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Antimicrobially impregnated catheters: An overview of randomized controlled trials

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ABSTRACT: In order to acquire an overview of the effectiveness of antimicrobially impregnated catheters on the prevention of catheter related bloodstream infections (CRI), we conducted a systematic review concentrating on randomized controlled trials (RCTs). The analysis end point was CRI; therefore, studies focussing only on catheter colonization were excluded. We did not consider abstracts for analysis. We identified 24 RCTs investigating the effectiveness of antimicrobially impregnated catheters. In addition, we discovered five meta-analyses and four studies investigating cost effectiveness. For the majority of antimicrobially impregnated catheter types only a few studies were available, and not enough to draw conclusions. Therefore, despite a relatively large number of RCTs available, the routine use of antimicrobially impregnated catheters as a measure for CRI prevention remains controversial, with a need for more high quality studies. (The Journal of Vascular Access 2003; 4: 102-10)

KEY WORDS: *Impregnated catheters, Catheter related infection, Randomized controlled trials*

INTRODUCTION

Catheter related bloodstream infections (CRI) are a major problem in intensive care units, according to data from nosocomial infection surveillance systems (1, 2). Therefore, prevention, or even a small reduction in CRI incidence, has a significant impact. Catheter modification to prevent the adherence of pathogens is one strategy for reducing CRI. Antimicrobial agents can either be applied only on the catheter surface or be incorporated in the entire catheter material. There are many published studies investigating these catheters, so many in fact, that it is difficult to gain an overall balanced view. Therefore, we performed a systematic review to analyze the situation in 2003.

METHOD

We searched MEDLINE for relevant trials from 1966 to June 2003, as well as reference lists of existing meta-analyses and randomized trials (RCTs). The search terms were 'impregnated catheters' and 'coated catheters'.

We only considered clinical studies with a randomized controlled design. We excluded animal studies and *in vitro* investigations. The articles identified were reviewed by title and/or abstract and in detail, if required. We also examined the reference lists of the articles found.

We did not consider for this investigation studies published only as abstracts because they did not allow careful study quality assessment. We excluded catheter colonization studies, because our main subject was CRI. In some cases, more information about a particular study was found by a meta-analysis from further contact with the authors. Studies dealing only with impregnated cuff catheters were also excluded.

The following information was taken from each identified article: authors, year of publication, setting in which the study was performed, diagnosis criteria for colonization and CRI, average duration of catheter use, relative colonization risk (as a possible surrogate end point) (3) and CRI. If not readily available, this information was calculated from the authors' data by using "EPI Info".

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The studies identified were categorized in the following groups:
- RCTs with chlorhexidine silver sulfadiazine (CHSS) impregnated catheters;
- RCTs with catheters impregnated with other silver compounds;
- RCTs with catheters impregnated with other antiseptic substances;
- RCTs with antibiotic coated catheters;
- Meta-analyses;
- Studies investigating the costs of using impregnated catheters;
- Studies investigating side-effects.

RESULTS

We found 21 RCTs that investigated the effectiveness of antiseptically impregnated catheters. Among them were 12 RCTs that studied CHSS impregnated catheters (Tab. I). A further five RCTs investigated various silver compounds (Tab. II), two RCTs studied the effectiveness of benzalkonium chloride and one of chlorhexidine alone (Tab. III). In addition, four RCTs investigated the use of antibiotics for impregnation; three studied the use of minocycline/rifampicin (M/R) (Tab. IV). One study was a triple arm study with a CHSS and an M/R arm (4). Another study did not compare the effectiveness of M/R with an uncoated catheter; instead, the authors compared the effectiveness of CHSS and M/R regarding impregnation (5).
Of the CHSS studies, only one showed a significant CRI reduction, whereas six demonstrated a significant positive effect of CHSS impregnation on catheter colonization. Five meta-analyses attempted to pool data from individual studies on CHSS impregnated catheters (Tab. V). All meta-analyses found some benefit from CHSS impregnated catheters, but this was significant only, when the following studies were included: those solely available as abstracts (6); studies investigating heparin bonded catheters (7) or when the analyses only focussed on studies with short-term catheterization (8-10).
In our investigation of the RCTs on other various silver compounds, no individual study showed any significant CRI reduction, the same being true for the level of catheter colonization. However, the silver compounds used differed, making data pooling impossible. This was the case for RCTs with benzalkonium chloride catheters and chlorhexidine impregnation alone, of which only one study found any significant advantage and where catheter colonization was the main end point for analysis (11).
All the studies evaluating the effectiveness of antibiotic impregnation showed a significant reduction in colonization of CRI.
The most extensive RCT investigating impregnated catheters even showed a significant CRI reduction when comparing antibiotic impregnated catheters with CHSS impregnated catheters instead of uncoated catheters (5). Four studies attempted to determine the cost-effectiveness of impregnated catheters, three of CHSS catheters and one of M/R impregnated catheters (Tab. VI). They all demonstrated cost-effectiveness, at least under specific circumstances. Side-effects of CHSS impregnated catheters were reported in at least four studies (Tab. VII), one of these reports originated from Europe (12).

DISCUSSION

CHSS impregnated catheters

Chlorhexidine and silver sulfadiazine are incorporated in the external surface of the catheter in order that they are slowly released into the surrounding area. Chlorhexidine is a broad spectrum antiseptic and is effective against nearly all nosocomial pathogens and fungi. Silver sulfadiazine has been used topically for burns for many years, delaying colonization and substantially reducing infection incidences.
Of the articles we found, those assessing CHSS impregnated catheters were the most frequent; therefore, this type of catheter would appear suitable for meta-analyses. However, a significant summary odds ratio of the study data pooled for this analysis was achieved only by additionally considering studies with short-term catheterization (<8 days). This conclusion seems reasonable, because the CHSS impregnated catheters included were coated only on their external surfaces, so that during a longer period intraluminal colonization possibly develops inside the catheter - this being the most common source of infection in long-term catheter use. Meanwhile, CHSS impregnated catheters impregnated on the internal and external surfaces, with a higher concentration of chlorhexidine have been developed and tested, but only abstracts are currently available.

Silver compounds for impregnation

Silver with its oligodynamic silver ion is effective against the majority of bacteria and fungi. Silver ions attach themselves to the SH groups of cellular membrane enzymes blocking pathogen metabo-

TABLE I - RESULTS OF STUDIES INVESTIGATING CHLORHEXIDINE SILVER SULFADIAZINE IMPREGNATED CATHETERS

Study	Year	Study population	Diagnosis colonization	Diagnosis infection	Average duration of use	Number of catheters	Relative risk colonization (C195)	Relative risk CRI (C195)
Bach et al. (22)	1996	Cardiac surgery	≥ 1 cfu from 1 ml after sonication and/or growth in the broth of catheter segment	P	8	233	0.72 (0.53-0.96)	No CRI in study group, p > 0.05
Ciresi et al. (23)	1996	Inpatients with TPN	≥ 15 cfu from catheter-tip or intra-cutaneous segment	P	13	251	0.86 (0.36-1.93)	1.02 (0.40-2.64)
Pemberton et al. (24)	1996	Inpatients with TPN	≥ 15 cfu from catheter tip	P	10	72	No data	0.84 (0.15-4.76)
George et al. (25)	1997	Transplant patients (heart, lung, both)	≥ 5 cfu from catheter tip	AR	No data	79	0.44 (0.24-0.84)	0.28 (0.03-2.60)
Logghe et al. (26)	1997	Heamatologic oncology unit	Not investigated	5 titer higher from line compared to BC	20	680	No data	1.13 (0.79-1.61)
Maki et al. (27)	1997	Medical-surgical ICU	≥ 15 cfu from catheter tip	T	6	403	0.56 (0.36-0.89)	0.21 (0.03-0.95)
Tennenberg et al. (28)	1997	Surgical wards+ ICU	≥ 15 cfu from catheter segment	P	5	282	0.31 (0.15-0.64)	0.60 (0.21-1.76)
Collin (29)	1999	Patients > 12 years with CVC placed in emergency or ICUs	≥ 15 cfu from catheter tip	P	8	237	0.13 (0.03-0.54)	0.36 (0.04-3.18)
Heard et al. (30)	1998	Surgical ICU	≥ 15 cfu from catheter tip or intracutaneous segment	AR	9	308	0.83 (0.63-1.09)	0.87 (0.27-2.80)
Hannan et al. (31)	1999	ICU	≥ 1000 cfu from catheter tip after wash off	P	8	351	0.74 (0.54-1.02)	0.34 (0.04-3.26)
Marik PE (4) (CHSS arm)	1999	Medical ICU	≥ 15 cfu from catheter tip	P	6	75	0.74 (0.31-1.74)	0.55 (0.05-5.86)
Sheng et al. (32)	2000	Surgical ICU	≥ 15 cfu from catheter tip	AR	9	235	0.34 (0.15-0.74)	0.17 (0.03-1.15)
Theaker et al. (33)	2002	ICU	≥ 1000 cfu from catheter tip after wash off	P	7	232	1.11 (0.77-1.60)	1.27 (0.59-2.71)

P= same species of pathogen, AR = + same antibiotic resistance, T = + same typing result, BC = blood culture

TABLE II - RESULTS OF STUDIES INVESTIGATED SILVER IMPREGNATED/COATED CATHETERS

Study	Year	Study population	Diagnosis colonization	Diagnosis infection	Average duration of use	Number of colonization (C195)	Relative risk colonization (C195)	Relative risk CRI (C195)
Goldschmidt H (13)	1995	Haematological, oncological+ rheumatological patients	≥ 15 cfu from intradermal + intravascular segments	P	13	233	0.99 (0.72-1.36)	0.52 (0.27-0.99)
Bach A (14)	1999	Cardiac surgery patients	≥10^3 cfu/cm catheter or ≥ 10^3 cfu/ml by luminal flush (Clerimethod)	P	?	67	1.20 (0.49-2.91)	0.97 (0.14-6.53)
Boswald S (15)	1999	Various departments of one university hospital	≥ 15 cfu from catheter tip	P, score system	9	165	0.66 (0.34-1.30)	0.31 (0.11-0.93)
Stoiser (16)	2002	2 ICUs with immuno-compromised patients	≥ 15 cfu from catheter tip	P, score system	11	97	0.73 (0.35-1.51)	0.94 (0.20-4.46)
Ranucci (17)	2003	Medical +surgical departments	≥ 15 cfu from catheter tip or > 1000 (sonication)	P	9	545	0.63 (0.46-0.86)	0.78 (0.33-1.83)

TABLE III - RESULTS OF STUDIES INVESTIGATING OTHER ANTISEPTIC SUBSTANCES

Study	Year	Study population	Diagnosis colonization	Diagnosis infection	Average duration of use	Number of catheters	Relative risk colonization (C195)	Relative risk CRI (C195)
Moss H (11)	2000	Patients admitted for routine surgical procedures	≥ 15 cfu from catheter tip + flushing of intra-cutaneous segment	P	4	204	0.63 (0.41-0.95)	0.47 (0.04-5.07)
Jaeger K (18)	2001	Patients suffering from malignant diseases/ chemotherapy	> 15 cfu from catheter tip or intra-cutaneous segment	P	17	50	1.0 (0.28-3.62)	1.0 (0.07-15.15)
Sherertz R (19)	1996	ICUs of four university hospitals	≥ 15 cfu from catheter tip or intra-cutaneous segment or sonication (≥100 cfu) or flush method (≥100 cfu)	P	8	254	1.06 (0.75-1.51)	2.30 (0.61-8.70)

TABLE IV - RESULTS OF STUDIES INVESTIGATING ANTIBIOTIC IMPREGNATED CATHETERS

Study	Year	Study population	Diagnosis colonization	Diagnosis infection	Average duration of use	Number of catheters	Relative risk colonization	Relative risk CRI
Kamal G (34) (Cefazolin)	1991	Surgical ICU	≥ 15 cfu from catheter tip	P	5	178	0.17 (0.04-0.74)	No CRI in both groups
Raad I (20) (M/R)	1997	Patients of 5 university hospitals	≥ 15 cfu from catheter tip +sub-cutaneous segment+ sonication (≥ 1000 cfu)	AB	6	298	0.36 (0.19-0.69)	No CRI in study group; $p < 0.01$
Marik PE (4) (M/R vs uncoated)	1999	Medical ICU	≥ 15 cfu from catheter tip	P	6	77	0.43 (0.15-1.26)	No CRI in study group; $p > 0.05$
Darouiche RJ (5)* (M/R vs. CHSS)	1999	Patients of 12 university hospitals	≥ 15 cfu from catheter tip +subcutaneous segment+ sonication (≥ 1000 cfu)	AB	8	738	0.39 (0.26-0.59)	0.09 (0.01-0.65)

M/R= minocycline/rifampicin

TABLE V - META-ANALYSES AND SYSTEMATIC REVIEWS (ONLY THOSE POOLING DATA WERE CONSIDERED)

First author	Year	Impregnation	Studies included for the outcome CRI	Summary odds ratio (CI95) for CRI	Conclusion
Veenstra D (6)	1999	CHSS	11 studies abstracts included	0.56 (0.37.0.84)	CHSS catheter appear to be effective in reducing CRI
Marin et al. (7)	2000	CHSS	11 studies heparin-bonded catheters included	0.58 (0.40-0.84)	Significant decreased CRI
Mermel LA (8)	2000	CHSS	6 studies (1 abstract included) with short-term catheterisation (less than 2 weeks)	0.4 (0.2-0.8)	Short-term use of a catheter impregnated with CHSS reduced the risk for CRI
Walder (9)	2002	CHSS M/R	10 studies 2 studies	0.73 (0.50-0.91) 0.14 (0.04-0.51)	Both are effective for short (approximately 1 week) insertion times
Geffers C (10)	2003	CHSS	11 studies (no abstracts)	0.69 (0.46-1.03) 0.34 (0.15-0.75) when only including studies with average duration of stay < 8 days	No influence of the study quality on the result of the metaanalysis, effective only for short average duration of stay ≤ 8 days

TABLE VI - STUDIES INVESTIGATING THE COSTS OF THE USE OF IMPREGNATED CATHETERS

First author	Year	Type of impregnation	Results	Conclusion
Veenstra D (35)	1999	CHSS	A decrease of cost of $ 196 per catheter used	Cost-effectiveness of CHSS impregnated catheters was shown
Marin et al. (7)	2000	CHSS+ Heparin coating		The modest additional cost for the use of these catheters relative to the considerable cost of treating even a single BSI makes their use cost-effective
Frank et al. (36)	2003	CHSS	A decrease of cost of € 2,434.80 per 1,000 catheters	The use of antiseptic-impregnated catheters in the ICU appears to be cost-effective
Marciante (37)	2003	M/R	The probability that M/R catheters are cost-effective in patients catheterised for 8 days was 91%, the probability that M/R catheters were cost-saving for patients catheterised 13 or more days was 97.4%	Cost-effectiveness of minocycline/rifampicin impregnated catheters was shown in patients catheterised for at least one week

TABLE VII - STUDIES INVESTIGATING SIDE EFFECTS

First author	Year	Type of impregnation	Side effect
Ellis ME (38)	1996	CHSS	Mechanical complication
Oda T (39)	1997	CHSS	Anaphylactic reaction
Terazawa E (40)	1998	CHSS	Anaphylactic reaction
Stephans R (12)	2001	CHSS	Anaphylactic reaction

lism. Although one RCT reported that silver coated catheters were effective (13), a later study by the same working group could not confirm this result (14). A second generation of silver impregnated catheters was subsequently developed using improved technology, without leading to any significant CRI rate reduction (15, 16). Meanwhile, a new catheter made of oligon, incorporating polyurethane, silver, carbon and platinum has been studied (17), but there are not enough studies available to draw any conclusions concerning this type of catheter.

Other antiseptics used for impregnation

The efficacy of benzalkonium chloride for CRI prevention has been investigated in two studies, but neither study was able to demonstrate that these catheters reduced CRI rates (11, 18). Chlorhexidine alone was also unsuccessful (19).

Antibiotically impregnated catheters

The development of catheters impregnated with antibiotics began with cephalosporines and vancomycin. However, the most substantial data available is for catheters impregnated with M/R. These catheters are impregnated on both surfaces (intraluminal and extraluminal). One RCT showed a significant CRI reduction with these catheters, as opposed to uncoated catheters (20). Another multicenter RCT demonstrated a significant advantage over CHSS catheters (5). Although the introduction of resistant micro-organisms, or adverse effects caused by the antibiotic concentrations used for impregnation are highly improbable, the risks from long-term use of promoting bacterial resistance are still unclear (21).

CONCLUSIONS

For most types of impregnated catheters, few studies are available, which is not enough to draw any conclusions regarding their use. In addition, many studies have methodological weaknesses making it, again, difficult to draw any conclusions from their results. One of the open methodological questions not discussed in many studies is the problem of diagnosing a CRI when the catheter is impregnated. The methods used in these studies to diagnose catheter colonization were evaluated with uncoated catheters. As evidence of catheter colonization is essential for defining CRI, further investigations are necessary in order to establish a method for culturing antimicrobially impregnated catheters which is not influenced by the coating substances (10). There seems to be a general bias towards identifying some benefit from using impregnated catheters, if a diagnostic method not – or much less – influenced by the coating could be employed for CRI diagnosis. Therefore, in spite of the relatively large number of RCTs available, the routine use of impregnated catheters as a measure for CRI prevention remains controversial. It is important to emphasize that considerably more studies are required, especially as many of the studies available revealed serious methodological flaws (9, 10).
When evaluating catheters, particularly new types, the following points must be considered:

- Although no single laboratory method has emerged as totally ideal for diagnosing CRI, a diagnostic method that does not potentially lead to an overestimation of the effectiveness of impregnation on CRI should be used.
- Secondary end points, i.e. duration of hospitalization, amount of antibiotics used etc should be included in the study.

When developing strategies for impregnated catheter use in an institution there needs to be a balance between the cost effectiveness of impregnated catheters and the average CRI rates in various patient groups.

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