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Chlorhexidine and silver-sulfadiazine coated central venous catheters in haematological patients—a double-blind, randomised, prospective, controlled trial

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Abstract *Background:* Central venous catheters (CVCs) are essential for the intensive care of patients with haematological illness. Catheter-related infections (CRI) are an important problem in modern medicine, which may lead to life-threatening situations, to prolonged hospitalisation and increased cost. In immunocompromised patients suffering from haemato-oncological diseases, CRI is a significant factor for adverse outcome. Several clinical studies have shown that CVCs coated with antiseptics such as chlorhexidine and silver-sulfadiazine (CHSS) reduce the risk of catheter-related bacteraemia. Most studies, however, were performed on intensive care patients not suffering from chemotherapy-induced immunosuppression. *Patients and methods:* A prospective double-blind, randomised, controlled trial was performed to investigate the effectiveness of CHSS-coated catheters in haemato-oncological patients. A total number of 184 catheters (median duration of placement, 11 days) were inserted into 184 patients (male 115, female 69), of which 90 were antiseptically coated. After removal, all catheters were investigated for bacterial growth. *Main results:* Catheters coated with CHSS were effective in reducing the rate of significant bacterial growth on either the tip or subcutaneous segment (26%) compared to control catheters (49%). The incidence of catheter colonisation was also significantly reduced (12% coated vs 33% uncoated). Data obtained show a significant reduction of catheter colonisation in CHSS catheters. There was no significant difference in the incidence of catheter-related bacteraemia (3% coated vs 7% uncoated). However, due to the overall low rate of CRI, we could not observe a significant reduction in the incidence of catheter-related bacteraemia. *Conclusion:* Our data show that the use of CHSS catheters in patients with haematological malignancy reduces the overall risk of catheter colonisation and CRI, although the incidence of catheter-related bacteremia was similar in both groups.

Keywords Central venous catheter · Chlorhexidine · Silver sulfadiazine · Catheter-related infection · Haematologic–oncologic patients

Introduction

Central venous access is essential for the intensive care of patients with haematological malignancies. Central venous catheters (CVCs) are used for the administration of fluids, drugs and total parenteral nutrition. An estimated 5 million CVCs are implanted in the U.S. alone each year, a figure likely to increase as patient care becomes more specialised and intensive [30] Complications of catheterisation include those associated with catheter insertion (pneumothorax, arterial and nerve injuries) and those associated with long catheter use (thrombosis and infection) [1, 6, 28]. Major com-

plications associated with the use of intravascular catheters are catheter-related bacteraemia and local catheter infections. In literature, the incidence of catheter-related infection (CRI) ranges from 5 to 15% [41]. The incidence of CRI in haematologic–oncologic patients was also reported to range from 18 to 45% [11, 25]. Infections associated with the use of central venous catheters can result in serious medical complications and expensive care [30]. Bloodstream infection is the most common and serious, life-threatening, complication associated with central venous access. Infectious complications due to the use of these devices were reported to range from 3 to 60% [16, 21, 24, 36]. Reasons for the wide range of catheter-related infections found in clinical studies include diverse types of catheters, different underlying diseases, various intravenous routes and varying definitions of CRI [2, 7, 14, 15, 31]. CRI represents an important risk factor influencing patient morbidity and mortality and hospital economics. They account for an estimated $3000–6000 increase in hospital costs [4, 29] and an extra week of hospital stay [18].

Central venous catheters are used more frequently in the routine management of immunocompromised patients. These patients bear a major risk of nosocomial infection due to a neutropenia- and treatment-associated immunosuppression.

In prospective, randomised clinical trials, the use of CVCs coated with chlorhexidine and silver sulfadiazine was associated with reduced rates of catheter colonisation and catheter-related bloodstream infection, compared with uncoated catheters [3, 5, 8, 13, 19, 22, 23, 27, 30, 34, 35, 38].

Several recent randomised trials have assessed the efficacy of these catheters in reducing catheter colonisation and catheter-related bloodstream infection. Although most of the studies have shown a significant reduction in catheter colonisation, only a single study [30] has reported a significant reduction in the major clinical complications of CRI.

In a meta-analysis of 12 studies by Veenstra et al. from January 1966 to January 1998 (n=2,611 CVCs), chlorhexidine silver-sulfadiazine coated central venous catheters with non-impregnated catheters were compared. The assessed outcome was catheter colonisation and catheter-related bloodstream infection confirmed by catheter tip culture. The combined odds ratio for catheter colonisation was 0.44 [95% confidence interval (CI), 0.36–0.54; p<0.001], indicating a significant decrease in catheter colonisation with impregnated catheters. Studies on the outcome of catheter-related bloodstream infection exhibited a combined odds ratio of 0.56 (95% CI, 0.37–0.84; p=0.005). The authors concluded that CVCs impregnated with chlorhexidine and silver-sulfadiazine appear to be effective in reducing the incidence of both catheter colonisation and catheter-related bloodstream infection in patients at high risk for catheter-related infections [39]. Mermel [32] and Veenstra et al. [39] have shown in recent meta-analyses that chlorhexidine-silver sulfadiazine-coated catheters reduce rates of catheter-related infections by at least 40%. A cost analysis by Veenstra et al. suggests that the use of antiseptic catheters is cost-effective in a patient population with an overall incidence of catheter-related infection of greater than 0.4 bloodstream infections per 1,000 catheter-days [39].

In the present study, we investigated a novel version of chlorhexidine and silver sulfadiazine coated catheters (ARROWgard Blue PLUS (ARROW Int., Redding, PA, USA) in a prospective, double-blind trial to determine the efficacy of antiseptic coating in preventing catheter-related infections amongst haematological patients undergoing chemotherapy.

Patients and methods

The study was conducted at the Department of Internal Medicine V serving haematological, oncological and rheumatological patients at the University Hospital of Heidelberg, a tertiary care and teaching hospital. The study period was from January 2000 and September 2001 and included patients with haematological malignancy and need of a central venous catheter for at least 7 days.

Standardised data collection forms were completed for all patients, including demographic characteristics, catheter insertion and removal dates, catheter insertion site, diagnosis, type and dosage of chemotherapy, and supportive care (type and duration of antibacterial and antifugal therapy). Additionally, clinical data like days of leucopoenia ($<1.0\times10^9$ WBC/l), days of fever (>38.5°C), platelet count, coagulation parameters, blood pressure and pulse rate were recorded twice daily.

Patients were checked for compliance with the enrolment protocol. The study protocol was approved by the Review Board of the university. All participants gave informed written consent.

Catheter care

Through randomisation, either an ARROW (ARROW International, Reading, PA, USA) double-lumen, non-coated catheter, or an ARROWgard Blue PLUS double-lumen, CHSS-coated catheter was inserted percutaneously in the internal jugular or subclavian vein, using the guidewire (Seldinger) technique. The two catheter types were indistinguishable to users and patients (double-blinded study design).

Experienced house staff inserted all the catheters under strict aseptic conditions. Prior to insertion, the skin was swabbed using 70% alcohol. Catheters were fixed with sterile tape strips. A transparent dressing was used to cover the catheter at the catheter entry site. Afterwards, protocolised catheter-site care was performed by experienced ward nurses. The decision to remove the catheter was made by the treating physician, who kept the catheter in place until it was no longer needed or until an adverse event, such as catheter-related infection, necessitated its removal. Catheters were removed under aseptic conditions by the investigators.

Microbiological methods

Blood cultures were obtained from catheters and one peripheral vein at the time of catheter removal. The skin of the catheter insertion site (an area of 2 cm^2) and the catheter's hub were swabbed with a sterile cotton swab. After removal, the catheter was cut into four segments by using sterile tweezers and scalpels. Two-centimetre segments (Table 1, Fig. 1) from the tips and subcutaneous sections were cultured using the methods of Maki (roll-plate) [31], Sherertz (sonication) [37] and Cleri (flushing of the lumen) [9]. The number of colonies from the catheter segments and the swabs from skin and hub were counted and recorded.

Blood cultures were taken from a peripheral vein. Blood aliquots were cultured with aerobic and anaerobic Bactec Plus/F media (Becton Dickinson Europe, Heidelberg, Germany). Aliquots of the bottles were subcultured onto adequate media. All micro-organisms were identified by standard microbiological procedures.

Pulsed field gel electrophoresis

To prove "real" catheter-related bacteraemia, all isolates from colonised catheters with positive blood cultures were subjected to pulsed field gel electrophoresis (PFGE). The cell DNA from bacterial isolates was prepared in low-melting-point agarose gel plugs, and lysis was performed. Lysostaphin was added to lysis buffer in the case of staphylococci. *Sma*I was used as a restriction enzyme. The digest were resolved by PFGE at 6 V/cm on a 1.0% agarose gel by clamped homogeneous electric fields (CHEF) in 0,5% TBE buffer (0.1 M Tris, 0.1 M boric acid, 0.2 mM EDTA). Electrophoreses of DNAs from isolates belonging to the same patient were done on the same gel. For all samples, the pulse times were 2–8 s for 11 h, and 10–40 s for the final 10 h. The runs were performed at 6 V/cm. The bacteriophage Lambda Ladder PFGE Marker was used as size standards. Isolates were assigned to the same subtype when band shifts were consistent with a single genetic event.

Definitions

Bacterial growth was defined as growth of >1 colony forming unit (CFU) in culture of catheter segments prepared via the roll-plate method or >5 CFU in segments processed by sonication method or flushing method (Table 2).

Catheter colonisation was defined as the growth of >15 CFU in culture of catheter segments prepared by roll-plate method or >100 CFU in cultures prepared by sonication method from either the tip or the subcutaneous segment of the catheter or a growth of >100 CFU for the flushing method.

Catheter-related bacteraemia was defined as the isolation of the same organism (i.e. the same species with identical electrophoretic pattern in the PFGE) from the colonised catheter and from peripheral blood.

Table 1 Catheter segments

Segments	Sections of the removed catheters	Method
A	catheter tip	Sherertz [37]
B	Proximal to segment A	Sherertz [37]
R	distal to segment C	Maki [31]
C	subcutaneous segment	Sherertz [37]

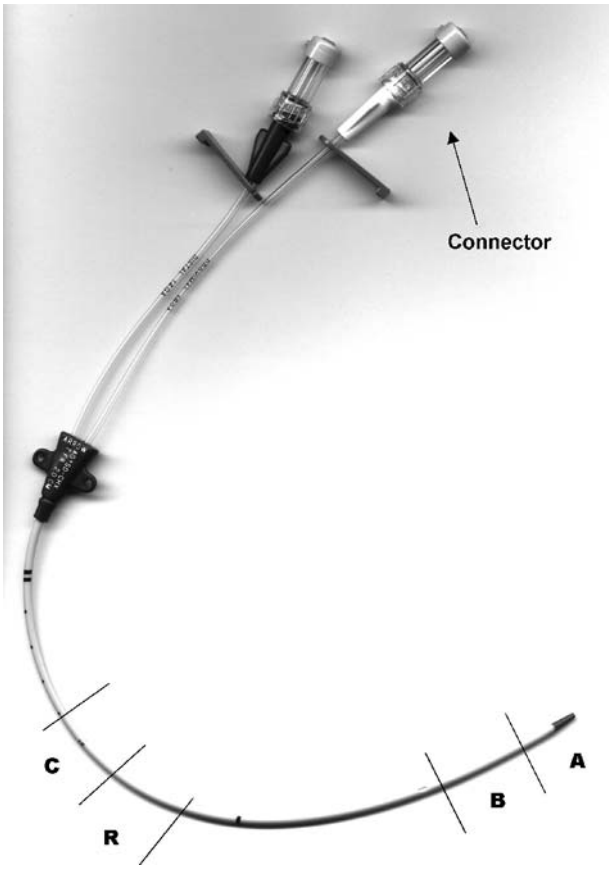

Fig. 1 Catheter segments: *A* catheter tip, *B* proximal to segment A, *R* distal to segment C, *C* subcutaneous segment

Statistical analysis

Statistical analysis was performed by use of Microsoft Excel 97 (Microsoft, Redmond, WA) and SPSS 10.0 (SPSS Inc., Chicago). For statistical analysis, patients were divided into two groups according to the type of catheter. Variables between catheter groups were compared by an uncorrected chi-square test. Because there were two groups of patients with comparable baseline characteristics, no indication of positive or negative confounding was needed

Table 2 Definitions concerning catheter colonisation, catheter-related bacteraemia, catheter-related septicaemia and local infection

Local infection	Growth of more than 15 colony-forming units (CFU) of an organism on semiquantitative culture of the intradermal or catheter tip segment and local sings of infection. Sterile blood cultures
Bacterial growth	Bacterial growth was defined as growth of more than one colony-forming unit in culture of catheter segments prepared by the roll-plate method or >5 CFU in segments processed by the sonication method or the flushing method
Catheter colonisation	Growth of more than 15 CFU of an organism on semiquantitative culture of catheter in the absence of signs of local or systemic infection
Catheter-related bacteraemia	Isolation of the same organism from catheter (more than 15 CFU) and blood culture without clinical signs of infection
Catheter-related septicaemia	Isolation of the same organism from catheter (more than 15 CFU) and blood culture with clinical signs of infection

to be controlled by Cox models. Statistical significance was established at α=0.05. All p values were based on two-tailed tests of significance.

Results

A total of 245 patients were enrolled in the study, comprising 103 female and 142 male patients. Sixty-one catheters were excluded because of patient's failure to notify the study team when the catheter was removed, or catheterisation <24 h.

One hundred eighty-four patients were evaluated in the study (68 female and 116 male patients).

A total of 94 catheters were uncoated (37 female/57 male patients) and 90 were coated (32 female/58 male patients) catheters. Demographic and clinical data were similar for both treatment groups (Table 3).

In most cases (88%), catheters were routinely removed at the end of treatment cycle. The mean length of catheter placement was 11 days (range 7–74 days). The total number of febrile days showed a mean of 1.6 days during catheterisation (0.7% of the catheter-days) and 29.4% of the days during neutropenia.

Local infection

At removal of the catheters the insertion site was inspected for local signs of infection (redness, swelling, pain on palpation and secretion). One hundred and thirteen patients were without symptoms of a local infection. Thirty-five patients with coated catheters showed local signs of infection. Thirty-nine patients with a control catheter had local signs of infection.

Table 3 Patients' characteristics

Characteristic	Uncoated catheters	Chlorhexidine silver sulfadiazine coated catheters	p
No. of patients	N=94	N=90	
Sex			
Female	37	32	0.719
Male	57	58	0.797
Age (years)			
Median	53	51	0.983
Duration of catheterisation (day)			
Mean	10.81	12.29	0.694
Range	1–29	1–74	
Median	10	12	0.617
Underlying disease (%)			
Multiple myeloma	42	47	0.546
Hodgkin's disease	4	8	0.628
Non Hodgkin lymphoma	18	15	0.510
Acute leukaemia	15	15	0.628
Amyloidosis	5	6	0.716
Other	16	9	0.739
Fever (day)			
Mean	1.25	1.9	0.688
Neutropenia (day)			
Mean	4.1	4.24	0.913
Median	3	3	0.958
Receiving systemic antibiotics (day)			
Mean	6.88	7.8	0.755
Median	6	7	0.730

Bacterial growth

Catheters coated with CHSS were effective in reducing the rate of significant bacterial growth (Fig. 2) on either the tip or subcutaneous segment (26%) compared with control catheters (49%). Coagulase-negative stahpylococci were the organisms cultured most often from the catheter segments (Table 4).Colonisation of catheters.

Catheter colonisation differed significantly (p=0.01) between both groups (Fig. 3); whilst 31 control catheters (33%) were positive, only 11 of the CHSS catheters (12%) yielded positive microbiological cultures.

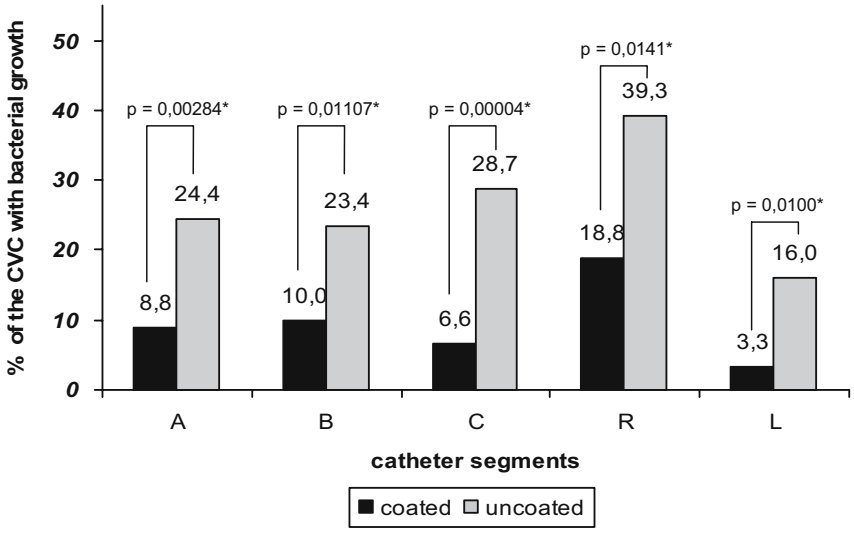

Fig. 2 Bacterial growth: *A* catheter tip, *B* proximal to segment A, *R* distal to segment C, *C* subcutaneous segment, *L* flushing of the lumen

Catheter-related bloodstream infection

The overall bloodstream infection rate during the study period was 10/184 (5.43%) and 4.7 per 1,000 catheter-days.

Table 4 Percent and types if isolates from cultured catheter segments

Organism	Uncoated catheters [%]	Coated catheters [%]
Staphylococcus epidermidis	87.6	76.2
Staphylococcus haemolyticus	0.7	7.9
Staphylococcus hominis	1.4	4.8
Staphylococcus capitis	5.4	1.6
Micrococcus roseans	0.6	3.2
Micrococcus lutens	2.1	1.5
Escherichia coli	0	3.2
Staphylococcus aureus	0	1.6
Others	2.2	0

Although the number of bloodstream episodes in patients with the CHSS catheters was lower than in patients provided with the control catheter (three vs seven episodes), this difference was not statistically significant (p=0.21). There were no deaths attributable to bloodstream infections.

Discussion

Reliable vascular access is one of the most essential features of modern medical care, especially in hospitalised granulocytopenic and thrombocytopenic patients requiring blood products and multiple drugs [20]. At the same time, they are the leading cause of primary blood stream infections with substantial morbidity and mortality. The pathogenesis of such infections is favoured by the microorganism's potential to adhere to polymer surfaces followed by colonisation and the production of an adherent biofilm. A variety of methods have been used to prevent these catheter-related infections. Recently, the use of antibiotic-coated or antiseptic-impregnated catheters to reduce the incidence of catheter-related bloodstream infections was evaluated [3, 5, 8, 13, 19, 22, 23, 27, 30, 34, 35, 38, 39]. Two recent analyses

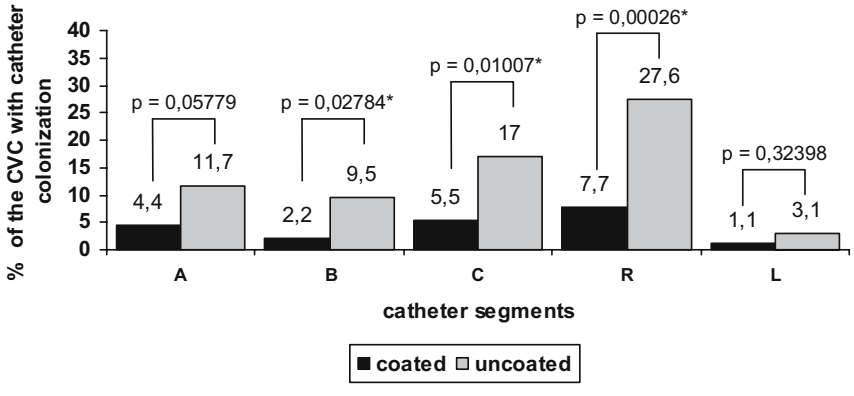

Fig. 3 Catheter colonisation: *A* catheter tip, *B* proximal to segment A, *R* distal to segment C, *C* subcutaneous segment, *L* flushing of the lumen

also concluded that catheters impregnated with the antimicrobial combination of chlorhexidine and silversulfadiazine (CHSS) were efficacious and cost-effective [40, 39].

The purpose of our study was to evaluate the efficacy of a CHSS central venous catheter in a specific patient population with an increased risk of infection. The two study groups in this trial were comparable with respect to underlying conditions that might predispose to catheter infection. In the evaluable patient population, we found minor differences concerning:

1. the length of catheterisation (CHSS catheters 12.3 days vs uncoated catheters 10.8 days),
2. signs of inflammation at the insertion site like redness and swelling (37.7 vs 41.4%), and
3. catheter-related bacteremia (3 vs 7%).

Our results show a tendency in favour of the coated catheter, but the differences did not reach statistical significance. The reason for the overall relatively short catheter placement duration was that all catheters were removed when there was no further need of the CVC. Thus, there were only few patients who had a CVC in place for more than 4 weeks. The ostensibly low reduction of the catheter-related bacteraemias must consider the overall low infection rate in our patient population, which is significantly lower than published data showing rates between 15 and 30%. To find a significant difference with respect to this outcome, the inclusion of several hundred patients would be more appropriate.

However, our microbiological data clearly show the advantage of the CHSS catheter. The overall incidence of catheter colonisation was significantly lower in the CHSS catheter (12 vs 33%), which is confirmed by a lower bacterial recovery rate either from tip or subcutaneous segment (26 vs 49%) as well as less positive intraluminal cultures (3.3 vs 15.9%). Considering the pathogenesis of either localised or generalised CVC-related infections, the reduced colonisation rate will result in the long run in lower infection rates. If these catheters are in place for an extended period of time, they are valuable devices for the prevention of catheter-related infections.

Redness of the skin and pain on palpation of the insertion are clinical signs for CRI caused by an extraluminal bacterial growing. Amongst the patients who received a control catheter, 41.4% had tenderness on pressure and redness. In the CHSS group, only 37.7% showed this signs.

This tendency was not significant.

The investigation of skin cultures and catheter cultures turn out to be superior for the comparison of study groups. Twenty-four patients of the control group had a positive skin culture. Twenty catheters from these 24 patients were positive concerning catheter colonisation.

Twenty patients from the CHSS group had a positive bacterial augmentation on the skin. Of these patients, only four catheters showed a positive catheter culture.

Catheters coated with CHSS were effective in reducing the rate of significant bacterial growth on either the tip or subcutaneous segment (26%) when compared with control catheters (49%). The incidence of catheter colonisation was also significantly reduced (12% coated vs 33% uncoated). However, there was no significant difference between the incidences of catheter-related bacteraemia (3% coated vs 7% uncoated). Although no significant difference in the incidence of catheter-related bacteraemia was observed (3% coated vs 7% uncoated), we found a trend towards a reduced catheter-related bacteraemia in this study. Due to the small sample size, a significant difference could not be reached. Most of the isolates were identified as coagulase-negative staphylococci (91.9%) which is in line with the general consensus in literature and our previous observations.

Our findings also support the theory of intra-luminal infections as a major complication of non-tunnelled, central venous catheters in oncological patients [10, 12, 17, 26]. Extended hospitalisation and delay in administration of further antineoplastic chemotherapy is often observed as well as pulmonary complications requiring a prolonged course of antibiotic treatment, leading to an increased risk of fungal infection [33]. The luminal bacterial growing was significant lower (3.3% of the CVC) in the CHSS group than in the control group (15.95%).

It could be anticipated that the intraluminal CHSS coating reduces bacterial growth on the catheter. In consequence, the rate of CRI would also be decreased.

In particular, during long-term catheterisation, as is often the case in chemotherapeutic treatment of haematologic and oncologic patients, the intraluminal coating of CVC is expected to prevent CRI and bacteraemia.

For the development of a CRI, the duration of placement plays a major role. In this study the median duration of placement of the control catheters (10.84 days) was 2 days shorter than the duration of the CHSS (12.29 days). Based on the coating, we would have expected a major difference between the two study groups. However, we have to note that in the CHSS group, a few catheters had been in place for very long periods. One CHSS, in particular, was in place for 74 days. In the control group the respective maximum duration was 29 days. Restrictively, we have to mention that most catheters were explanted due to the end of therapy and not because of the presumption diagnosis of a CRI.

Future studies are needed to evaluate our results in patients requiring longer periods of catheter use such as patients undergoing chemotherapy due to acute leukemics, who comprised only about 15% of all patients.

We conclude that the use of CHSS catheters is an effective tool in patients with haematological malignancy. CHSS coated catheters lead to a lower rate of bacterial colonisation of the CVCs. On this basis, we expect a reduction of the overall risk of bacterial growth and catheter-related infection. In case of extended duration of catheterisation, we assume a significant decrease in the incidence of catheter-

related infections on the ground of less bacterial growth and less bacterial catheter colonisation in immunocompromised patients.

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