A prospective, controlled, randomized study of the effect of a slow-release silver device on the frequency of urinary tract infection in newly catheterized patients

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Objective To test the effect on urinary tract infections (UTIs) in patients needing continuous indwelling catheterization, of a newly designed urine-collecting system containing an antibacterial device which slowly releases silver ions onto the inner surface of the system.

Patients and methods The study comprised a prospective controlled randomized trial; 213 patients fulfilled the inclusion criteria. They were randomized to a urine drainage system (comprising a Unometer 400 metering system or PP 2000N closed urine-bag system, both from Maersk Medical, Denmark) either with or without the antibacterial device. The efficacy was assessed as the number of UTIs and the time to infection in the 170 patients eligible for analysis.

Results There were fewer UTIs in those using the system containing the antibacterial device (19% vs 24%), but the difference was not statistically significant ($P < 0.05$).

Conclusion The potential importance of different infection routes were highlighted, suggesting that modifications to Foley catheters and urine-collecting systems attempting to prevent UTIs should focus not only on the intraluminal pathway, but on the internal and external pathways of infection.

Keywords Urine collecting systems, nosocomial infection, urinary tract infections, retrograde infection, silver

Introduction

The urinary tract is the most frequent site of nosocomial infection; ≈40% of such infections origin from the urinary tract and are mostly caused by instrumentation and indwelling catheterization of the lower urinary tract [1]. In a multicentre study from eight European countries, the overall prevalence of urinary bladder catheterization in hospitalized medical patients was 11% [2]. In a study population of 1581 hospitalized patients, 1341 nursing-home residents and 743 patients receiving home care, Zimakow *et al.* [3] reported a prevalence of indwelling catheterization of 13.2%, 4.9% and 3.9%, respectively. A Dutch study [4] found that 16% of patients admitted to a chronic-care centre had an indwelling urinary catheter. In Maryland, a study of 53 nursing homes found that 9.4% of the women and 6.4% of the men were using indwelling catheterization [5].

The incidence of UTI among patients catheterized for <7 days is 10–40% [6,7], with female gender, duration of catheterization, absence of systemic antibiotics and catheter care being the most important variables affecting the incidence [8]. Although a UTI is often considered a relatively harmless infection, Jepsen *et al.* [2] found that the bacteraemia rate among hospitalized, catheterized patients was three times that of uncatheterized patients. Other studies, e.g. [9], have shown that the acquisition of a UTI during indwelling bladder catheterization among hospitalized patients was associated with a nearly threefold increase in mortality compared with catheterized patients with no UTI. It therefore seems reasonable to try to prevent or postpone UTI in newly catheterized patients for as long as possible.

Apart from the disconnection of the catheter and the urine-collection system, and the microbial contamination arising from insertion of the catheter [6], there are two routes of infection in a closed urine-collecting system, i.e. the extraluminal and the intraluminal route. In the extraluminal route, bacteria from the periurethral and perineal area gains entry to the urethra and bladder along the catheter surface and the mucosa of the urethra [10,11]. In the intraluminal route entry is via the bottom outlet valve, followed by growth in the drainage bag and retrograde spread along the inner surfaces of the tubing and the catheter to the bladder [6,8, 12–15].

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To prevent retrograde intraluminal infections using bactericidal agents, a major problem is maintaining a constant release of sufficient agent in the collecting system and maintaining this concentration throughout the entire period of use. Another major demand on these devices is that the systems must be easy to use, causing the minimum extra manipulation and time involved in handling the systems compared with conventional systems.

Gilchrist *et al.* [16] described a slow-release polymer (SRP) composed of sodium-calcium phosphate glass which released silver ions while dissolving in water. The SRP could be designed with different release profiles related to the purpose and intended time for use. The broad-acting antibacterial (AB) spectrum of silver ions [17] released by the device suggested that it could be a relevant agent for preventing retrograde infections from the urine-collecting bag and the related tubing. Stickler *et al.* [15] showed the superiority of such an integral AB device within the internal pathway in a laboratory study. The conclusion of their study was 'that the incorporation of the silver-releasing device into the drainage systems produced an antibacterial barrier which protected the catheterized bladder from intraluminal contamination for at least 10 days. These *in vitro* tests suggest a useful role for the device in controlling infection in patients undergoing short-term indwelling catheterization.'

The present study was designed to test the clinical value of an AB system *in vivo*, under conditions as close as possible to daily clinical practice, on a relatively mixed patient population undergoing indwelling bladder catheterization for a period of up to 10 days.

Patients and methods

The study was carried out at the Copenhagen University Hospital, Herlev; patients who were >18 years of age and needing continuous indwelling bladder catheterization were recruited from the departments of Medical Gastroenterology, Surgical Gastroenterology, Nephrology, Cardiology, Gynaecology and Obstetrics, Urology, Haematology, Orthopaedic surgery and Intensive Care. None were excluded from the study for underlying illness, with the exception of UTI; those receiving antibiotics or other medication for reasons other than UTI were not excluded. Patients with micro-organisms present in their urine at any concentration on the first day and any patients developing a UTI ($>10^5$ c.f.u./mL) within the first 48 h of the study were excluded. The trial was designed as a prospective, randomized, controlled study, with blinded test samples for the clinical microbiology laboratory. An equal number of patients was allocated to the two groups, being randomized from a list of random numbers in blocks of 10. Two interim analyses were conducted to assess the main variable, the comparison of UTI incidence and time to infection, between the groups.

Sampling and identification of micro-organisms

A common procedure was established for urine sampling through the sampling port, including disinfecting the port with chlorhexidine before sampling. The urine was assessed routinely for microbes the time of catheterization, and after 6 and 10 days of catheterization. The urine was examined daily using a dipstick test and if positive for leukocytes and/or nitrite, or if the dipstick was unreadable for any reason, the sample was cultured. If a patient was withdrawn for any reason (e.g. removal of the catheter or transferral to another hospital), a urine sample was then obtained and cultured.

All urine samples were cultured according to standard procedures. Growth was evaluated according to colony morphology and Gram stain, and quantified (as a pure or mixed culture) by the magnitude of the number of colonies, e.g. 10^3 to $>10^5$ c.f.u./mL. Isolates were identified by standard phenotypic reactions.

Urine drainage systems

The patients were randomized between a control system and an active AB system containing a silver-releasing sodium-calcium phosphate ingot, designed to release the silver ions into the urine passing through (Fig. 1) for a period of $\geqslant 10$ days. Two systems were used, a urine meter system (Unometer 400) and a closed urine-bag system (PP 2000N, both Maersk Medical A/S, Denmark). The former contains wide-bore tubes, a sampling port, a measuring chamber with a non-return valve and a collection bag with a non-return valve, a hydrophobic bag vent and bottom outlet. The closed urine bag system comprised a wide-bore tubing system with an integrated sampling port, a drip chamber, a non-return valve, a hydrophobic bag vent and bottom outlet. In all the systems the junction between the catheter and the urine bag tube was sealed with red tape to avoid any unintended or unnecessary disconnection. The indwelling catheters used were those normally prescribed by the relevant department. The indwelling catheter was inserted following the standard procedure of the respective departments, as was the daily care of the catheter and urine-bag system. A common procedure was used if there was a disconnection of the catheter and bag, by disinfecting the two connecting parts in chlorhexidine.

The study population was described using simple summary statistics. The main outcome variable (time to infection) was analysed using a log-rank test for censored

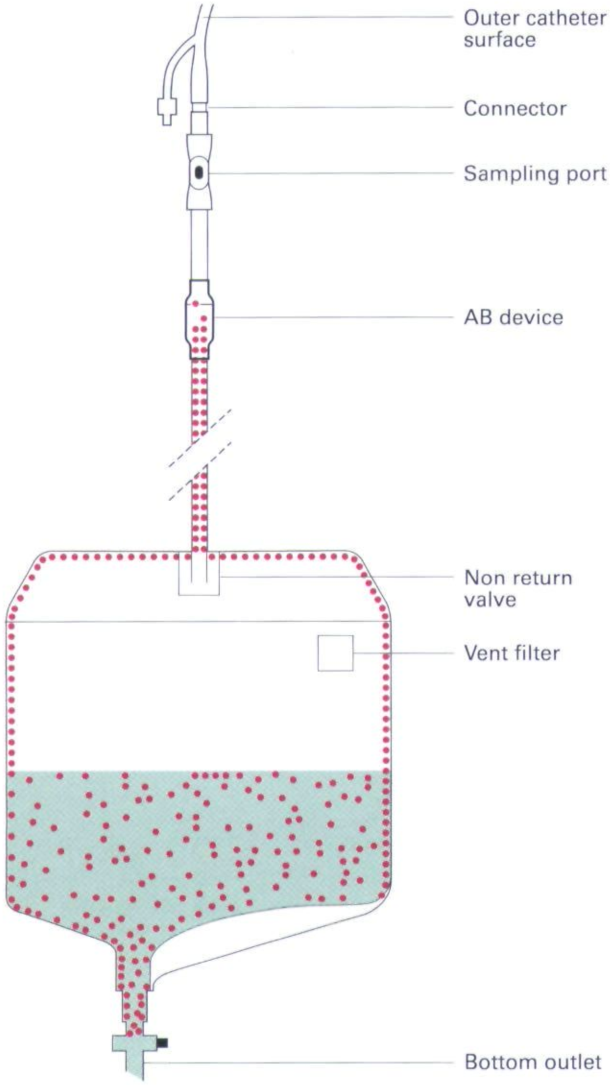

Fig. 1. A schematic drawing of the urine-collecting system with the silver-releasing AB device. The red dots indicate the released silver ions.

and grouped observations, where no difference between the groups is equivalent to a hazard ratio of 1. The proportionality of hazards was assessed graphically. The proportion of patients remaining uninfected over time was estimated using the Kaplan–Meier method. The proportions of antibiotic-treated patients were compared using the χ^2-test. A one-sided test was chosen for the main variable and a two-sided test for the proportions of antibiotic-treated patients; in all cases $P<0.05$ was considered to indicate significance.

Results

Of the 243 patients recruited, 43 were ineligible for analysis; 28 had micro-organisms present (at any concentration) on the first day, four had a UTI within the first 48 h and 11 patients withdrew for other reasons. Thus 170 patients were eligible for analysis, 83 in the AB group and 87 in the control group. Table 1 shows the distribution of patients between the groups in relation to sex, age, use of the urine meter and use of antibiotics. Except for the Gynecology/Obstetric department all other departments had comparable numbers of males and females in the two groups. The use of urine meters was comparable in both groups and for both sexes; the urine meter was predominantly used in the Intensive Care department. The use of antibiotics was comparable in both groups. After 6 days, 45% of the patients remained in the study (i.e. they had a catheter in place with no UTI); after 10 days, 7% remained.

During the study period 37 patients had a UTI, comprising 16 in the AB group and 21 in the control group; Table 2 shows the number of infections and censoring on each day, together with the Kaplan-Meier estimate of the probability of remaining uninfected as a function of time (the survivor curve). The Kaplan–Meier curve is shown in Fig. 2. The probability of remaining uninfected with the AB bag system was greater than that with the control bag. However, after 5 days the probability estimates were based on few samples and thus subject to large variability. Table 2 also shows the log-rank test for no difference between the survivor curves for the AB and control bag; the χ^2 value was 1.55 (1 d.f., $P = 0.11$, one-sided). The hazard ratio (the probability of having a UTI using an AB bag compared with a control bag) was 0.68, with a two-sided 95% CI of 0.33–1.28. A separate analysis for each sex showed no significant difference in UTIs detected.

The effect of antibiotics (Table 3) was calculated as the difference between the ratio of antibiotics given within one type of bag system and the infection ratio between the systems in patients receiving antibiotics. For the AB group four of 15 infected patients were given antibiotics,

Table 1 The distribution of patient characteristics and the use of urine meters and antibiotics in the two groups

Characteristic	*AB-group*	*Control*
No. of patients analysed	83	87
Female	54	52
Male	29	35
Median age (years)	59.3	60.8
Urine meter		
Yes	33	31
No	48	56
Antibiotics		
Yes	35	33
No	48	54

Table 2 Numbers of UTIs and censored patients in the two groups (the results for day 11 were collected because data were missing for day 10). The patients 'at risk' represent those still in the study and free of UTI

	AB-group			*Control*		
Sample (day)	*Censored*	*UTI*	*At risk*	*Censored*	*UTI*	*At risk*
1	1	–	83	3	–	87
2	10	–	82	13	–	84
3	6	1	72	9	3	71
4	9	2	65	6	6	59
5	10	3	54	10	2	47
6	9	8	41	12	7	35
7	9	0	24	3	2	16
8	4	1	15	2	0	11
9	6	0	10	1	0	9
10	2	0	4	5	1	8
11	1	1	2	2	0	2

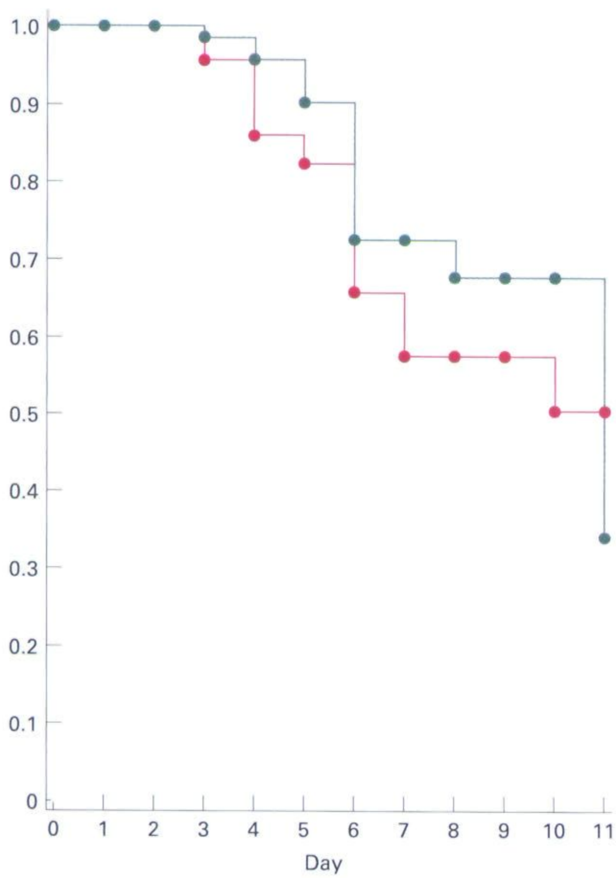

Fig. 2. The Kaplan–Meier curve showing the probability of remaining uninfected in 170 patients using the AB system (green) or control system (red).

Table 3 Number of patients with or without UTI in relation to antibiotic treatment in the two groups

	Antibiotic treatment		
Group UTI?	*No*	*Yes*	*Total*
AB			
No	36	31	67
Yes	12	4	16
Total	48	35	83
Control			
No	40	26	66
Yes	14	7	21
Total	54	33	87

compared with 31 of 67 censored patients (46%; not significantly different, $P = 0.12$). In the control group, the corresponding proportions were seven of 21 (33%) vs 26 of 66 (39%), which again was not significantly different ($P = 0.62$). Between the AB and the control group, the infection ratio among patients receiving antibiotics was four of 35 (11%) in the AB group vs seven of 33 (21%) in the control group; this difference was not significantly different from zero ($P = 0.62$). Table 4 shows the bacteria isolated from the urine samples.

Discussion

The relative importance of the different routes and the time to reach the bladder has been examined in a few, although important, studies. Daifuku and Stam [11] found that 70% of infections in women derived from the extraluminal route and only 30% did so in men. Garibaldi *et al.* [10] showed in acute-care patients that meatal colonization within 24 h of catheterization increased the risk of bacteriuria. In the study of Nickel *et al.* [13],

Table 4 Number and type of isolated micro-organisms

Micro-organism	*AB group*	*Control group*
Staphylococcus aureus	1	0
Coagulase negative staphylococci	2	4
α-haemolytic streptococci	1	1
Enterococcus faecalis	6	7
Corynebacterium spp.	1	1
Escherichia coli	7	8
Klebsiella pneumoniae	2	6
Pseudomonas spp.	1	5
Proteus spp.	1	0
Candida spp.	1	1
Total	23	33

contamination of the bottom outlet of the drainage bag or accidental disconnection of the drainage tube resulted in bacteriuria within 32–48 h, while the entry time for the extraluminal route in a strictly managed closed system was 76–120 h.

Wille *et al.* [18], in a study on 251 patients, reported the discriminative strength of their trial sufficient for 5 days and concluded that the admission of bacteriuria during the first 120 h of catheterization was not influenced by additional complex features to prevent the intraluminal spread of bacteria. Their test compared the 'Curity' infection control system (Kendall Co., Boston, USA) which had a povidone-iodine releasing cartridge in line with the bottom outlet, with a simpler closed system (Urias A-4, Svend Andersen Export, Haarlev, Denmark) . The study of Wille *et al.* [18] was in contrast to a previous study of Al-Juburi and Cicmanec [19] comparing the same 'Curity' system and a standard closed drainage system; they concluded that in their patients the main entry for bacteria leading to UTI was through the collection bag.

In the present study, overall there were fewer UTIs (24% in the control and 19% in the AB group) over 10 days, giving a hazard ratio of 0.68 (95% CI 0.33–1.28) in the AB group. However, this result was not significant ($P = 0.11$). The difference between the groups appeared from the fifth day and remained throughout the study period. The study confirms the findings of Wille *et al.* [18] for the first 5-day period, but during the last 5-day period shows a decrease in UTI, corresponding to a reduction ratio of 20%, although not statistically significantly so.

Although patients receiving antibiotic treatment showed a tendency to fewer UTIs than those not so treated, the use of prophylactic antibiotic treatment in patients undergoing indwelling urinary catheterization cannot generally be recommended. Such a protocol would increase the risk of selecting resistant micro-organisms in the patient and in the hospital environment, and the subsequent risk of spread of these resistant micro-organisms to other patients.

There was no statistically significant benefit of the AB system on the frequency of UTI in newly catheterized patients; this may have arisen because of failure to eliminate intraluminar micro-organisms, or through the retrograde extraluminar spread of micro-organisms. The former could be caused by increased diuresis, resulting in premature washout of the sodium-calcium phosphate ingot, or by intentional/unintentional breakage of the system. There was no evidence that the frequency of breakage differed in the two groups. There was an equal ratio of patients acquiring a UTI in the two groups in the intensive-care department, where increased diuresis is most frequent, indicating that the extraluminal spread of micro-organisms is probably the main route of infection.

The present study underlines that any indwelling Foley catheters and urine-collection systems attempting to prevent UTI in patients should focus on the extraluminal and the intraluminal pathway to obtain the maximal effect.

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