis* and 1 resistant strain of an α-haemolytic streptococcus were cultured from the faecal specimens of a placebo patient and a ciprofloxacin-treated patient, respectively.

Data for follow-up analysis were available from 164 patients. Patients were recorded as lost to follow-up if a completed questionnaire was not obtained. No episodes of dysuria were observed between catheter removal and discharge from hospital in patients that had received ciprofloxacin, but 2 patients in the placebo group complained about dysuria and urinary frequency. 1 of these patients received nitrofurantoin at discharge; the other was not given antibiotics and was readmitted within 4 days because of septicaemia. At six-weeks' follow-up dysuria, urinary frequency, and fever were reported by patients in each of the three study arms. Bacteriuria ($\geq 10^5$ cfu/ml) was more prevalent in the placebo group (28%) than in patients who had received 250 mg per day (13%) or 1000 mg per day (21%) ciprofloxacin. In addition, pyuria was more prevalent among placebo patients (24%) than among either the 250 mg (9%) or 1000 mg (7%) treatment groups, and placebo patients were more likely to have received therapeutic antibiotics between discharge and follow-up (22%, 13%, and 14%, respectively). Compared with all ciprofloxacin-treated patients, placebo patients were significantly more prone to bacteriuria (RR [95% CI] 1·7 [1·2–2·5]) and pyuria (RR 3·0 [1·4–6·5]) at follow-up, and to have had dysuria (RR 1·8 [1·0–3·2]) after discharge.

The overall incidence of hospital-acquired infections in 1988, before the start of this study, was about 5% in each hospital.[12] The rate of nosocomial infections, other than those found in the study groups, did not vary substantially during the trial. Importantly, multiple-antibiotic resistance did not emerge among aerobic gram-negative bacilli causing nosocomial infections in other patients admitted to the hospitals during the study.

Discussion

This study shows that postoperative catheter-associated urinary-tract infection in patients requiring temporary bladder drainage can be prevented with prophylactic ciprofloxacin. Prophylaxis with ciprofloxacin significantly reduced the incidence of bacteriuria and pyuria and gave a fourfold lower incidence of urinary-tract-associated infectious morbidity.

The sterile closed drainage system has been the only accepted measure thought to be effective in lowering the incidence of catheter-associated urinary-tract infection. This method was introduced after a non-comparative study in which 82% of patients received antibiotics at some stage during catheterisation,[7] and it was noted that patients given antimicrobial agents (mostly penicillin and streptomycin) had sterile urine for longer than those left untreated. Sterile closed drainage failed to prevent urinary-tract infection in patients with a catheter in place for 7 to 14 days unless they had also received antimicrobial therapy. Although the reduction in catheter-associated infections in patients given antibiotics was confirmed by other studies,[6,10,11] controlled prospective trials of antibiotic prophylaxis in selected groups of patients with a catheter did not produce unequivocal results.[5,18-22] Differences in prophylactic regimens, inclusion criteria, the number of days catheters were in place, and the definitions of significant bacteriuria do not allow comparison of these studies. Nevertheless, it appears that antimicrobial prophylaxis is of no value in patients with a catheter in place for more than 14 days.[4,5] However, most patients will have bladder drainage for less than 14 days,[7,11] and we found that 90% of patients in our institutions had bladder drainage for less than 14 days. Importantly, 68% of all hospital-acquired catheter-associated urinary-tract infections were recorded in patients with bladder drainage for 3 to 14 days.[11]

Antibiotic prophylaxis during temporary bladder drainage has been opposed on the grounds that multiple-antibiotic-resistant bacteria might emerge in hospitals leading to serious infections, and because of fear of a higher incidence of drug-related toxicity.[2,3,14] It has also been argued that catheter-associated urinary-tract infections are usually benign, they need treatment only when symptomatic, and are then easy to treat.[4,18] In addressing these objections, the selection of patient groups and the choice of antimicrobial agent for prophylaxis is of great importance. Based on the results of our previous survey,[11] we focused on surgical patients who were scheduled to have postoperative bladder drainage for 3 to 14 days. All patients

belonged to well-defined, easily identifiable groups that permitted selection in advance. Ciprofloxacin was chosen for prophylaxis because it is easy to administer, is well absorbed orally, is effective in the treatment of uncomplicated and complicated urinary-tract infection,[23] has been used prophylactically in patients with granulocytopenia with success,[24] and because it has few side-effects.[25]

Ciprofloxacin prophylaxis caused a complete but transient disappearance of enterobacteriaceae species and glucose-non-fermenting gram-negative bacilli from the faecal flora, confirming previous findings.[24,26] Eradication of the aerobic gram-negative gut flora may be an important determinant of ciprofloxacin's efficacy in preventing nosocomial infection since most urinary-tract infections are thought to be due to bacteria from the gut. At six-weeks' follow-up, bacteriuria and pyuria were less common in patients that had received ciprofloxacin than in placebo patients, indicating that the protective effect of ciprofloxacin may last for weeks after its discontinuation. Since dysuria was also prevented this long-lasting effect seems clinically relevant.

Development of resistance to ciprofloxacin among initially sensitive, clinically important bacteria is uncommon. Bacterial resistance to fluoroquinolones is mediated by chromosomal mutations altering DNA gyrase, which confer resistance to quinolones alone, or by changes in the permeability of the cell wall, which may prevent penetration of other antibiotics and thus confer cross-resistance.[27] Ciprofloxacin-resistant strains of enterobacteriaceae or glucose-non-fermenting gram-negative species were not observed in this study. Yet, ciprofloxacin-resistant aerobic gram-positive bacteria, mostly α-haemolytic streptococci and *S epidermidis*, were cultured from the faecal and urine samples of pateints given ciprofloxacin; ciprofloxacin-resistant *S aureus* was not found. Thus, ciprofloxacin prophylaxis altered the aerobic microflora of patients in favour of those species that are inherently less sensitive or completely resistant to fluoroquinolones, but did not lead to the emergence of resistant strains of species that are normally sensitive to fluoroquinolones. Surveillance of hospital-acquired infections showed that wards that took part in the study and other wards in our hospitals did not experience an increase in the frequency, or changes in the spectrum, of antibiotic-resistant organisms causing nosocomial infections.

We conclude that ciprofloxacin can be safely prescribed postoperatively to selected patients receiving bladder drainage; once daily doses of 250 mg are probably sufficient. Although we have not observed emergence of ciprofloxacin-resistant strains of aerobic gram-negative bacteria, we must caution against overinterpretation of our results. The use of other classes of antimicrobials (eg, β-lactams or sulphonamides) in this setting has been associated with failure of prophylaxis and emergence of resistance.[28] We believe that ciprofloxacin prophylaxis should be reserved for well-defined groups of patients that will have bladder drainage for more than 2 days but less than two or three weeks. Active surveillance of hospital-acquired infections, including monitoring for resistant nosocomial pathogens, is essential.

We thank Dr R. Andriesse, Dr M. A. V. M. Kroeks, Dr P. Leguit, Dr W. Derks, and Dr J. W. R. Nortier for their clinical support, and the nursing staff of the participating wards for their cooperation in this study.

This study was supported by the Diakonessen Hospital Research Foundation, and a clinical research grant from Bayer AG, Leverkussen, Germany.

REFERENCES

1. Centers of Disease Control: nosocomial infection surveillance, 1984. *Surveillance Summaries* 1986; **35:** 17SS–29SS.
2. Turck M, Stamm WE. Nosocomial infection of the urinary tract. *Am J Med* 1981; **70:** 651–54.
3. Kunin CM. Genitourinary infections in the patient at risk: extrinsic risk factors. *Am J Med* 1984; **73:** 130–39.
4. Shapiro M, Simchen E, Izraeli S, Sachs T. A multivariate analysis of risk factors for acquiring bacteriuria in patients with indwelling urinary catheters for longer than 24 hours. *Infect Control* 1984; **5:** 525–32.
5. Verbrugh HA, Mintjes-de Groot AJ, Andriesse R, Hamersma K, van Dijk A. Postoperative prophylaxis with norfloxacin in patients requiring bladder catheters. *Eur J Clin Microbiol Infect Dis* 1988; **7:** 490–94.
6. Platt R, Polk BF, Murdock B, Rosner B. Reduction of mortality associated with nosocomial urinary tract infection. *Lancet* 1983; i: 893–97.
7. Kunin CM, McCormack RC. Prevention of catheter-induced urinary tract infections by sterile closed drainage. *N Engl J Med* 1966; **274:** 1151–61.
8. Burke JP, Larsen RA, Stevens LE. Nosocomial bacteriuria: estimating the potential for prevention by closed sterile urinary drainage. *Infect Control* 1986; 7 (suppl): 96–99.
9. Martinez OV, Civetta JM, Anderson K, Roger S. Murtha M, Malinin TI. Bacteriuria in the catheterized surgical intensive care patient. *Crit Care Med* 1986; **14:** 188–91.
10. Givens CD, Wenzel RP. Catheter-associated urinary tract infections in surgical patients: a controlled study on the excess morbidity and costs. *J Urol* 1980; **124:** 646–48.
11. Hustinx WNM, Mintjes-de Groot AJ, Verkooyen RP, Verbrugh HA. Impact of concurrent antimicrobial therapy on catheter-associated urinary tract infection. *J Hosp Infect* 1991; **18:** 45–56.
12. Verbrugh HA, Mintjes-de Groot AJ, Verkooyen RP. Surveillance and prevention of hospital-acquired infections in a general hospital. *Ned Tijdschr Geneeskd* 1990; **134:** 490–95.
13. Mulhall AB, Chapman RG, Crow RA. Bacteriuria during indwelling urethral catheterisation. *J Hosp Infect* 1988; **11:** 253–62.
14. Petersdorf RG, Curtin JA, Hoeprich PD, Peeler RN, Bennett IL. A study of antibiotic prophylaxis in unconscious patients. *N Engl J Med* 1957; **21:** 1001–09.
15. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988; **16:** 128–40.
16. Platt R. Quantitative definition of bacteriuria. *Am J Med* 1983; **75:** 44–52.
17. Wenzel RP, Osterman CA, Hunting KJ, Gwaltney JM. Hospital-acquired infections. I: surveillance in a university hospital. *Am J Epidemiol* 1976; **103:** 251–60.
18. Polk BF, Trager IB, Shapiro M, Goren-White B, Goldstein P, Schoenbaum SC. Randomised clinical trial of perioperative cefazolin in preventing infection after hysterectomy. *Lancet* 1980; i: 437–41.
19. Jaffe R, Altaras M, Fejgin M, Ben-Aderet N. Prophylactic single-dose cotrimoxazole for prevention of urinary tract infection after abdominal hysterectomy. *Chemotherapy* 1985; **31:** 476–79.
20. Grabe M, Forsgren A, Bjork T, Hellsten S. Controlled trial of a short and a prolonged course with ciprofloxacin in patients undergoing transurethral prostatic surgery. *Eur J Clin Microbiol* 1987; **6:** 11–17.
21. Mountokalakis T, Skounakis M, Tselentis J. Short-term versus prolonged systemic antibiotic prophylaxis in patients treated with indwelling catheters. *J Urol* 1985; **134:** 506–08.
22. Little PJ, Pearson S, Peddie BA, Greenslade NF, Utley WLF. Amoxicillin in the prevention of catheter-induced urinary infection. *J Infect Dis* 1974; **129:** S241–42.
23. Sanders WE Jr. Efficacy, safety and potential economic benefits of oral ciprofloxacin in the treatment of infections. *Rev Infect Dis* 1988; **10:** 528–43.
24. Rozenberg-Arska M, Dekker AW, Verhoef J. Ciprofloxacin for selective decontamination of the alimentary tract in patients with acute leukaemia during remission induction treatment: the effect on faecal flora. *J Infect Dis* 1985; **152:** 104–07.
25. Ball P. Ciprofloxacin: an overview of adverse experiences. *J Antimicrob Chemother* 1986; **18** (suppl D): 187–93.
26. Brumfitt W, Franklin I, Grady D, Hamilton-Miller JMT, Iliffe A. Changes in the pharmacokinetics of ciprofloxacin and faecal flora during administration of a 7-day course to human volunteers. *Antimicrob Agents Chemother* 1984; **26:** 757–61.
27. Hooper DC, Wolfson JS, Ng EY, Swarts MN. Mechanisms of action and resistance to ciprofloxacin. *Am J Med* 1987; **82** (4A suppl): 12–20.
28. Macfarlane DE. Prevention and treatment of catheter-associated urinary tract infections. *J Hosp Infect* 1985; **10:** 96–100.