Reduced colonization and infection with miconazole–rifampicin modified central venous catheters: a randomized controlled clinical trial

Nedim Yücel1*, Rolf Lefering2, Marc Maegele1, Martin Max3, Rolf Rossaint3, Andrea Koch4, Rosemarie Schwarz5, Michael Korenkov1, Josef Beuth6, Alfons Bach7, Jörg Schierholz8, Gerhard Pulverer9 and Edmund A. M. Neugebauer2

12nd Department of Surgery, Klinikum Merheim; 5Microbiological Laboratory, Klinikum Merheim; 2Biochemical and Experimental Division, Medical Faculty; 4Institute of Scientific Evaluation of Naturopathy; and 9Institute of Medical Microbiology and Hygienics, University of Cologne, Cologne; 3Department of Anesthesiology, RWTH University of Aachen, Aachen; 4Institute of Medical Microbiology and Hygienics and 7Department of Anesthesiology, University of Heidelberg, Heidelberg; 8Center of Advanced European Studies and Research (CAESAR), Bonn, Germany

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Objective: Central venous catheters (CVC) are a major cause of nosocomial bloodstream infections. Catheters modified with miconazole and rifampicin that constantly and slowly release antimicrobial substances are assumed to be beneficial in reducing rates of colonization and catheter-related infections.

Design and setting: Prospective controlled non-blinded randomized clinical trial in two German university hospitals.

Patients: 223 adult inpatients with CVC between October 2000 and February 2002. Baseline characteristics, APACHE II score and therapeutic interventions were comparable.

Intervention: Randomization to receive either a miconazole and rifampicin modified catheter (n = 118) or a standard triple-lumen CVC (n = 105).

Measurements, definitions: Microbiological evaluation was done after CVC removal. A catheter was considered colonized if growth of >15 cfu was found by semi-quantitative roll-plate technique from a proximal or distal catheter segment. A catheter-related infection (CRI) was defined as a colonized catheter with local signs of inflammation. A catheter-related bloodstream infection (CR-BSI) was defined as a colonized catheter with isolation of the same organism from the patient’s blood with accompanying clinical signs of infection.

Results: A colonization of CVC was observed in six patients (5.1%) with a modified catheter and 38 patients (36.2%) with a standard catheter (P < 0.001). Five patients in the modified group (4.2%) and 18 in the standard group (17.1%) developed CRI (P = 0.002). One assumed CR-BSI was detected in the standard group, with none in the modified group. No adverse effects related to the modified catheters and no antimicrobial resistance were observed.

Conclusion: CVC supersaturated with miconazole and rifampicin were associated with a significantly lower risk for catheter colonization and catheter-related infections compared to standard catheters.

Keywords: randomized controlled trials, CVCs, prevention, bloodstream infections, antimicrobial agents

*Corresponding author. Tel: +49-221-89070; Fax: +49-221-89073928; E-mail: n.yuecel@t-online.de
Introduction

During the last decade, central venous catheters (CVC) have gained widespread use in the management of critically ill patients. Nowadays, 50–65% of all intensive care unit (ICU) patients receive central venous catheterization; the main reasons for this intervention are drug administration, parenteral nutrition, fluid replacement, and haemodynamic monitoring. However, the benefits from central venous catheterization are offset by an increased risk of nosocomial bloodstream infections. On average, approximately 850 000 catheter-related infections (CRI), and >50 000 catheter-related bloodstream infections (CRI-BSI) are annually reported in the United States with mortality rates ranging from 14% to 28%.

A European multicentre study involving more than 10 000 patients revealed an incidence rate for CRI of >5%. Similar results were reported in the National Nosocomial Infections Surveillance (NNIS) System Report (Data Summary from January 1992 to April 2000, issued June 2000). Potential risk factors for CRI are catheter type (single versus multi-lumen), frequency of port manipulations, catheter care, underlying disease, catheter indwelling time and localization of the catheter.

A reasonable approach to reduce the risk of CRI is the use of antimicrobially modified catheters. Recently, both antiseptic CVCs impregnated with silver or chlorhexidine silver-sulfadiazine and antimicrobial CVCs coated with TDMAC–rifampicin–minocycline or cefazolin have been investigated clinically but with somewhat conflicting results.

In this study, a novel antimicrobial combination, i.e. miconazole and rifampicin, has been developed for the prevention of CVC colonization and subsequent CRI. Both agents, embedded in a supersaturated state in the catheter matrix, showed a broad spectrum in vitro activity against staphylococci, other Gram-positive bacteria, C. albicans and various Gram-negative bacilli with the half-life of antimicrobial activity exceeding 3 weeks.

We conducted a controlled prospective randomized multicentre trial to compare catheters modified with miconazole and rifampicin versus non-modified standard catheters with respect to catheter colonization and infection rates.

Materials and methods

Patients

The present trial was conducted between October 2000 and February 2002 in two university hospitals in Germany, the 2nd Department of Surgery, University of Cologne in Cologne-Merheim, and the Department of Anaesthesiology, University of Aachen, Aachen. Hospitalized adults (18–80 years) assumed to require a CVC for at least 3 days and undergoing first central venous catheterization were eligible. Exclusion criteria were allergy to miconazole and/or rifampicin, anatomic defect or skin contamination by microorganisms on the skin surface, and two 3 cm long segments were aseptically cut, with sterile scissors, each from its tip and its subcutaneous part. During removal, the site of catheterization was inspected for clinical signs of infection such as redness, induration/swelling, purulent secretion, and pain. No topical antiseptic was applied to the insertion site before CVC removal. In case of unexpected event, e.g. fever or other clinical signs of infection, by the physician on duty. The site of catheterization was cleaned with 72% alcohol (propanol), covered with sterile gauze, taped securely and inspected for signs of infection. The inserted CVCs remained in place until no longer medically needed or in case of unexpected event occurred, e.g. assumed catheter-related infection or catheter occlusion. The decision for CVC removal was made by the attending physician, or in case of unexpected event, e.g. fever or other clinical signs of infection, by the physician on duty. CVC removal was carried out by either a study nurse or the physician in charge of this study. The catheter was carefully removed with a sterile gauze, taped securely and inspected for signs of infection. The inserted CVCs remained in place until no longer medically needed or in case of unexpected event occurred, e.g. assumed catheter-related infection or catheter occlusion. The decision for CVC removal was made by the attending physician, or in case of unexpected event, e.g. fever or other clinical signs of infection, by the physician on duty. CVC removal was carried out by either a study nurse or the physician in charge of this study. The catheter was carefully removed with the outside portion pointing upwards to reduce potential contamination by microorganisms on the skin surface, and two 3 cm long segments were aseptically cut, with sterile scissors, each from its tip and its subcutaneous part. During removal, the site of catheterization was inspected for clinical signs of infection such as redness, induration/swelling, purulent secretion, and pain. No topical antiseptic was applied to the insertion site before CVC removal. Immediately thereafter, the catheter segments were transported each in a sterile tube for rapid microbiological evaluation.

Microbiological evaluation

After removal both catheter segments were semi-quantitatively cultured using the roll-plating method as described by Maki et al. In all but 20 patients, a broth flush culture was additionally carried out to detect luminal colonization. In brief, 3 mL of broth was flushed through each lumen of the proximal and distal catheter segment, followed by surface plating on blood agar plates. Detected organisms were identified according to standard microbiological procedures. Coagulase-negative staphylococci were classified as Gram-positive cocci in clusters producing catalase but not coagulase. A detailed analysis on the susceptibilities of the isolates to the antimicrobial agents used, e.g. miconazole and rifampicin, was not carried out.
Definitions

According to the CDC (Centers for Disease Control) guidelines for prevention of intravascular device-related infections, \( \geq 15 \) colony forming units (cfu) detected by the roll-plate technique from a proximal or distal catheter segment. A local catheter-related infection (CRI) was characterized by a colonized catheter with accompanying signs of inflammation at the site of insertion (redness, induration/swelling, purulent secretion, and pain); and a catheter-related bloodstream infection (CR-BSI) was defined as a colonized catheter with the isolation of identical organisms from separate percutaneously drawn blood cultures of a patient, with accompanying clinical symptoms of bloodstream infection and no other apparent source of infection. General clinical signs of infection were white blood cell count \( > 12,000 \) cells/mL, temperature \( > 37.9°C \). The indications for obtaining blood cultures (peripheral anaerobe and aerobe blood culture) were temperatures above \( 37.9°C \) and local signs of infection.

Statistical analysis

The study was designed as a group sequential trial with two interim analyses according to Fleming et al.\(^{25}\) The \( P \) values for interim and final analyses were 0.01, 0.01 and 0.04, respectively. The maximum sample size \( (n = 300) \) would be able to detect a reduction in colonization rates from 30% to 16%, or from 20% to 8%, assuming error rates of \( \alpha = 0.04 \) and \( \beta = 0.20 \) for the final analysis. The study was terminated after the second interim analysis. Incidence rates and dichotomous variables in the two study groups were compared using Fisher’s Exact Test. Continuous variables were compared using non-parametric rank statistics (U-test). Incidence of colonization and catheter-related infections were also evaluated using Kaplan–Meier curves, with the duration of catheterization as time variable, and differences were evaluated with the log-rank test. Except for the main outcome parameter \( (P < 0.01; \text{second interim analysis}) \), a \( P \) value less than 0.05 was considered significant.

Results

Characteristics of patients and catheters

A total of 316 patients could be randomized. Primary dropouts totalled 56 cases (30 patients with a modified CVC/26 patients with a standard CVC) where no catheter was placed due to retraction of indication (20/15), the patient’s deterioration (1/2), miscommunication (2/4), technical problems (6/4), or unavailability of study CVC (1/1) (Figure 1). Secondary dropouts with study catheters in place but with missing evaluation according to the protocol totalled 37 cases (8/29) resulting from accidental removal of the catheter by medical staff (1/22) or the patient (1/4), patient’s death (1/2), or missing microbiological analysis (5/1), leaving 223 catheters with complete data and final microbiological evaluation (Figure 1). In both study centres, the number of modified CVCs being available for statistical analysis was slightly higher than the number of standard catheters, a fact that may be explained in part by the higher number of accidentally removed standard catheters without microbiological evaluation.

Main demographic and clinical characteristics as well as clinical diagnoses of patients enrolled were similar in both groups as summarized in Table 1.

Table 1. Demographic and clinical characteristics of study patients

<table>
<thead>
<tr>
<th></th>
<th>Standard CVC (( n = 105 ))</th>
<th>Modified CVC (( n = 118 ))</th>
<th>Total (( n = 223 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range)</td>
<td>61 (21–80)</td>
<td>62 (29–80)</td>
<td>61 (21–80)</td>
</tr>
<tr>
<td>Male gender, ( n ) (%)</td>
<td>72 (68.6%)</td>
<td>82 (69.5%)</td>
<td>154 (69.1%)</td>
</tr>
<tr>
<td>Body mass index, mean (range)</td>
<td>26.8 (18–64)</td>
<td>26.8 (15–57)</td>
<td>26.8 (15–64)</td>
</tr>
<tr>
<td>APACHE II score on the day of insertion, mean (range)</td>
<td>6.5 (0–17)</td>
<td>6.7 (0–19)</td>
<td>6.6 (0–19)</td>
</tr>
</tbody>
</table>

Diagnosis

- cancer: 41 (39%) | 43 (36%) | 84
- heart/vascular surgery: 23 (22%) | 33 (28%) | 56
- peripheral vascular surgery: 15 (14%) | 17 (14%) | 32
- gastroenterology: 13 (12%) | 15 (13%) | 28
- traumatology: 10 (9%) | 5 (4%) | 15
- urology: 2 (2%) | 2 (2%) | 4
- plastic surgery: 1 (1%) | 1 (1%) | 2
- neurology: – | 2 (2%) | 2

Figure 1. Patients screened and included in the trial. Primary and secondary dropout rates were similar in both study centres.
problems during catheterization occurred equally in both study groups, e.g. dislocation of the catheter (1 in the standard group/2 in the modified group), a possible CVC leak (1:1), and obstruction of lumina (2:1). Medication during catheterization was similar in both groups.

Colonization of catheters and catheter-related infections

Catheter colonization was observed in 6/118 patients (5.1%) in the group with modified catheters and in 38/105 patients (36.2%) with a standard CVC ($P < 0.001$, Fisher’s Exact Test; Table 3). Five patients with a modified CVC additionally developed a CRI compared to 18 of 38 in the standard CVC group ($P = 0.002$; Table 3). When additional flush technique was applied, only a few more cases of colonization ($n = 3/1$) and CRI ($n = 3/1$) were detected as shown in Table 3. However, this technique allowed the identification of one patient in the standard group who developed CR-BSI in contrast to none in the modified group.

<table>
<thead>
<tr>
<th>Type of catheter</th>
<th>Microorganism standard</th>
<th>Microorganism modified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulate-negative staphylococci</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Acinetobacter baumannii/lwoffii</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Corynebacterium spp.</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>2</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 2. Duration of catheterization and indication for CVC removal

<table>
<thead>
<tr>
<th>Duration of catheterization, mean, median (range)</th>
<th>Standard CVC ($n = 105$)</th>
<th>Modified CVC ($n = 118$)</th>
<th>Total ($n = 223$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of catheterization, mean, median (range)</td>
<td>6.7, 6 (2–19)</td>
<td>7.5, 6 (2–36)</td>
<td>7.1, 6 (2–36)</td>
</tr>
<tr>
<td>Regular termination of catheterization, $n (%)$</td>
<td>87 (83%)</td>
<td>104 (88%)</td>
<td>181 (86%)</td>
</tr>
<tr>
<td>Preterm removal of CVC (total)</td>
<td>18</td>
<td>14</td>
<td>32</td>
</tr>
<tr>
<td>Reasons for preterm removal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>redness and/or pain at the site of insertion</td>
<td>5</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>fever or suspected infection</td>
<td>8</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>technical problems</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>death</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3. Results of microbiological evaluation and clinical findings after CVC removal

<table>
<thead>
<tr>
<th>Colonization of catheter</th>
<th>Standard CVC ($n = 105$)</th>
<th>Modified CVC ($n = 118$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonization of catheter including flush technique</td>
<td>38 (36.2%)</td>
<td>6 (5.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Catheter-related infection (CRI) including flush technique</td>
<td>18 (17.1%)</td>
<td>5 (4.2%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Catheter-related bloodstream infection (CR-BSI) including flush technique</td>
<td>– (0%)</td>
<td>– (0%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant.

Colonization of catheters and catheter-related infections

Catheter colonization was observed in 6/118 patients (5.1%) in the group with modified catheters and in 38/105 patients (36.2%) with a standard CVC ($P < 0.001$, Fisher’s Exact Test; Table 3). Five patients with a modified CVC additionally developed a CRI compared to 18 of 38 in the standard CVC group ($P = 0.002$; Table 3). When additional flush technique was applied, only a few more cases of colonization ($n = 3/1$) and CRI ($n = 3/1$) were detected as shown in Table 3. However, this technique allowed the identification of one patient in the standard group who developed CR-BSI in contrast to none in the modified group.

A total of 18 different pathogens were identified from colonized catheters (Table 4). In nine patients, more than one pathogen was identified; among those patients, there was only one with a modified catheter. Modified catheters were dramatically less likely to be colonized by staphylococci (Table 4).

Indwelling time and colonization

Catheters modified with miconazole and rifampicin were not only less likely to be colonized but also, if colonized at all, at a later time point after insertion compared with standard catheters. This is demonstrated by the Kaplan–Meier estimates of the risk of catheter colonization with respect to the length of catheterization ($P < 0.001$; log-rank test; Figure 2). It is noteworthy that both curves have a substantial uncertainty with respect to longer observation periods as the sample size decreases dramatically beyond day 14. However, after 1 and 2 weeks, the rates of colonized standard CVCs were 40% and 60%, respectively, whereas the rate for modified catheters was less than 10% until day 14. Beyond day 14 the rate of sterile catheters in the modified group dropped dramatically though still remaining superior to the rate of the standard group (Figure 2). Whether this difference between the groups at the end of the observation period was still significant could not be determined due to only very small sample sizes at this time point of the study.
Clinical signs and colonization

An increase in body temperature by the time of CVC removal was observed in 10 patients (6 in the standard group/4 in the group with modified CVC). CVC was colonized in five of these 10 cases (3:2, respectively) so that the CVC might have been responsible for the increased temperature.

In one patient with a standard CVC, there were clinical signs of local as well as systemic infection, e.g. swelling, rubor, and fever (39.6°C), but the roll-plate method failed to show colonization (≥15 cfu) on both catheter segments. However, S. aureus was identified on the patient’s skin surface and the flushing fluid of the catheter lumen. Since the same pathogen was found in blood samples drawn on the day of CVC removal, a CR-BSI could be assumed, although not formally proven according to our definitions. In addition, fever decreased in this patient after CVC removal, providing further evidence for a causal relationship.

Discussion

Infections are the most frequent and serious complications associated with the use of CVCs, being responsible for increased morbidity and mortality, longer hospitalization and thus economic costs. In order to reduce the risk of CVC-associated infections, different strategies have been introduced. Nowadays, a logical and promising approach for prevention of microbial colonization is reflected by the incorporation of bactericidal, highly biocompatible antimicrobials in the catheter matrix. In this study, CVCs modified with a combination of miconazole and rifampicin in the catheter matrix were examined for the first time in a prospective controlled randomized clinical trial versus conventional standard catheters.

According to our results, the use of CVCs modified with miconazole and rifampicin was associated with significantly lower rates of catheter colonization and of catheter-related infections compared to standard catheters. One patient in the standard group developed CR-BSI, but none in the modified group. Similar results have been reported earlier from comparative studies using CVCs impregnated either with minocycline and rifampicin or with chlorhexidine and silver sulfadiazine (CSS), with the anti-infective efficacy of the combination of minocycline and rifampicin being superior to that of the latter. In these studies, differences in efficacy between the two antimicrobial-modified catheters have been attributed in part to the presence of antimicrobial activity. Unlike catheters impregnated with minocycline and rifampicin with antimicrobial properties located on both external and internal surfaces of the catheter, the antimicrobial activity in CSS-coated catheters is limited to the external surface. Other factors that may influence efficacy of coated catheters include particular methods in incorporating antimicrobial agents into the catheter matrix and subsequently the availability of those on the catheter surface. With particular respect to CSS-coated catheters, it appears noteworthy that they have quite frequently been associated with anaphylactic reactions leading to a ban of these catheters from clinical use in Japan. In contrast, no adverse effects related to the modified catheters with miconazole and rifampicin were observed in our study.

Experimental studies demonstrated high antimicrobial in vitro efficacy of miconazole–rifampicin-modified catheters by the zone of inhibition against Gram-positive bacteria (>25 mm) and Candida albicans (14 mm), compared to chlorhexidine, silver and sulfadiazine-coated catheters (>13 mm versus 6.9 mm). Zones of inhibition >15 mm are considered highly predictive for in vivo efficacy. In this context, the potential efficacy against Gram-negative bacteria as estimated by zone of inhibition (10–20 mm) is less pronounced however, it is still present. This assumption was confirmed here by the spectrum of pathogens identified in the modified group after CVC removal (Table 4).

The concept of CVC modification is to use the whole of the catheter matrix as a pharmaceutical reservoir for antimicrobial agents. Compatibility of these agents with hydrophobic polyurethanes is a prerequisite for permitting controlled release from the catheter material over a long period. The substances are embedded in a molecularly distributed state in the deep matrix of the catheter material. Both a fine dispersed state and thermodynamic drug supersaturation with the polyurethane matrix give a sustained drug delivery system exceeding the local minimal inhibitory concentrations in the microenvironment of the catheter material, however, with magnitudes of order below a single therapeutic dose. In this scenario, a long period of slow release was chosen in order to protect the inner and outer surface of the catheter during the entire indwelling time. The antimicrobial activity of such systems exceeds 3 weeks, thus offering a unique possibility for long-term application. As a result of these features, a significantly higher rate of sterile CVC was found in this study with respect to long-term application (Figure 2).

Insertion of CVC into the subclavian vein is associated with lower potential risk for infection. In this study, more than 90% of CVC were inserted into the jugular vein. The reason for this procedure was our estimation that the risk for mechanical complications, such as pneumothorax, could exceed that of possible infections. The final decision was made by the physician carrying out the procedure. However, colonization rates as well as the rate of catheter-related bloodstream infections (CR-BSI), observed in our study were comparable to other investigations. In a recent review by Eggimann and Pittet, In a recent review by Eggimann and Pittet, colonization rates (22.1–52.2%) and catheter-related
bloodstream infection (CR-BSI) rates (0–6.6%) were in accordance with the results of this study.

A major aspect in the assessment of antimicrobial catheters is related to the detection of both extraluminal and luminal colonization. In this study, the Maki roll-plate method which detects colonization on the external surfaces was used in all patients whereas the flush technique was used in all but 20 patients. This lack was due to miscommunication at the beginning of the study. In general, the number of infections that were additionally detected via flush technique was rather low (n = 4). This phenomenon may be attributed, at least in part, to the relatively short duration of catheterization (mean 7.1 days) due to the enrolment of only patients with elective surgery yielding low mean APACHE II scores (6 points). As shown by Schierholz et al., catheter infections involving catheter lumens usually do not occur within the first week after catheterization. Instead, there appears to be a temporal sequence in which different locations of the inserted catheters are colonized beginning with the subcutaneous segment, mostly due to contamination at the time of insertion, followed by the catheter tip (mean 8 days), obviously from a haematogenous source, and finally, involving the catheter lumens (mean 13 days), most likely from accessing catheter hubs.19

Furthermore, the study was not blinded because the modified catheters were red coloured, in contrast to the white standard catheters. This may be an explanation for the accidental removal of some standard catheters not identified as study catheters, without obtaining microbiological evaluation according to the protocol. As a consequence, all study patients received information sheets on their beds in addition to special marks in each individual medical chart.

One aspect of potential concern is the possible selection of resistant strains by using antimicrobial-impregnated CVC. Although a very low likelihood of antibiotic resistance has been reported with the use of antimicrobial-impregnated catheters, surveillance for potential resistance is constantly mandatory with respect to the future clinical use of those modified catheters. Pharmacokinetic investigations clearly demonstrated that maximum antimicrobial concentrations detected systemically when using miconazole and rifampicin modified CVCs, as done here in this study, are far below MICs.31 It may be assumed that some antibiotic concentration may be present in the surrounding tissue of modified catheters leading to resistant skin bacteria. Rifampicin, at inocula <10^5 cfu, does not lead to selection or regrowth of resistant staphylococci; at concentrations above the MIC highly resistant strains may be selected provided the number of bacteria is high.40 The skin around the insertion site is usually colonized by numbers lower than 10^6 cfu. Following standard catheter care with antiseptics such as alcohol, the number of resident bacteria may be much lower. Clinical segments of conventional catheters have been found to be colonized with greater than 10^6 cfu thus indicating a higher risk for the development of resistant bacteria. However, oral continuous release of antibiotics from the surface of loaded catheters allowed a persistent antimicrobial effect over an extended period of time as demonstrated by negative bacterial counts in 85% of the modified catheters in this study. Thus dense colonization with high numbers of susceptible bacteria after insertion of modified catheters is very improbable.31,41

The combination of rifampicin with miconazole (4:1, w/w) is characterized by multiple target sites of action, which makes it difficult for staphylococci to adapt.18 For the future, it will be of great interest how antibiotic-modified catheters perform in clinical environments with many complex selective pressures.

In conclusion, our results clearly demonstrate that the use of CVC modified with miconazole and rifampicin is associated with a significantly lower risk for colonization and catheter-related infection compared to standard catheters. However, no conclusion could be drawn from the presented data whether modified catheters were able to prevent Candida infections or even CR-BSI due to limited number of cases available.

Acknowledgements

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References

Efficacy of antibiotic-loaded CVCs


