Rifampicin-impregnated central venous catheters: a meta-analysis of randomized controlled trials

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Background: The use of antimicrobial-impregnated central venous catheters (CVCs) for the prevention of CVC microbial colonization and catheter-related bloodstream infection (CRBSI) remains controversial. Methods: We performed a meta-analysis of randomized controlled trials (RCTs) evaluating CRBSI and colonization of CVCs impregnated with rifampicin-based antimicrobial combinations. Our main analysis compared the occurrence of CRBSI with rifampicin/minocycline-impregnated CVCs with that of non-rifampicin-impregnated CVCs. The PubMed and Cochrane Central Register of Controlled Trials databases were searched (until October 2006). Results: Eight RCTs were included in the analysis. The main analysis (seven RCTs) demonstrated that rifampicin/minocycline-impregnated CVCs were associated with fewer CRBSIs compared with catheters not impregnated with rifampicin/minocycline (OR 0.23, 95% CI 0.14–0.40). The same was true regarding colonization (OR 0.46, 95% CI 0.31–0.69). Further analysis, comparing rifampicin-based CVCs with non-rifampicin-impregnated CVCs, demonstrated superiority of rifampicin-based CVCs in reducing colonization (OR 0.38, 95% CI 0.24–0.62) and CRBSI (OR 0.24, 95% CI 0.14–0.40). Similar results, suggesting superiority of rifampicin/minocycline-impregnated CVCs, were noted in a subgroup analysis of colonization and CRBSIs in which rifampicin/minocycline-impregnated CVCs were compared with simple, non-tunnelled, non-antimicrobially impregnated CVCs, a subgroup analysis that was performed by excluding low quality RCTs, and a subgroup analysis for colonization comprising studies in which the sonication technique was used. No serious adverse events and no difference in mortality between the two treatment groups were reported. No clear conclusions can be made regarding the impact of the use of rifampicin/minocycline-impregnated CVCs on the development of antimicrobial resistance based on the available data. Conclusions: The available evidence suggests that rifampicin/minocycline-impregnated CVCs are safe and effective in reducing the rate of catheter colonization and CRBSI. Further research should focus on the possible development of resistance and on pharmacoeconomic issues related to the use of rifampicin/minocycline-impregnated CVCs.

Keywords: bacteraemia, biofilms, microbial, RCTs, coated, coating, antibiotics, antiseptics, CVCs, prevention, chlorhexidine/silver sulfadiazine, CHSS, tunnelled catheters, miconazole, impregnation

Introduction

Central venous catheters (CVCs) are indispensable in modern-day clinical medicine. The most common and life-threatening complication of central venous catheterization is catheter-related bloodstream infection (CRBSI). In the USA, >200 000 cases of nosocomial bloodstream infections (BSIs) are reported to occur annually.1–5 CVCs are the most frequent cause of BSIs.1,3,5

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These episodes of CRBSI are associated with an attributable mortality rate ranging from 14 to 28%. Prolongation of hospitalization by 10–40 days, and additional costs to the healthcare system of up to $35,000 per episode.

A prodrome stage of a catheter-related infection is microbial colonization of the catheter surface. Microorganisms are able to adhere to catheter surfaces and embed themselves in a layer of biofilm, a product of the microorganism and the human body. Using scanning and transmission electron microscopy techniques, Raad et al. have shown that the majority of CVCs become colonized with microorganisms very soon after their insertion in the human body.

In an attempt to prevent CVC colonization and CRBSIs, many intervention measures have been studied. These include, among others, aseptic techniques for handling the CVC, skin disinfection and the use of ports, of catheters coated with antimicrobial agents and of antibiotic lock solutions. The use of CVCs coated with antimicrobial agents is a topic that has generated intense discussion. Thus, we sought to perform a meta-analysis of randomized controlled trials (RCTs) on catheters impregnated with antibiotics, focusing on rifampicin, to pool data examining the hypothesis that this strategy is effective in preventing CRBSIs.

Methods

We searched (latest search performed on 30 October 2006) the PubMed and the Cochrane Central Register of Controlled Trials databases using the terms: rifampin, rifampicin, catheter and infection, and combinations of these terms. In addition, we reviewed references of the initially retrieved studies. No exclusion criteria were set for the date or language of the publications. We included in the analysis all RCTs that compared clinical outcomes of patients who had CVCs impregnated with rifampicin alone or in combination with other antimicrobial agents with patients who had CVCs not impregnated with rifampicin. Two investigators (I. C. and K. F.) independently looked for relevant studies, decided upon their inclusion in the meta-analysis and extracted the pertinent data. Any disagreements between the reviewers were discussed in meetings of all authors.

A quality review of each RCT was performed to include details of randomization, double-blind procedure, as well as information on dropouts and withdrawals. One point was awarded for the specification of each criterion (Jadad score); the maximum score for a study is 5. RCTs were considered of high quality if they scored more than 2 points according to the reported methodology.

The assessed primary outcome was CRBSI. The analysed secondary outcomes were microbial colonization of the catheter, the occurrence of adverse events, emergence of microbial resistance to the catheter-impregnating antimicrobial agents and all-cause mortality. Mortality and toxicity were analysed both on an intention-to-treat (ITT) and a per-protocol basis, whereas the other three outcomes were analysed only per protocol.

The outcome definitions adopted for our meta-analysis were based on those proposed by the Centers for Disease Control and Prevention. Catheter colonization was defined as (i) isolation of ≥15 cfu of any organism from the tip or the subcutaneous segment of the CVC, using the roll plate technique or (ii) isolation of >1000 cfu of any organism using the sonication technique. We defined as CRBSI the isolation of an organism from at least one blood specimen obtained by peripheral venipuncture in a patient with concurrent signs and symptoms of infection (fever, chills, hypotension). In addition, the catheter had to be colonized with the same microorganism.

We defined as the main analysis, the analysis of outcomes of RCTs that compared the efficacy of rifampicin and minocycline-impregnated CVCs with that of non-rifampicin-impregnated CVCs. A subgroup analysis of outcomes included RCTs that compared non-tunnelled, rifampicin/minocycline-impregnated CVCs with simple, non-tunnelled, non-antimicrobially impregnated CVCs. In addition, another subgroup analysis included RCTs that compared CVCs impregnated with any rifampicin-based combination of antibiotics or antifungals with non-rifampicin-impregnated catheters. Furthermore, a subgroup analysis was performed by excluding low-quality RCTs. Finally, given that the roll-plate technique can miss a proportion of endoluminal colonizations, a subgroup analysis for colonization was performed, comprising studies in which the sonication technique was elaborated.

Statistical analyses were performed using the computer program Review Manager (RevMan) Version 4.2 for Windows (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003). Pooled odds ratios and 95% confidence intervals (CI) for all primary and secondary outcomes were calculated, by using both the Mantel–Haenszel fixed effects and the DerSimonian–Laird random effects models. The heterogeneity between studies was assessed by using the χ² test (P < 0.1 was considered suggestive of heterogeneity). For all analyses, results from the fixed effects model are presented only when there was no heterogeneity between studies; otherwise results from the random effects model, as well as from the χ² test are presented. Publication bias was assessed by the funnel plot method using Egger’s test.

Results

Study selection and study characteristics

One hundred and fifty-three potentially relevant studies were initially identified by our search. Figure 1 is a flow diagram showing the steps that we followed in order to identify the RCTs fulfilling the inclusion criteria of our meta-analysis. The majority of the studies were excluded because they did not evaluate antibiotic-impregnated catheters. In addition, a significant number of the excluded publications referred to catheters other than central venous ones. As shown (Figure 1), eight RCTs were finally considered eligible for inclusion in our meta-analysis.

The eight RCTs included 3452 and 3081 catheters in the intention-to-treat analysis for CRBSIs and colonization, respectively, with 3000 and 2610 catheters, respectively, being finally evaluable on a per-protocol basis (total dropouts and exclusions: 13.1% and 15.3%, respectively). In three studies, each patient was allowed to participate only once, and in another study this occurred without being an inclusion criterion (356 catheters were inserted in 355 patients). Two studies did not report data in detail regarding the number of catheters per patient, whereas in the other two, there were 1036 catheters inserted...
in 1001 patients.\textsuperscript{21,37} Thus, re-randomization of a patient was relatively rare, at least in the studies that reported on this issue.

The results of the quality assessment of the RCTs included in this meta-analysis are presented in Table 1. As shown in Table 1, all but one of the RCTs were of high quality (Jadad score \( \geq 2 \)). The mean score of the included RCTs was 3.5, which is considered high. Reasons for patient or catheter exclusion from the analysis were presented in detail in all RCTs. Points were mainly deducted due to the absence of details regarding the blinding procedure (most importantly whether the catheters looked identical regarding the material used, size or colour). The authors of the eight RCTs were not contacted for more information on the methodological quality.

The main study and patient characteristics are presented in Table 2. All studies included seriously ill patients with significant co-morbidity. Specifically, two studies evaluated the effectiveness of the impregnated catheters in patients with cancer\textsuperscript{35,36} and two more\textsuperscript{33,38} in ICU-hospitalized patients. There was variability among the trials regarding the insertion site of the CVCs, their manufacturing material and number of lumens. Subclavian

**Figure 1.** Flow diagram of reviewed articles. CNS, central nervous system.
tunnelled CVCs were used as controls. In all RCTs, antibiotic-impregnated CVCs in preventing catheter colonization and CRBSI in long-term dwell time. Antibiotic-impregnated CVCs demonstrated that these catheters are associated with a significant reduction in the CRBSI rate compared with CVCs not impregnated with the rifampicin/minocycline combination (OR 0.23, 95% CI 0.14–0.40, fixed effects model) (Figure 2). An analysis of the seven trials that compared rifampicin/minocycline-impregnated CVCs with simple, non-impregnated, non-tunnelled catheters also demonstrated lower rates of CRBSI in the rifampicin/minocycline study group (OR 0.25, 95% CI 0.14–0.44, fixed effects model, four studies). In addition, subgroup analysis of high-quality studies (Jadad score >2) that evaluated rifampicin/minocycline-impregnated CVCs in comparison with other catheters again demonstrated statistically significant superiority (fewer CRBSIs) of rifampicin/minocycline-impregnated CVCs (OR 0.25, 95% CI 0.14–0.44, six studies, fixed effects model). An analysis of the RCTs evaluating CVCs impregnated with rifampicin-based antimicrobial combinations (all eight RCTs) demonstrated that they are associated with a reduced rate of CRBSI compared with CVCs that are not impregnated with such combinations (OR 0.24, 95% CI 0.14–0.40, fixed effects model).

Secondary outcomes

Information on CVC colonization rates was available in six of the seven trials that compared rifampicin and minocycline-impregnated CVCs with non-rifampicin-impregnated CVCs (main analysis). In three of these, the control group consisted of non-tunnelled, non-antimicrobially coated catheters; in two RCTs the controls were platinum, silver and carbon; and CHSS-coated CVCs while in another RCT the control group consisted of tunnelled non-antibiotic-impregnated CVCs. Result pooling demonstrated that rifampicin/minocycline-impregnated non-tunnelled CVCs were effective in reducing the rate of catheter microbial colonization compared with CVCs that lacked such antibiotic impregnation (OR 0.46, 95% CI 0.31–0.69, random effects model; χ² test for heterogeneity: P = 0.01) (Figure 3). In the six aforementioned studies, the catheters were cultured quantitatively by the sonication method.

Table 1. Quality assessment of randomized controlled trials included in the meta-analysis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Randomized</th>
<th>Double blind</th>
<th>Quality of randomization</th>
<th>Quality of double blinding</th>
<th>Detailed description of withdrawals and dropouts</th>
<th>Jadad score (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raad et al. 1997</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Chatzinikolaou et al. 2003</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>-1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Leon et al. 2004</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Hanna et al. 2004</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Darouiche et al. 1999</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Fräenkel et al. 2006</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Darouiche et al. 2005</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Yucel et al. 2004</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

*Yes’ and ‘Good’ were awarded +1 point, ‘No’ and ‘Not reported in detail (NR)’ 0 points, and ‘Poor’ –1 point.
Table 2. Patient and central venous catheter (CVC) characteristics of randomized controlled trials included in the meta-analysis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Jadad score</th>
<th>Patient population</th>
<th>Antibiotic coating/ type of control catheter</th>
<th>Site of insertion</th>
<th>Catheter material/ number of lumens</th>
<th>Number of catheters in the ITT groups</th>
<th>Duration of catheterization [median (range) or mean ± SD]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raad et al. 1997</td>
<td>4</td>
<td>cancer, cardiopulmonary, surgical (CNS, head, abdomen)</td>
<td>rifampicin, minocycline/ uncoated</td>
<td>subclavian, internal jugular, femoral veins</td>
<td>polyurethane/triple lumen</td>
<td>147</td>
<td>6 (1–21) 6 (1–28)</td>
</tr>
<tr>
<td>Chatzinikolaou et al. 2003</td>
<td>3</td>
<td>cancer</td>
<td>rifampicin, minocycline/ uncoated</td>
<td>femoral vein</td>
<td>polyurethane/double lumen</td>
<td>71</td>
<td>6 (1–32) 7 (1–32)</td>
</tr>
<tr>
<td>Leon et al. 2004</td>
<td>4</td>
<td>ICU</td>
<td>rifampicin, minocycline/ uncoated</td>
<td>subclavian, internal jugular veins</td>
<td>polyurethane/triple lumen</td>
<td>228</td>
<td>10.3 10.4</td>
</tr>
<tr>
<td>Hanna et al. 2004</td>
<td>5</td>
<td>cancer</td>
<td>rifampicin, minocycline/ uncoated</td>
<td>subclavian, cephalic, basilic veins</td>
<td>silicone/single and double lumen</td>
<td>192</td>
<td>66 ± 31 63 ± 31</td>
</tr>
<tr>
<td>Darouiche et al. 1999</td>
<td>4</td>
<td>cancer, cardiopulmonary, CNS</td>
<td>rifampicin, minocycline/CHSS</td>
<td>subclavian, internal jugular, femoral veins</td>
<td>polyurethane/triple lumen</td>
<td>414</td>
<td>6 (1–55) 7 (1–36)</td>
</tr>
<tr>
<td>Fraenkel et al. 2006</td>
<td>3</td>
<td>ICU</td>
<td>rifampicin, minocycline/silver, platinum and carbon</td>
<td>subclavian, internal jugular, femoral veins</td>
<td>polyurethane/triple lumen</td>
<td>319</td>
<td>5.8 (NR) 5.8 (NR)</td>
</tr>
<tr>
<td>Darouiche et al. 2005</td>
<td>2</td>
<td>cancer, cardiopulmonary, CNS</td>
<td>rifampicin, minocycline (non-tunnelled)/ tunnelled uncoated</td>
<td>subclavian, internal jugular veins</td>
<td>silicone/single and double lumen</td>
<td>188</td>
<td>29 (1–137) 38 (1–275)</td>
</tr>
<tr>
<td>Yucel et al. 2004</td>
<td>3</td>
<td>cancer, gastroenterology, CNS urology, surgical (cardiovascular, trauma, plastic)</td>
<td>rifampicin, miconazole/ uncoated</td>
<td>internal jugular</td>
<td>polyurethane/triple lumen</td>
<td>156</td>
<td>7.5 (2–36) 6.7 (2–19)</td>
</tr>
</tbody>
</table>

CNS, central nervous system; CVC, central venous catheter; ICU, intensive care unit; CHSS, chlorhexidine/silver sulfadiazine; ITT, intention-to-treat; NR, not reported.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Colonization (%)</th>
<th>CRBSI (%)</th>
<th>Mortality ITT (%)</th>
<th>Mortality per protocol (%)</th>
<th>Systemic toxicity ITT (%)</th>
<th>Systemic toxicity per protocol (%)</th>
<th>Local toxicity* ITT (%)</th>
<th>Local toxicity* per protocol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raad et al. 1997</td>
<td>11/130 (8)</td>
<td>36/136 (26)</td>
<td>0/130 (0)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Chatzinikolaou</td>
<td>13/66 (20)</td>
<td>16/64 (25)</td>
<td>0/66 (0)</td>
<td>16/71 (23)</td>
<td>16/66 (24)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Leon et al. 2004</td>
<td>20/187 (11)</td>
<td>45/180 (25)</td>
<td>6/187 (3)</td>
<td>41/228 (18)</td>
<td>27/187 (14)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hanna et al. 2004</td>
<td>NR</td>
<td>NR</td>
<td>3/182 (2)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Darouiche et al.</td>
<td>28/356 (8)</td>
<td>87/382 (23)</td>
<td>1/356 (0.3)</td>
<td>0/356 (0)</td>
<td>2/382 (0)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Fraenkel et al.</td>
<td>25/280 (9)</td>
<td>43/294 (15)</td>
<td>4/280 (1)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Darouiche et al.</td>
<td>41/166 (25)</td>
<td>41/146 (28)</td>
<td>2/186 (1)</td>
<td>0/188 (0)</td>
<td>0/186 (0)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Yucel et al. 2004</td>
<td>7/118 (6)</td>
<td>41/105 (39)</td>
<td>0/118 (0)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

CRBSI, catheter-related bloodstream infection; CVC, central venous catheter; ITT, intention-to-treat; MR, minocycline (miconazole in the last study) plus rifampicin; NR, not reported.

*aLocal inflammation, ‘aseptic thrombophlebitis’.

*bMortality due to bloodstream infection.
After excluding from the six studies the only study with low quality score results did not change substantially (OR 0.38, 95% CI 0.29–0.49, fixed effects model). In addition, subgroup analysis of the studies in which the rifampicin/minocycline-impregnated CVCs were compared with non-tunnelled non-antibiotic-impregnated catheters demonstrated even lower rates of catheter colonization favouring the minocycline-rifampicin study group (OR 0.38, 95% CI 0.26–0.56, fixed effects model, three studies). Adding to the primary analysis group, the RCT evaluating rifampicin/miconazole-impregnated CVCs, the pooled data analysis demonstrated that CVCs impregnated with any rifampicin-based antibiotic combination had a lower rate of microbial colonization compared with CVCs not impregnated with rifampicin (OR 0.38, 95% CI 0.24–0.62, random effects model; \( \chi^2 \) test for heterogeneity: \( P < 0.001 \)).

Mortality in all randomized patients (ITT) and in patients included in the per-protocol analysis were reported in four studies each (Table 3). Meta-analysis of these data showed that no statistically significant difference in mortality existed between the two treatment arms (mortality in the ITT analysis: OR 1.16, 95% CI 0.77–1.74, and mortality in the per-protocol analysis: OR 1.30, 95% CI 0.80–2.11, fixed effects model for both analyses). Few data were available regarding the development of systemic toxicity due to the use of the catheters, a phenomenon that seems to be very rare (Table 3). Data regarding local toxicity (local inflammation or aseptic thrombophlebitis) were reported in four studies in the per-protocol analysis, and no difference in toxicity development existed between the two CVC groups (OR 0.67, 95% CI 0.35–1.26, fixed effects model).

There were limited data in the studies included in this meta-analysis regarding the possible association between the use of antibiotic-impregnated CVCs and development of antimicrobial resistance to the antibiotics used for CVC impregnation. The issue was evaluated from two viewpoints in some of the included studies, namely the development of resistance in initially susceptible isolates that colonized or caused a CRBSI and the appearance (colonization or CRBSI) of isolates with intrinsic resistance to rifampicin/minocycline in patients treated with CVCs impregnated with this combination. The main results of the included studies regarding the emergence of resistance are shown in Table 4.

![Figure 2](https://academic.oup.com/jac/article-abstract/59/3/359/842939)

Figure 2. Meta-analysis of trials evaluating rifampicin and minocycline-impregnated central venous catheters (CVCs) (treatment) versus CVCs without rifampicin/minocycline impregnation (control): catheter-related bloodstream infection. Vertical line = ‘no difference’ point in catheter-related bloodstream infection between the two types of catheters. Horizontal lines = 95% CI. Square = odds ratio; the size of each square denotes the size of the trial. Diamond = pooled odds ratio for all studies.

![Figure 3](https://academic.oup.com/jac/article-abstract/59/3/359/842939)

Figure 3. Meta-analysis of trials evaluating rifampicin and minocycline-impregnated central venous catheters (CVCs) (treatment) versus CVCs without rifampicin/minocycline impregnation (control): colonization. Vertical line = ‘no difference’ point in bacterial colonization between the two types of catheters. Horizontal lines = 95% CI. Square = odds ratio; the size of each square denotes the size of the trial. Diamond = pooled odds ratio for all studies.
technique. Regarding the definition used for CRBSI, the majority used a lower threshold (as far as the semi-quantitative roll-plate technique is concerned, Hanna et al. defined as catheter colonization the isolation of any microorganism from the catheter tip or its subcutaneous segment. One study, although it had the same cutoff point as far as the semi-quantitative roll-plate technique is concerned, used a lower threshold (>1000 cfu) for the quantitative sonication technique. Regarding the definition used for CRBSI, the majority of the studies were uniform. In particular, CRBSI was defined as the isolation of the same microorganism from a paired blood-culture specimen obtained through a peripheral vein and through the implicated CVC, in a patient with signs and symptoms of infection that cannot be attributed to an infection at a different site other than the catheter. Additionally, four studies used molecular techniques in order to relate genetically the microorganisms isolated from the catheter and the peripheral vein-collected blood culture.

In most studies included in the meta-analysis, a reduction in the rate of bacterial colonization of the catheter was observed that was translated in a reduction in the rate of CRBSI. Two studies demonstrated that antibiotic-impregnated catheters were as likely as tunnelled catheters to become colonized and less likely than them to be associated with bloodstream infection. The authors of the one study comment that a possible explanation might be that the antimicrobial impregnation may alter the structure of the biofilm reducing the likelihood of detachment of biofilm-embedded microorganisms from the catheter surface to the bloodstream. In addition, microbial cultures are less sensitive than confocal or scanning laser microscopy in detecting microbial presence on the catheter surface. Finally, in one study, the reduction in the rate of bacterial colonization of the catheter was not accompanied by a reduction in the rate of CRBSI.

The benefit of using rifampicin and minocycline-impregnated non-tunnelled catheters was not only demonstrated when these catheters were compared with non-impregnated non-tunnelled catheters, but was also statistically significant when compared with CHSS-coated catheters. The inferiority of the studied CHSS-coated catheters might be explained by the fact that only their exterior surface was coated, whereas both the external and internal surfaces of the antibiotic-impregnated catheters were coated. Moreover, the combination of rifampicin and minocycline exhibits anti-staphylococcal surface activity that is superior to CHSS, and the antibiotic-impregnated catheter retains its surface antimicrobial activity in situ for longer periods. However, we should note that the current second generation of CHSS-coated catheters have tripled the antimicrobial concentration and include both external and luminal coating, including the extension pieces and hubs. Two recent RCTs reported that a significant decrease in colonization and CRBSI rates was achieved by second-generation CHSS-coated catheters compared with regular catheters.

### Table 4. Reporting of development of resistance in the randomized controlled trials included in the meta-analysis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Fresh catheters impregnated with rifampicin/minocycline showed inhibitory activity against organisms isolated from indwelling catheters. There was no evidence suggesting emergence of resistance.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raad et al. 1997</td>
<td>MICs of rifampicin/minocycline for coagulase-negative staphylococci (CoNS) isolates cultured from rifampicin-minocycline-impregnated and non-impregnated catheters were similar.</td>
</tr>
<tr>
<td>Chatzinikolaou et al. 2003</td>
<td>Colonization by CoNS was significantly more frequent in non-impregnated than in rifampicin/minocycline-impregnated central venous catheters (CVCs), whereas Candida species were more commonly found on impregnated CVCs (relative risk, 5.84; 95% CI 1.31–26.1).</td>
</tr>
<tr>
<td>Leon et al. 2004</td>
<td>MIC of rifampicin/minocycline was somewhat lower for CoNS isolates from rifampicin/minocycline-minocycline-impregnated than from non-impregnated CVCs (no statistical testing was reported).</td>
</tr>
<tr>
<td>Hanna et al. 2004</td>
<td>Ranges of MICs and minimum bactericidal concentrations (MBCs) of rifampicin/minocycline were similar for S. epidermidis and enterococci isolates from rifampicin/minocycline-impregnated and chlorhexidine/silver sulfadiazine-impregnated catheters.</td>
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<tr>
<td>Darouiche et al. 1999</td>
<td>In rifampicin/minocycline-impregnated catheters, Candida, Klebsiella, Enterobacter and Pseudomonas species were mainly isolated, whereas in silver/platinum/carbon-impregnated catheters, Enterobacter, enterococci, S. aureus and S. epidermidis were mainly isolated.</td>
</tr>
<tr>
<td>Fraenkel et al. 2006</td>
<td>Statistically insignificant trends were noted, with fungal colonization being more common in rifampicin/minocycline catheters (relative risk, 2.94; 95% CI 0.82–10; P = 0.09) and, on the contrary, Gram-negative bacteria being more common in tunnelled, non-impregnated catheters (relative risk, 2.56; 95% CI 0.80–8.13; P = 0.15) as well as polybacterial colonization (relative risk, 2.27; 95% CI 0.80–6.50; P = 0.19).</td>
</tr>
<tr>
<td>Yucel et al. 2004</td>
<td>No data reported.</td>
</tr>
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### Discussion

The findings of this meta-analysis indicate that non-tunnelled CVCs impregnated with rifampicin and minocycline are effective in reducing the incidence of catheter colonization and catheter-related bloodstream infection compared with non-impregnated catheters. The reduction of the occurrence of catheter colonization and CRBSI is significant in the main analysis and in all the subgroup analyses we performed. In addition, there was no evidence, although limited by the scarcity of the data available, of development of microbial resistance to the antibiotics used for catheter impregnation. The studies included in the meta-analysis used similar and up-to-date definitions in order to determine catheter colonization and CRBSI. More precisely the majority of the studies defined as catheter colonization the isolation of ≥15 cfu (roll plate technique) or >1000 cfu (sonication technique) of any microorganism from the catheter tip or its subcutaneous segment. One study, although it had the same cutoff point as far as the semi-quantitative roll-plate technique is concerned, used a lower threshold (>100 cfu) for the quantitative sonication technique. Regarding the definition used for CRBSI, the majority of the studies were uniform. In particular, CRBSI was defined as the isolation of the same microorganism from a paired blood-culture specimen obtained through a peripheral vein and through the implicated CVC, in a patient with signs and symptoms of infection that cannot be attributed to an infection at a different site other than the catheter. Additionally, four studies used molecular techniques in order to relate genetically the microorganisms isolated from the catheter and the peripheral vein-collected blood culture.

In most studies included in the meta-analysis, a reduction in the rate of bacterial colonization of the catheter was observed...
A major point of expressed concern associated with the use of antibiotic-impregnated catheters is the possibility of development of antimicrobial resistance during treatment with impregnated catheters.\textsuperscript{34-36} From the published studies, three that used short-term catheters\textsuperscript{21,36,37} (duration of catheterization less than 14 days) and one that evaluated long-term catheters,\textsuperscript{35} all impregnated with rifampicin and minocycline, failed to show evidence of development of resistance to either agent. However, more data are clearly needed to further clarify the possibility of development of resistance. Thus, continued surveillance is required, especially in the setting of long-term catheterization.

The majority of trials did not demonstrate that the use of antibiotic-impregnated CVCs has affected the kind of microorganisms that usually colonize CVCs. However, one RCT\textsuperscript{38} included in the meta-analysis recorded a significant increase in CVC colonization with 	extit{Candida} spp. in the arm of rifampicin/minocycline-impregnated CVCs compared with non-impregnated ones and the opposite for coagulase-negative staphylococci (CoNS). Similarly, Darouiche et al.\textsuperscript{34} described a (statistically) non-significant higher likelihood of fungal colonization of antimicrobial-impregnated non-tunneled CVCs compared with non-antibiotic-impregnated, tunneled catheters, whereas Gram-negative bacteria and polymicrobes tended to colonize tunneled catheters more frequently than antimicrobial-impregnated catheters. Finally, Fraenkel et al.\textsuperscript{33} mentioned that among the isolated organisms, 	extit{Candida} was common in rifampicin/minocycline-impregnated catheters, whereas staphylococcal infections were common in silver/platinum/carbon-impregnated CVCs. Thus, overall, there is some evidence that rifampicin/minocycline-impregnated catheters are prone to be colonized with specific pathogens (especially 	extit{Candida}), whereas they are protected from others (especially CoNS).

Our meta-analysis is not without limitations. No clear conclusions can be made regarding the costs related to the use of this novel technology. Only three studies\textsuperscript{21,34,35} provide a basic calculation of costs, favouring the use of the antibiotic-impregnated catheters in accordance with a related editorial.\textsuperscript{47} We believe that RCTs with more thorough financial calculations are necessary to clearly present the economic aspect of the introduction of such technology in daily clinical practice. Our meta-analysis is also limited by the lack of RCTs evaluating the use of the rifampicin-coated catheters in long-term catheterization. Currently, only two such trials have been published.\textsuperscript{34,35}

Since the pathophysiology of CRBSI is affected by the duration of catheterization, and there are a large number of chronically and seriously ill patients benefiting from the use of CVCs, studies evaluating the antibiotic-impregnated catheters in long-term catheterization settings will be very useful. It is important to note that antibiotic-coated catheters might not offer the same benefits in all patient populations and settings. For example, in cancer patients with severe mucositis or transplantation patients with graft versus host disease, other sites such as mucosa or an inflamed or obstructed gastrointestinal tract can be sources of CRBSI. Similarly, antibiotic-coated catheters may not lead to a significant decrease in the number of BSIs in a hospital with high rates of Gram-negative BSIs, an issue that has not been systematically examined in clinical studies. Also, it should be emphasized that concerns may exist regarding the appropriateness of the blinding process in the included studies, since the coated and uncoated catheters may have looked slightly different. However, in only one double-blind study included in the meta-analysis is it stated that the catheters had different colours.\textsuperscript{36}

Another limitation is that we did not perform a pooled analysis of events per observation-time (e.g. CRBSI/1000 catheter-days). In addition, the absence of molecular techniques in order to relate genetically the microorganisms isolated from the catheter and the peripheral vein-collected blood culture, in three studies,\textsuperscript{35,36,39} represents a methodological deficiency of these studies. This may have caused some false-positive results in cases of presumed infections, especially those in which CoNS were isolated from the catheters. Furthermore, chlorhexidine gluconate was not used as a standard care for cutaneous antisepsis in any of the analysed studies. Chlorhexidine is now strongly recommended by the CDC guidelines, since it has been demonstrated to decrease both colonization and CRBSI substantially.\textsuperscript{38} Thus, the use of chlorhexidine for skin preparation may have comparable efficacy to the use of rifampicin-coated catheters, since both approaches are likely to prevent infection from similar organisms. However, no study has examined this issue systematically yet. Also, another limitation that should be emphasized is the weakness of the definition of CRBSI regarding CoNS species (contamination versus infection). Finally, our meta-analysis was not able to draw any clear conclusions on the important issue of development of microbial resistance to the antibiotics used for impregnation.

In conclusion, our meta-analysis demonstrates that CVCs impregnated with rifampicin and minocycline are safe and efficacious in reducing the rate of catheter colonization and catheter-related bloodstream infection. Large, appropriately designed and sufficiently powered, RCTs are needed in order to further clarify the issues of the possibility of emergence of microbial resistance, to evaluate more their benefits in long-term catheterization, to compare them with the newer generations of CHSS catheters that are coated on both surfaces, and to evaluate the pharmacoeconomic aspects of their use.

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Transparency declarations

None to declare.

References


