REVIEW ARTICLE

Antimicrobial Impregnated Catheters in the Prevention of Catheter-Related Bloodstream Infection in Hospitalized Patients

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Catheter-related bloodstream infections have a significant impact on increasing health care costs and morbidity and mortality in hospitalized patients. Many technologies have been created in an attempt to decrease the incidence of catheter-related bloodstream infection. One of these is the impregnation of central venous catheters with antiseptics (e.g., chlorhexidine and silver sulfadiazine) or antibiotics (e.g., minocycline and rifampin). While studies evaluating the efficacy of impregnated catheters have been conducted, the data are limited and their use remains variable across institutions. This paper will discuss catheter-related factors that predispose patients to catheter-related bloodstream infection, the types of antimicrobial-impregnated catheters in use today, studies evaluating their efficacy, and common concerns associated with the use of these catheters. Issues related to the cost-effectiveness of impregnated catheters and future directions for the prevention of catheter-related bloodstream infection will also be presented.

KEYWORDS antiseptic, antibiotic, antimicrobial impregnated catheters, catheter-related bloodstream infection

J Pediatr Pharmacol Ther 2007;12:77-90

INTRODUCTION

Nosocomial bloodstream infections (BSI) are a significant cause of increased health care costs and length of hospital stay. In the United States, more than 200,000 nosocomial bloodstream infections occur per year, accounting for an additional 3.5 million hospital days and 3.5 billion dollars in health care costs.[1] Twenty percent of these bloodstream infections are thought to be associated with central venous catheters.[1] The use of antimicrobial impregnated catheters has become a popular yet controversial method for prevention of catheter-related BSI.[1-3]

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CATHETER-RELATED BLOODSTREAM INFECTIONS

Organisms

The Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) program has evaluated 22,609 nosocomial BSIs from 49 pediatric and adult centers.[4,5] The predominant organisms in pediatric and adult patients

ABBREVIATIONS BSI, bloodstream infection; CDC, Centers for Disease Control and Prevention; CHSS, chlorhexidine and silver sulfadiazine; CFU, colony forming units; CONS, coagulase negative staphylococci; CVCs, central venous catheters; MIC, minimum inhibitory concentration; MR, minocycline and rifampin; PICC, peripherally inserted central (venous) catheter; PICU, pediatric intensive care unit; PVC, polyvinyl chloride; SCOPE, Surveillance and Control of Pathogens of Epidemiologic Importance Project; VRE, vancomycin resistant enterococcus

were gram-positive, which accounted for 65% of infections in both groups. There was also no difference in the incidence of gram-negative BSI (25% pediatric vs. 24% adult) or infections attributed to fungi (11% pediatric vs. 9% adult). The predominant organisms were the same regardless of age, with coagulase negative staphylococci (CONS) being the predominant pathogen. It was followed by *Staphylococcus aureus,* enterococci, and finally *Candida* species. Mortality with CONS bacteremia has ranged from 18.5% to 57%.[6-10] Martin et al. used matched historical controls to study CONS bacteremia in 171 adult and pediatric patients and reported an estimated attributable mortality of 13.6%.[11] Crude mortality from the SCOPE data for pediatric and adult patients, respectively, are as follows: CONS 10.6% and 20.7%, enterococci 11.8% and 33.9%, *Staphylococcus aureus* 12% and 25.4% and *Candida* 19.6% and 39.2%.[4,5] *Candida* was seen more often in patients with neutropenia.

Routes of Infection

The most common route of infection is migration of skin organisms at the insertion site into the catheter tract with colonization of the catheter tip.[12] Contamination of the catheter hub can also lead to intraluminal colonization. For these reasons, special care should be taken when accessing the catheter hub and inserting central venous catheters (CVCs). Proper hand hygiene, full sterile barrier precautions and proper sterilization of the site are mandatory. Contaminated infusate, although rare, can introduce organisms into the catheter lumen as well, especially in fluids that are ideal mediums for microbial growth (e.g., intravenous lipid emulsions). Catheters can also become seeded by hematogenous spread of infection from another site.

Biofilm Formation

The risk of catheter-related BSI begins the moment the catheter is inserted. The bacteria form a biofilm on the surface of the catheter, which provides a safe-haven for organisms. This film is formed by irreversible attachment of microorganisms to the surface of the catheter, producing a matrix of extracellular polymeric substances.[13] The biofilm provides protection to the microorganism via three distinct mechanisms: 1) inhibiting diffusion of antimicrobials into the matrix, 2) allowing reduced growth rates for the microorganisms, thereby affecting the killing capability of certain antimicrobials, and 3) providing an environment that inhibits antimicrobial uptake into cells.[13]

Catheter-Related Risk Factors

The Centers for Disease Control and Prevention (CDC) Guidelines for the Prevention of Intravascular Catheter-Related Infections note that the risk of catheter-related BSI is influenced by catheter type.[12] The likelihood of infection is lowest with implantable catheters and highest with non-tunneled CVCs. Infection with the remaining catheter types is less common with peripheral, midline, tunneled CVCs and peripherally inserted central catheters (PICC), listed in order of increased risk.[12] Most catheters sold in the United States are made of Teflon or polyurethane. These catheter materials are more resistant to the adherence of organisms and are therefore associated with lower rates of infection than catheters made of polyvinyl chloride (PVC) or polyethylene.[12]

The incidence of catheter-related BSI is influenced by duration of catheter placement. Longer dwell times allow for an increased number of manipulations at the catheter hub which can lead to intraluminal colonization. Short-term use catheters (≤ 10 days) usually become infected by microbial colonization along the external surface of the catheter, which is caused by migration of skin flora at the time of insertion.[14] Catheters that are placed for longer periods of time (> 10 days) also become infected via intraluminal colonization. This, however, is often due to hub contamination.[15] Subcutaneous tunneling decreases the incidence of catheter-related infections. Tunneling may decrease the migration of skin pathogens by increasing the distance between the skin insertion site and venous insertion site.[16]

Other Risk Factors

Many studies have evaluated the actual risk factors for catheter-related BSI in adult and pediatric populations. In a multivariate analysis in 367 adult patients, renal failure was the only independent risk factor for central venous catheter-related BSI.[17] A second multivariate analysis conducted in 1,314 adult

patients found that duration of catheterization, coexisting infections, intra-aortic balloon counterpulsation, and elevated temperature were independent risk factors for catheter-related BSI.[18] Pediatric intensive care unit (PICU) patients seem to have an increased risk for catheter-related BSI. Compared to the usual rate seen in adults of 3.3 per 1,000 catheter days, PICU patients experience 7.7 infections per 1,000 catheter days.[19] In their retrospective study of 1,043 PICU patients, Odetela et al. found extracorporeal life support, presence of multiple central intravascular access devices (e.g., extracorporeal life support, renal replacement therapy, CVCs) and total duration of catheterization as risk factors in pediatric patients.[20] A prospective cohort study found that the use of multiple CVCs, arterial catheters and transfer of patients out of the PICU to the operating room or radiology were independent risk factors for catheter-related BSI.[21]

METHODS FOR PREVENTION

Catheter Placement

Maximal barrier precautions should be used when CVCs are inserted. Before insertion, the site should be prepared using an antiseptic such as chlorhexidine. Chlorhexidine has greater efficacy in reducing infection rates when compared to povidone-iodine.[22] One study found the incidence of local catheter infection was 2.3 vs. 9.3 per 100 catheters with chlorhexidine and povidone-iodine respectively.[22] Although no randomized studies have adequately compared infection risk among catheter insertion sites, the CDC guidelines recommend that catheters be placed in the subclavian vein, rather than jugular or femoral sites, whenever possible.[12] CDC guidelines recommend that CVCs ideally be placed using maximal sterile barrier precautions.[12] Emergent placement under less than optimal conditions (e.g., trauma or a bedside emergency situation) is associated with an increased incidence of catheter-related BSI.

Catheter Care

As stated previously, maximal barrier precautions and sterile technique are crucial to decreasing the rate of catheter-related BSI. Likewise, proper maintenance of the catheter is also important. Proper hand hygiene before manipulating the catheter is important to prevent contamination of the catheter hub.[12] The use of transparent dressings is equally efficacious to the traditional gauze and tape dressings.[12] Moreover, transparent dressings allow for easy visual inspection of the site and proper hygienic care of the patient without saturation of the site, requiring less frequent dressing changes than gauze and tape dressings.[12] Ideally, a catheter should be manipulated and accessed as little as possible. Critically ill patients are at a higher risk of catheter-related infection because they receive multiple medications and require frequent monitoring thereby necessitating more frequent manipulation of catheters. Education is extremely important in this population. It is imperative that nursing staff are trained and educated on proper catheter care and that efforts are taken to minimize manipulation of the catheter (i.e., decreasing daily infusions of a medication or changing medications to other agents that require less frequent dosing when appropriate).

In-Line Filters

No data support the use of in-line filters as a means to decrease catheter-related BSI. However, it has been hypothesized that in-line filters: 1) reduce the risk of infection from contaminated infusate, 2) remove particulate matter that might contaminate the infusate, and 3) filter out endotoxin produced by gram-negative organisms.[12] However, catheter-related BSI due to the infusate is rare. Importantly, solutions containing intravenous lipid emulsions require the use of a larger filter (1.2 micron), which may allow certain particles, organisms and pyrogens to pass through the filter.

DIAGNOSIS OF CATHETER-RELATED BLOODSTREAM INFECTIONS

Catheter-related infections begin with asymptomatic colonization that may progress to clinically significant catheter-related BSI. Evaluation of a suspected infection should be performed only when there is clinical suspicion of disease (e.g., new onset fever, elevated white blood cell count, fever upon initiating infusion, erythema or inflammation at the insertion site). Inappropriate evaluation in an asymptomatic

Table 1. Guidelines for the Diagnosis of Catheter-Related BSI

When maintaining the catheter	Blood samples from 2 locations (peripheral and from catheter)
Paired cultures	Quantitative method: Positive if catheter sample yields colony count 5-10 times > than peripheral sample (sensitivity 90%, specificity 99%)
	Qualitative method: Positive if catheter sample is positive
Differential time to positivity	2 hours earlier than peripheral sample (sensitivity 91%, specificity 94%)
When removing the catheter	Confirmation of catheter-related BSI if the same organism is isolated from a peripheral culture in a patient with clinical signs and symptoms
	Catheter Tip Culture
	Quantitative method (vortex or sonication): significant if $\geq 10^2$ CFU (sensitivity 80%)
	Semi quantitative method (roll-plate): significant if ≥ 15 CFU (sensitivity 60%)
Cultures that grow normal skin flora (*Staphylococcus epidermidis*)	Not significant unless > 1 set grows the same strain (by species and antimicrobial susceptibility profile)

BSI, bloodstream infection; CFU, colony forming units
Adapted from Clin Infect Dis 2001;32:1249-1272.

patient can lead to false positive results, possibly due to contamination, which may expose the patient to unnecessary antibiotics, catheter removal and replacement, emergence of resistant organisms and increased cost.[14] For these reasons, guidelines for the diagnosis of catheter-related BSI have been established by a task force consisting of the Infectious Diseases Society of America, the American College of Critical Care Medicine, and the Society of Healthcare Epidemiology of America.[23] These are summarized in Table 1.

In certain patient populations with a select organism and when clinically possible, it would be best to diagnose and treat a catheter-related BSI without having to remove the catheter. For example, long-term parenteral nutrition patients have limited access sites, therefore, saving the line instead of inserting a new catheter at a new site would be beneficial to the patient. There are two methods for such a diagnosis. The first method involves paired quantitative cultures of blood samples collected through the catheter hub and peripherally (non-catheter sample). If the CVC sample yields a five- to ten-fold greater colony count than the peripheral sample, the patient is considered to have a catheter-related BSI. The second method is differential time to positivity testing, which involves collection of one blood sample drawn peripherally (non-catheter sample) and one from the CVC. These samples are then monitored continuously in the lab (using radiometric methods) for growth. Confirmation of a catheter-related infection can be made if the CVC sample is positive two hours earlier than the peripheral sample. This method is more commonly used due to the complexity and cost of the paired quantitative culture method.

In those cases in which the CVC is removed from the patient, the most commonly used methods for diagnosis of catheter-related BSI are either semi-quantitative (roll-plate) or quantitative (vortex or sonication).[23] Qualitative cultures are rarely used because a single microbe could result in a positive culture. Semi-quantitative assessment works well for catheters that have been in place less than one week, because they are most commonly colonized along the external surface by skin microorganisms. Catheters that have been in place for more than one week may have intraluminal

colonization as well. In this case, quantitative cultures are preferred because (either through vortex or sonication) they obtain samples from both the intraluminal and external surface of the catheter.[23] Although the quantitative technique has been proven to be > 20% more sensitive than the semi-quantitative method, it is unclear whether this is clinically significant.[23] The semi-quantitative technique is more commonly used due to the cost and complexity of the quantitative culture technique.[23]

PREVENTION THROUGH IMPREGNATED CATHETER USE

Type of Antimicrobial-Impregnated Catheters

Impregnated catheters were first introduced to clinical practice around 1990. The impregnated catheters commonly used today contain either chlorhexidine and silver sulfadiazine (CHSS) or minocycline and rifampin (MR). Over the last 5 decades, chlorhexidine has been used in clinical practice as a cutaneous disinfectant and antiseptic. It is bactericidal against gram-positive and gram-negative bacteria and it is fungicidal against yeasts. Silver sulfadiazine is a potent bactericidal and fungicidal agent commonly used in patients with burns. Minocycline is a tetracycline derivative that binds the 30s and possibly 50s ribosomal subunit of susceptible bacteria. Rifampin is a semisynthetic derivative of rifamycin. It inhibits bacterial RNA synthesis by binding to the beta subunit of DNA-dependent RNA polymerase thereby blocking RNA transcription.[24] Since minocycline and rifampin are also used therapeutically as systemic antibiotics, concern exists that the use of catheters impregnated with these agents may result in the development of bacterial resistance. To date, no *in vivo* resistance has been reported. Studies to assess this concern are ongoing.

Studies Evaluating Use

Twenty-four randomized trials have evaluated catheters impregnated with either CHSS or MR (Table 2). Studies have shown that the use of impregnated catheters reduces colonization of the catheter when compared to non-impregnated catheters. Many studies have evaluated the ability of these catheters to reduce catheter colonization and subsequently decrease the incidence of catheter-related BSI. Numerous studies have shown a statistically significant decrease in catheter colonization rates when using impregnated catheters versus standard catheters, and some have reported a reduction in catheter-related BSI as well. All of the twenty-four studies listed in Table 2 are randomized, prospective trials. Nineteen studies reported a statistically significant decrease in catheter colonization with the impregnated catheters. Four of the studies did not evaluate colonization. Eight studies showed a statistically significant decrease in catheter-related BSI with the use of impregnated catheters. Other studies exhibited a trend toward significance in reducing catheter-related BSI in the impregnated catheter group. It is possible that these studies made a Type 2 error due to lack of sufficient power. Due to the low incidence of catheter-related BSI, a large multi-center trial enrolling thousands of patients would be required to avoid a Type 2 error.

McConnell and colleagues published a paper that critically evaluated eleven of these studies.[1] They assessed study methodology, inclusion of key patient characteristics, and methodological flaws in the studies. The authors found that many of the studies had inconsistent definitions of catheter-related BSI, sub-optimal statistical analysis, failed to account for confounding variables and lacked clinically relevant endpoints. In eight of the eleven studies, impregnated catheters significantly reduced bacterial colonization. However, only two of these reported a significant decrease in the rate of catheter-related BSI. Although the authors concluded that the use of impregnated catheters does decrease colonization, they recommended that more reliable studies be conducted before one can conclude that impregnated catheters decrease the incidence of catheter-related BSI.

Crnich and Maki published a review a year later that evaluated eighteen randomized studies comparing the efficacy of impregnated versus non-impregnated catheters.[3] Nine of the studies were the same ones evaluated by McConnell et al. Fifteen of the studies evaluated catheter colonization. Eleven of these found a statistically significant reduction or a trend towards reduction of catheter-related BSI. Crnich and Maki performed an aggregate

Table 2. Studies Evaluating the Efficacy of Impregnated Catheters in the Prevention of Catheter-Related BSI

Ref	Catheter numbers (Population)	RESULTS			
		Catheter Days	Catheter Colonization		CRBSI
25	199 CHSS and 189 Control (Inpatient)	10.9 CHSS 10.9 Control	23% CHSS 33% Control*		0.5% CHSS 2% Control
26	14 CHSS and 12 Control (Postoperative, Septic)	7	Sub-Q segment 21% CHSS 50% Control	IV segment 21% CHSS 67% Control*	NR
27	181 (in each group NR) (ICU, Leukemia, BMT)	11.21 CHSS 6.73 Control*	13% CHSS 25% Control*		3.28% CHSS 4.6% Control
28	117 CHSS and 116 Control (CV Surgery)	NR	Sub-Q segment 23% CHSS 39% Control*	IV segment 21CHSS 36 Control*	0 CHSS 3% Control
29	124 CHSS and 127 Control (TPN)	NR	NR		10.9% CHSS 12.1% Control
30	32 CHSS and 40 Control (TPN)	10 CHSS 11 Control	NR		6% CHSS 8% Control 6 vs 7 per 1,000 CD
31	28 CHSS and 26 Control (ICU)	5-7	14% CHSS 38% Control*		NR
32	44 CHSS and 35 Control	NR	23% CHSS 71% Control*		9% CHSS 29% Control*
33	338 CHSS and 342 Control (Hematology/Oncology)	20	NR		5% CHSS 4% Control
34	208 CHSS and 195 Control (ICU)	6	13% CHSS 24% Control*		0.9% CHSS 4% Control* 1.6 vs 7.6 per 1,000 CD
35	130 MR and 136 Control (Inpatient)	6	8% MR 26% Control*		0% MR 5% Control* 0 vs 7.34 per 1,000 CD
36	137 CHSS and 145 Control (ICU)	5.2 CHSS 7.8 Control	28% CHSS 49% Control*		3.8% CHSS 6.4% Control
37	151 CHSS and 157 Control (ICU)	8.5 CHSS 9 Control	40% CHSS 52% Control*		3.3% CHSS 3.8% Control
38	98 CHSS and139 Control (Trauma ER, ICU)	9 CHSS 7.3 Control	2% CHSS 18% Control* 2.3 vs 24.7 per 1,000 CD*		1% CHSS 3% Control 1.1 vs 4 per 1,000 CD
38	213 CHSS (Trauma)	9	3.8% 4.5 per 1,000 CD		1 0.6 per 1,000 CD
39	356 MR and 382 CHSS (ICU high risk pt)	8.4 MR 8.2 CHSS	7.9% MR 22.8% CHSS*		0.3% MR 3.4% CHSS*
40	174 CHSS and 177 Control (ICU)	7.5 CHSS 7.6 Control	27% CHSS 40% Control*		1.7% CHSS 4.4% Control
41	36 CHSS, 38 MR and 39 Control (ICU)	6 CHSS 6 MR 6 Control	19% CHSS 11% MR 28% Control* MR vs Control		3% CHSS 0 % MR 5% Control MR vs Control*
42	113 CHSS and 122 Control (ICU)	9.1 CHSS 8.2 Control	7.1% CHSS 20.5% Control*		0.9% CHSS 4.9% Control*
43	101 CHSS and 131 PP (ICU)	7.4 CHSS 7.2 PP	40% CHSS 42% PP		12% CHSS 9% PP
44	237 CHSS and 223 Control (Hospital wide)	8.4 CHSS 7.8 Control*	6% CHSS 13% Control* 6.87 vs 16.9 per 1,000 CD*		0.8% CHSS 2.7% Control 0.98 vs 3.38 per 1,000 CD
45	182 MR and 174 Control (Oncology)	66.2 MR 63 Control	NR		1.6% MR 8% Control* 0.25 vs 1.28 per 1,000 CD
46	188 CHSS and 175 Control (ICU)	10.5 CHSS 12 Control	3.7% CHSS 13.1% Control*		2.1% CHSS 6.3% Control 2 vs 5.2 per 1,000 CD
47	228 MR and 237 Control (ICU)	10.3 CHSS 10.4 Control	36% MR 74% Control*		3.2% MR 6.1% Control
48	51 CHSS and 55 Control (Oncology)	14.3 CHSS 16.6 Control	9.8% CHSS 16.4% Control*		2% CHSS 15% Control*

BMT, bone marrow transplant; BSI, bloodstream infection; CD, catheter days; CV, cardiovascular; CRBSI, catheter-related bloodstream infection; CHSS, chlorhexidine silver sulfadiazine; ER, emergency room; ICU, intensive care unit; IV, intravenous; MR, minocycline/rifampin; NR, not reported; Pt, patient; PP, pure polymer; Sub-Q, subcutaneous; TPN, total parenteral nutrition

*$P \leq .05$

analysis with a total of 4,250 catheters and reported that impregnated catheters are associated with a 40% reduction in catheter-related BSI when compared with non-impregnated catheters (61 of 2129 impregnated vs. 101 of 2118 non-impregnated; [OR 0.6 (95% CI, 0.44-0.82)] P = .001). The authors concluded that although many studies evaluating impregnated catheters have not been ideally designed and statistically analyzed, they have been prospective, randomized trials with balanced treatment groups which have shown a consistent reduction in colonization of CVCs.

To date, the published literature generates more questions than answers regarding the efficacy of impregnated catheters. Given the low incidence of catheter-related BSI, a multicentered study that enrolled a large number of patients would be required to achieve sufficient power to answer many of these questions.

Another extremely important question is whether colonization is an appropriate endpoint in predicting catheter-related BSI. One study evaluated colonization in control (n = 177) and CHSS impregnated (n = 174) catheters that were removed because they were no longer medically necessary. While a significant difference was observed in colonization between the control and CHSS groups (40.2% vs. 27.2%; P < .01), the difference in systemic evidence of BSI was not significant between the groups (4.7% vs. 1.7%; P > .1).[40] A second study also attempted to answer this question by using 60 study groups from previously published studies.[49] The authors found a statistically significant linear correlation between catheter colonization and catheter-related BSI:

incidence of catheter-related BSI = 0.73 + 0.17 × incidence of catheter colonization ($r = 0.69$, $r^2 = 0.48$; P < .001).

This finding led the authors to support the use of catheter colonization as an appropriate endpoint in predicting catheter-related BSI.

Comparison of Chlorhexidine Silver Sulfadiazine and Minocycline plus Rifampin Impregnated Catheters

Another controversy surrounding the use of impregnated catheters focuses on which impregnated catheter is superior. MR catheters are coated on the external and internal surfaces, thereby decreasing intraluminal and possibly hematogenous sources of colonization whereas CHSS catheters commonly used today are only coated on the external surface. The *in vitro* half-life of activity in MR versus CHSS catheters is 25 days versus 3 days.[50] Although MR catheters are more expensive than CHSS, they have been shown to be more effective in patients who require longer duration of catheterization.[51] While there are newer CHSS catheters that are coated on both the internal and external surfaces, no data has been reported regarding their efficacy compared to MR catheters.

One randomized, blinded study has evaluated the incidence of colonization or catheter-related BSI in triple lumen catheters impregnated with either MR or CHSS.[39] Cultures were performed on catheter tips, subcutaneous segments and skin swabs at insertion and removal (when catheter no longer needed or when infection/occlusion occurred). Peripheral blood cultures were also obtained if a patient had clinical signs of infection. The study also used molecular typing (isolates from different sites in the same patient) and antimicrobial susceptibility (isolates from colonized catheters of both groups). Colonization was defined as growth of greater than 15 colony forming units (CFU) by the roll plate method or greater than 1,000 CFU by the sonication method for the catheter segments. Catheter-related BSI was defined as isolation of the same organism from the catheter and the peripheral blood in a patient with clinical signs of sepsis and no other known source of infection. Complete data was obtained for 738 catheters (356 MR and 382 CHSS) in 698 adult patients (350 received MR and 370 received CHSS). Eighty-seven of the 382 CHSS catheters and 28 of the 356 MR catheters were colonized (RR 2.9 [95% CI, 1.94-4.33] P < .001). Thirteen MR catheters and 45 CHSS were colonized at seven days or less (P < .001), while 15 of 139 MR and 42 of 172 CHSS catheters were colonized at greater than 7 days (P < .002). MR catheters were less likely to be colonized with CONS (P < 0.001), gram-positive bacilli (P = .04), and gram-negative bacilli (P = .007). The rate of colonization with *Staphylococcus aureus*, *Enterococcus*, and yeast was not different between the two catheters. Thirteen cases of catheter-related BSI were found in the CHSS group compared to one in the MR group

(RR 12.05 [95% CI, 1.59-90.9] P<.002). Kaplan-Meier plots determined the risk of infection to be similar in the first 10 days, but increased in the CHSS impregnated catheters beyond this length of time. The authors concluded that CHSS catheters offered the same protection as MR catheters in patients expected to be catheterized less than ten days.[39]

Resistance

One of the greatest concerns with the use of antimicrobial-impregnated catheters is the emergence of drug resistant organisms. This is of particular concern with MR catheters since these agents are used as systemic antibiotics for treating active infection. To date, no resistance has been shown *in vivo*, yet *in vitro* resistance has been seen for *Staphylococcus epidermidis* and *Escherichia coli*.[1] Development of resistance as a result of impregnated catheter use is unlikely for a variety of reasons: 1) resistance to minocycline and rifampin is caused by mutations that occur at a rate of 10^{-6}, 2) peripheral blood samples collected from patients with MR impregnated catheters at various intervals after placement had undetectable concentrations of minocycline and rifampin, 3) minocycline and rifampin in combination act synergistically, hence, resistance is rare under these conditions, and 4) superinfections are unlikely because minocycline and rifampin have activity against all organisms commonly found in colonized catheters (gram-positive, gram-negative and *Candida* species).[35] Using the Kirby-Bauer technique, Raad and colleagues tested all organisms isolated from indwelling catheters upon their removal.[35] Zones of inhibition against staphylococcal species cultured from both MR and uncoated catheters were compared and minimum inhibitory concentrations (MIC) determined. They found no difference between the zones of inhibition among the two groups (P > .2). Minimum Inhibitory Concentrations (MIC) for CONS and *Staphylococcus aureus* isolated from MR catheters were < 1 μg/mL and < 2 μg/mL, respectively.

With these considerations in mind, it can be concluded that resistance would most likely occur in areas of high colonization. In clinical trials, MR catheters were rarely colonized. In the Raad study,[35] only 5% of these catheters were colonized with greater than 10^4 CFU per catheter segment. In addition, it is unlikely that bacteria in the body at distant sites from the catheter would develop resistance. Also, it has been postulated that impregnated catheters may decrease the need for systemic antibiotics thereby decreasing the incidence of resistance to these agents.

In an *in vitro* study by Munson et al., gram-positive and gram-negative organisms common in catheter-related BSI were exposed to MR impregnated catheter segments and no development of resistant organisms was seen.[52] Hanna et al. prospectively studied oncology patients in an intensive care unit (ICU) setting in two phases over a two year period. The initial phase evaluated patients over one year with uncoated catheters, while the second phase evaluated patients over the subsequent year with MR catheters after implementation of the use of impregnated catheters in the ICU. The authors documented a significant decrease in catheter-related BSI as well as in vancomycin resistant enterococcal (VRE) bacteremia with the use of MR impregnated catheters.[53]

Adverse Events

Concerns for toxicity and hypersensitivity reactions with these catheters also exist. Reactions to topical and intra-urethral chlorhexidine have been seen in the United States.[54] Although not seen in the United States, there are reports of hypersensitivity to chlorhexidine catheters in Japan.[54,55] Thirteen Japanese patients experienced an anaphylactoid reaction with insertion of a CHSS impregnated catheter.[54] Clinical symptoms were hypotension, tachycardia and chest pain. One patient expired; however, the exact cause of death was unknown. It has been proposed that the Japanese may have a genetic predisposition to this sensitivity since it has not been seen elsewhere.[56] The manufacturer issued a letter to health care professionals recommending screening for hypersensitivity via anamnesis (prick test) in Japan, but anaphylactic reactions were seen even after these safety measures were used. This product was voluntarily withdrawn from the market in Japan in 1997.[57]

Lupus-like syndromes have been associated with minocycline in patients taking the drug orally for acne.[58] It is unlikely this would occur due to the very low concentrations of

minocycline in the impregnated catheter and negligible concentrations in the blood. Due to the negligible concentrations in the blood, concern over the use of minocycline in pediatric patients with regards to tooth staining is not warranted. Potential toxicity, though rare, should be considered and monitored in patients receiving these catheters.

COST IMPLICATIONS

As with all therapies, the benefits of intervention must be carefully weighed against the associated costs. Many investigators have seen increased costs and length of stay among patients who develop catheter-related BSI.[59-62] DiGiovine et al. studied mortality and costs of nosocomial BSI in ICU patients.[61] After controlling for severity of illness, they found that patients with nosocomial BSI experienced increased costs ($60,650 vs. $36,899; P = .0006) and length of stay (24.16 vs. 20.29 days; P = .0047) when compared to uninfected matched controls.[61] No difference in mortality was seen between the two groups. Dimick et al. found catheter-related BSI was associated with an increased hospital cost of $56,167 (95% CI, $11,523 to $165,735; P = .001) and an increased ICU cost of $71,443 (95% CI, $11,960 to $195,628; P < .001) in critically ill surgical patients.[62] A statistically significant increase in length of stay (18 days vs. 40 days; P < .001) contributed to most of the increased costs reported. Importantly, the authors reported a statistically significant increase in mortality among patients with catheter-related BSI (56% vs. 21%; P = .02).

Veenstra et al. conducted a cost analysis using data from randomized, controlled trials, meta-analyses, and case-control studies to construct a decision model.[63] They found that the use of CHSS impregnated catheters resulted in cost savings of about $196 per catheter and also decreased costs, morbidity and mortality in high-risk (ICU, parenteral nutrition, or immunosuppressed) patients.[63] They estimated that for every 300 impregnated catheters used, approximately $59,000 would be saved, 7 catheter-related BSIs avoided, and 1 death prevented.[63] The authors concluded that impregnated catheters resulted in such significant cost savings because they are a disease prevention strategy. Savings are due to decreased incidence of catheter-related BSI and decreased need to place new catheters.

Marciante et al. evaluated cost-effectiveness of MR catheters compared to CHSS catheters using data from a trial that randomized patients to MR or CHSS catheters and tracked infection incidence for up to 55 days.[39,51] These authors found that in patients expected to be catheterized for more than one week, MR catheters, although more expensive, were superior to CHSS catheters and led to cost savings in these patients.[51]

Shorr et al. evaluated the cost-effectiveness of the newer CHSS and MR catheters that are coated on both the intraluminal and exterior surface.[64] They employed a decision model analysis and found that both catheters lead to substantial cost savings in institutions where the catheter-related BSI rate is greater than 0.5%.[64] Although CHSS and MR impregnated catheters are more expensive than standard CVCs, the ability to prevent catheter-related BSI makes them cost effective.

Most institutions have catheter-related BSI rates of about 3%.[63] The CDC concurs with many of the cost analysis studies and states that impregnated catheters may be cost effective in patient populations where the rate of infection exceeds 3.3 per 1,000 catheter days.[12]

OVERVIEW OF GUIDELINES

The CDC recommends using impregnated catheters in adults whose catheters are expected to remain in place longer than five days. This recommendation is for institutions where infection rates remain above institution based or benchmark rates after implementing a comprehensive strategy to reduce infection rates.[12] This strategy should include education of personnel who insert and maintain CVCs, use of maximal sterile precautions, and 2% chlorhexidine preparation for skin antisepsis at the time of insertion. This is a category 1B recommendation (strongly recommended for implementation and strongly supported by some experimental, clinical, or epidemiologic studies, and a strong theoretical rationale).[12] The CDC makes no recommendation for the use of impregnated catheters in pediatric patients. This issue is designated as an unresolved issue

in the guidelines. Most likely this is due to the lack of pediatric studies using these catheters. Like many medications that are used in pediatrics, these catheters are used in many PICU settings by extrapolating adult data and applying it to the pediatric population.

FUTURE DIRECTIONS

Pure polymer catheters have unique physical properties; they are microscopically smooth, hydrophilic, and have been reported to resist bacterial and platelet attachment. Theaker et al. conducted a randomized trial to compare pure polymer catheters to catheters impregnated with CHSS.[43] Overall, 232 catheters were placed (131 pure polymer and 101 CHSS). Fifty-five pure polymer catheters and 40 CHSS catheters were colonized; there was no statistical difference between these two groups. There were 12 catheter-related BSI in each group. Given the concern for the emergence of resistance, this method would be an improvement over using antibiotic or antiseptic impregnated catheters if proven effective. Furthermore, larger studies comparing pure polymer catheters to MR catheters are needed to investigate whether this is a superior option for preventing catheter-related BSI.

CHSS catheters impregnated on both the intraluminal and extraluminal surfaces are now in use and being compared against MR catheters in randomized trials. Other new technologies such as iodinated catheter hubs (available in Europe), chlorhexidine impregnated sponge dressings,[65] heparin coated catheters,[66] oligon (polyurethane combined with silver, carbon and platinum) treated catheters,[67] and catheters impregnated with miconazole and rifampin are being studied.[68] Researchers are attempting to isolate and define the chemical messengers that control biofilm formation among bacteria in order to develop potential inhibitors of these messengers. As we continue to learn more about the pathogenesis of these infections, many new technologies will be created to prevent catheter-related BSI.

A randomized, multicenter, comparative trial has been proposed by Maki and Siman and is supported by the NIH (National Institutes of Health).[69] They plan to compare CHSS, MR and non-impregnated catheters. Maki and Siman hope to finally answer whether the incidence of catheter-related BSI is lowered by impregnated catheters versus placebo, and if so, which impregnated catheter is more efficacious and least likely to induce resistance. Hopefully, through this large multicenter trial and the introduction of other new catheters, many questions regarding the efficacy and use of impregnated catheters will be answered.

CONCLUSIONS

The use of antimicrobial-impregnated catheters is effective in preventing colonization of central venous catheters. However, no reliable studies have shown that colonization truly increases the risk of catheter-related BSI. The cost effectiveness of these catheters is based on their ability to decrease the incidence of catheter-related BSI. Many questions are left unanswered regarding the use of impregnated catheters. Given the extremely low risk of toxicity (with exception of the reports in Japan), resistance and the ability of these catheters to decrease colonization, they seem to be an appropriate step in utilizing extra precaution in high-risk patients by eliminating an additional potential source of infection. Larger, randomized, multicenter trials are needed to establish that antimicrobial-impregnated catheters reduce the rate of catheter-related BSI and support the use of these catheters in populations who do not have a high risk for infection.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

ACKNOWLEDGMENTS Consistent with JPPT editorial standards Kathleen Gura, PharmD, served as the Editor of this paper directing all aspects of the Journal's disposition of this paper. Neither Dr. Phelps nor any of her co-authors were aware of or contributed to the identification or selection of the three author-blinded expert peer reviewers. Dr. Gura assured scientifically sound reconciliation of all necessary revisions prior to manuscript acceptance for publication.

A portion of the salary for Dr. Crill is supported in part by a Center of Excellence Grant in Pediatric Pharmacokinetics and Therapeutics. At the time the paper was written, Dr. Wassil was a pediatric pharmacotherapy resident at The University of Tennessee Health Science Center and Le Bonheur Children's Medical Center.

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