American Journal of Infectious Diseases 8 (1): 50-59, 2012
ISSN 1553-6203

Antimicrobial-Impregnated Discs for Prevention of Intravenous Catheter-Related Infections

[1]Kelly R. Daniels and [2]Christopher R. Frei
[1]The University of Texas at Austin, College of Pharmacy, Austin, TX, USA
[2]The University of Texas Health Science Center at San Antonio,
Pharmacotherapy Education and Research Center, San Antonio, TX, USA

Abstract: Problem statement: Healthcare-associated infections are the 5th leading cause of death in the United States. Catheter-Related Bloodstream Infections (CRBSIs) comprise 14% of all healthcare-associated infections and contribute to increased mortality and financial costs. Antimicrobial-impregnated sponge discs to be used surrounding the catheter insertion site are a newer addition to the options available for the prevention of catheter-related infections. **Approach:** This review critically appraises the literature regarding the utility of antimicrobial-impregnated discs. We performed a literature search using the MEDLINE (1948-November 2011) database. Only controlled clinical trials were included and the electronic database search was performed using the following MeSH and keyword search terms: ("Biopatch" or "chlorhexidine") and ("dressing" or "sponge") and ("catheter"). **Results:** Our search yielded eight trials. Chlorhexidine-impregnated discs are effective in preventing catheter colonization in hospitalized patients and outpatients; however, effectiveness in preventing CRBSIs may be limited to hospitalized, critically ill patients. Although many studies have evaluated the effectiveness of several pharmaceutical agents for the prevention of catheter-related infections, there are still significant gaps in the literature regarding these infections, including the effectiveness of Polyhexamethylene Biguanide (PHMB)-impregnated discs and the cost-effectiveness of PHMB-impregnated discs compared to chlorhexidine-impregnated discs. It is also unclear if antimicrobial-impregnated discs are effective in specific populations, like in outpatients, patients at high risk compared to low risk patients and patients with long-term catheters. **Conclusion:** Chlorhexidine-impregnated discs should be utilized for the duration of catheterization in high risk, critically ill patients and in hospitals where catheter-related infection rates are persistently high despite other preventative strategies. Futher investigation of the effectiveness of these discs in other populations and of other antimicrobial-impregnated discs is needed.

Key words: Catheter-Related Bloodstream Infections (CRBSIs), United States (US), Polyhexamethylene Biguanide (PHMB), Coagulase-Negative Staphylococcus (CoNS), Central Venous Catheters (CVCs), National Institutes of Health (NIH)

INTRODUCTION

Catheters contribute to an estimated 250,000 nosocomial catheter-related bloodstream infections (CRBSIs) annually in the United States (U.S.) (Klevens *et al*., 2007). This has led to significant increases in patient mortality, length of stay and financial costs (Kluger and Maki, 1999; Beyersmann *et al*., 2006; Perencevich *et al*., 2007; Carrico, 2009). Several pharmaceutical agents have been studied for the prevention of catheter-related infections, including skin antiseptics, antimicrobial lock solutions and antimicrobial-impregnated catheters. Antimicrobial-impregnated discs are newer agents available; however, data examining the effectiveness of these agents have not been critically reviewed and recommendations for use have not been well established. This review appraises the literature regarding the utility of antimicrobial-impregnated discs.

Pathogenesis of catheter-related infections: Catheter-related infections can present as local or systemic infections. Local infections include exit site infections, tunnel infections and port infections which are characterized by erythema and signs of local inflammation at the exit site, catheter tunnel track, or

Corresponding Author: Kelly R. Daniels, Pharm D the University of Texas Health Science Center, Pharmacotherapy Education and Research Center 7703 Floyd Curl Drive, MSC-6220 San Antonio, TX 78229-3900 USA Tel: 1-210-567-8355 Fax: 1-210-567-8328

port, respectively (Pearson, 1996). Catheter colonization may be a precursor to local or systemic infections and is defined by either the semiquantitative method (>15 colony forming units (cfu)/plate) or the quantitative method (>1,000 cfu mL^{-1}) (Pearson, 1996; Raad *et al*., 1993). The semiquantitative method is a process in which the catheter tip is rolled on agar, allowing for bacteria on the outer surface of the catheter to be grown and counted (Maki *et al*., 1977). The quantitative method uses sonication or flushing in order to obtain bacteria from the catheter external surface as well as the catheter lumen (Cleri *et al*., 1980; Sherertz *et al*., 1990). Finally, catheter insertion can result in a systemic bloodstream infection, which is defined as the isolation of the same organism from the catheter and from at least two concurrent blood cultures drawn from a peripheral vein with no identified alternative source of infection (Pearson, 1996).

There are several potential routes of infection that contribute to the development of catheter-related infections (Syndman *et al*., 1982; Bjornson *et al*., 1982). The most common source of infection is colonization of the skin surrounding the catheter insertion site. Organisms migrate from the catheter wound along the catheter-subcutaneous track. A study by Armstrong *et al*. (1990) demonstrated a significant increase in catheter colonization when the skin surrounding the catheter insertion site was colonized with at least 50 cfu (53%) compared to patients colonized with less than 50 cfu (8%) ($p<0.001$).

Other sources of infection include contamination of the catheter or infusate and secondary seeding. Catheter-related infections may develop as a result of contamination of the catheter lumen or hub, usually due to the patient's or healthcare worker's skin flora. Although this may occur in any catheterized patient, a stronger association has been seen in patients with long-term catheters compared to shorter duration catheters (Raad *et al*., 1993). Contamination of the infusate may also result in catheter-related infections. This is likely due to lack of aseptic technique, but occurs rarely (Maki, 1981). Finally, secondary seeding from a bloodstream infection may also occur, but is more likely in critically ill patients (Mermel *et al*., 1991).

Several organisms are implicated in CRBSIs, including Gram-positive aerobes, Gram-negative aerobes and fungi. Coagulase-negative *Staphylococcus* (CoNS) is the most common organism isolated in CRBSIs (> 30%). Other common organisms include *S. aureus* (22%), *Enterococcus* (8%) and *Candida* (8%) (Wisplinghoff *et al*., 2004). CoNS is part of the normal flora of the skin and was once thought of as a contaminant in cultures of suspected CRBSIs; however, it is now believed to be a legitimate cause of CRBSIs. For this reason, stricter diagnostic criteria are applied to the diagnosis of CRBSIs due to CoNS. Not only should the patient have positive cultures from both the catheter and the blood, they should also have clinical signs and symptoms of infection (Central-line Associated Bloodstream Infection (CLABSI), 2010). Susceptibility and/or genetic testing of the organism may be performed to determine concordance between isolates from each culture site.

Antimicrobial-impregnated discs for the prevention of catheter-related infections:

The Food and Drug Administration first approved antimicrobial-impregnated sponge discs to be used as devices surrounding the catheter insertion site in 2001. The effectiveness of these agents stems from the pathogenesis of catheter-related infections. Since the most common route of catheter-related infection is migration of organisms along the catheter due to heavy skin colonization, reducing skin colonization surrounding the catheter insertion site should reduce the incidence of catheter-related infections. There are three types of discs currently marketed. These contain silver, chlorhexidine, or Polyhexamethylene Biguanide (PHMB). The discs are primarily used surrounding Central Venous Catheters (CVCs), Peripherally-Inserted Central Catheters (PICCs) and external fixation device insertion sites.

Antimicrobial-impregnated discs have both pharmacological and non-pharmacological mechanisms of action. First, the disc is comprised of polyurethane foam, which is highly absorptive. The foam allows for the absorption of wound discharge that could lead to bacterial overgrowth and diminished wound healing (Jones and Milton, 2000). Second, in vitro data suggest that antimicrobial agents (specifically chlorhexidine and PHMB), embedded within the foam, provide a sustained antimicrobial action over a seven-day period (McGhee *et al*., 2009). Due to this sustained drug release, discs are generally changed every seven days, unless they become soiled. These antimicrobials have a broad spectrum of action and are effective against the most common organisms implicated in CRBSIs (CoNS, *S. aureus* and *Enterococci*), but also have activity against less common fungal and Gram-negative pathogens (*Candida, E. coli, Klebsiella, Pseudomonas*). Also, these products may have a low risk for the development of antimicrobial resistance because these agents are applied topically, have non-specific mechanisms of action and are not susceptible to efflux pumps.

Antimicrobial-impregnated discs are well tolerated. A meta-analysis by Ho and Litton (2006) demonstrated local cutaneous reactions or contact dermatitis in 5.6% of patients who used chlorhexidine-impregnated discs surrounding the catheter site; 0.2% in adults and 5.4% in infants and neonates. No published studies have

reported systemic adverse events or anaphylactic reactions associated with the use of these discs; however, case reports have demonstrated the possibility of anaphylactic reactions with both PHMB and chlorhexidine (Kautz *et al*., 2010; Krautheim *et al*., 2004).

Antimicrobial-impregnated discs may provide benefits beyond skin antisepsis alone. The discs provide a longer duration of action, providing up to seven days of antimicrobial action compared to approximately 24 h with skin antisepsis alone (McGhee *et al*., 2009). This allows for less frequent dressing changes, which not only increase convenience, but may limit the skin toxicity associated with more frequent dressing changes (Laura *et al*., 2000). Also, because the discs are made of polyurethane foam, they readily absorb wound discharge, unlike standard skin antiseptic preparations.

In the remainder of this article, the effectiveness of chlorhexidine-impregnated discs is assessed in different populations. In each of these studies, the Biopatch® was the agent evaluated.

MATERIALS AND METHODS

Chlorhexidine-impregnated discs have been studied in humans for the prevention of intravenous catheter-related infections. Data regarding the effectiveness of PHMB or silver-containing discs are limited to in vitro pharmacokinetic data. We performed a literature search using the MEDLINE (1948-November 2011) database. Only controlled clinical trials were included and the electronic database search was performed using the following MeSH and keyword search terms: ("Biopatch" or "chlorhexidine") and ("dressing" or "sponge") and ("catheter"). The search yielded 44 articles, which were subsequently narrowed by titles and abstracts to those trials addressing specifically intravenous infections in hospitalized patients.

RESULTS AND DISCUSSION

To date, there have been eight trials that have evaluated the effectiveness of chlorhexidine-impregnated discs in this population. These trials differ in their patient population, as well as outcomes of interest; therefore, each study will be discussed individually with the purpose of summarizing currently available literature. Each trial is also summarized in Table 1.

Effectiveness of chlorhexidine-impregnated discs in hospitalized patients: One of the first studies to evaluate the effectiveness of chlorhexidine-impregnated discs was published, in abstract form (Maki *et al*., 2000). This was a large prospective, randomized, controlled, multicenter study with the primary objective of evaluating the effectiveness of chlorhexidine-impregnated discs in reducing catheter colonization and CRBSIs. Hospitalized patients were included if they were catheterized with a central venous, pulmonary artery, or peripheral catheter. These patients were randomized into one of two groups: chlorhexidine-impregnated disc plus transparent film dressing (treatment) or transparent film dressing alone (controls). The primary outcome of the study was the proportion of patients who developed catheter colonization or a CRBSI. Overall, 1,401 catheters (736 randomized to the control group, 665 randomized to chlorhexidine disc) were included in the analysis. Of those randomized, 216/736 catheters (29%) in the control group and 109/665 (16%) in the treatment group became colonized (RR, 0.38; 95% CI, 0.49-0.78). Also, significantly more CRBSIs were seen in the control group (3.3%) than the treatment group (1.2%) (RR, 0.38; 95% CI, 0.16-0.89). The authors concluded that the use of the chlorhexidine-impregnated discs reduced the risk of catheter colonization and CRBSIs in hospitalized patients with peripheral or central venous catheters.

Although the Maki trial has a strong study design and included both high and low risk catheters, it has several limitations. Because this study was only published in abstract form, it was not subjected to rigorous peer review and much information is lacking, including: baseline patient characteristics, catheter duration, investigator blinding, use of skin antisepsis prior to dressing, further analysis for CoNS and control for confounding variables in the statistical analysis. Also, dressings were changed more frequently in the control group than the treatment group (two days vs. seven days) and this could have contributed to higher infection rates in the control group due to more exposure of the catheter exit site to healthcare personnel. These limitations diminish the application of these data to specific populations. Although these are promising results, this study may not be the definitive answer for recommending the use of chlorhexidine-impregnated discs.

Ruschulte *et al*. (2009) also performed a large trial evaluating the effectiveness of chlorhexidine-impregnated discs for the prevention of catheter-related infections. This was a prospective, randomized, controlled, single-center trial. The trial included adult patients receiving chemotherapy for hematological malignancies through triple lumen central venous catheters at least five days. The patients were randomized to one of two groups: chlorhexidine/silver sulfadiazine-impregnated catheter plus chlorhexidine-impregnated disc (treatment) or chlorhexidine/silver sulfadiazine-impregnated catheters alone (controls).

Table 1: Trials evaluating the effectiveness of chlorhexidine-impregnated discs in the prevention of catheter-related infections

Trial and design	Population	Interventions	Outcomes	Results	Conclusions/Comments
Maki *et al*. (2000) Prospective, randomized, multicenter	1,401 hospitalized adults with central venous, pulmonary artery or peripheral catheter	Treatment: chlorhexidine disc Controls: no disc (no indication skin antisepsis that used during dressing changes)	Catheter colonization CRBSIs	Catheter colonization Treatment: 109/665 (16%) Controls: 216/736 (29%) RR 0.62; 95% CI 0.49-0.78 CRBSIs Treatment: 8/665 (1.2%) Controls: 24/736 (3.3%) RR 0.38, 95% CI 0.16-0.89	Chlorhexidine-impregnated discs prevent catheter colonization and CRBSIs in critically ill adults Published in abstract form only
Garland *et al*. (2001) Prospective, randomized, multicenter	705 critically ill neonates central requiring a catheter venous catheter ≥ 48 h	Treatment: 70% alcohol antisepsis + chlorhexidine disc Controls: 10% povidone iodine antisepsis	Catheter colonization CRBSIs	colonization Treatment: 47/314 (15%) Controls: 82/341 (24%) RR 0.6, 95% CI 0.5-0.9 CRBSIs Treatment: 12/314 (3.8%) Controls: 11/341 (3.2%) RR 1.2, 95% CI 0.5-2.7	Chlorhexidine-impregnated discs decrease catheter colonization, not CRBSIs in critically ill neonates Mean duration: 17 days Different antiseptics used
Chambers *et al*. (2005) Prospective, randomized, single-center	95 (114 catheters) neutropenic oncology patients receiving chemotherapy via tunneled central venous catheters	Treatment: chlorhexidine disc Controls: no disc (no indication that skin antisepsis used during dressing changes)	Exit site infection Tunnel infection	Exit site infections and/or tunnel infections Treatment: 5/58 (9%) Controls: 23/54 (43%) OR 0.13, 95% CI (0.04-0.37)	Chlorhexidine-impregnated discs reduce the incidence of exit site/tunnel infections in neutropenic patients CRBSIs not evaluated -lack of blood cultures in 22 patients
Levy *et al*. (2005) Prospective, randomized, single-center	145 critically ill cardiac pediatric patients post-cardiac surgery requiring central catheter ≥ 48 h	Treatment chlorhexidine antisepsis + chlorhexidine disc Controls: chlorhexidine antisepsis + no disc	Catheter colonization CRBSIs	Catheter colonization Treatment: 11/74 (14.8%) Controls: 21/71 (29%) RR 0.62, p=0.0446 CRBSIs Treatment: 4/74 (5.4%) Controls: 3/71 (4.2%) P = 1.00	Chlorhexidine-impregnated discs decreased catheter colonization, but not CRBSIs in critically ill pediatrics Did not meet study power to detect a difference in CRBSIs
Onder *et al*. (2009) Retrospective, Observational cohort	78 pediatric patients undergoing hemodialysis antisepsis	Treatment: povidone iodine +chlorhexidine disc Controls: povidone iodine antisepsis + no disc	Exit site infections CRBSIs P<0.05	Exit site infections Treatment: 3/40 (8%) Controls: 9/38 (24%) CRBSIs in hemodialysis CRBSIs Treatment: 32/40 (80%) Controls: 32/38 (84%) P>0.05	Chlorhexidine-impregnated discs decrease exit site infections, but not High rate of CRBSIs -did not use CDC definition of CRBSI
Ruschulte *et al*. (2009) Prospective, randomized, single-center	601 adults receiving chemotherapy for hematological malignancies through triple lumen central catheters ≥ five days	Treatment chlorhexidine/ silver sulfadiazine catheter + chlorhexidine disc Controls: chlorhexidine/ silver sulfadiazine catheter	CRBSIs	CRBSIs Treatment: 19/300 (6.3%) Controls: 34/301 (11.3%) RR 0.54, 95% CI 0.31-0.94	Chlorhexidine-impregnated discs decreased the incidence of CRBSIs in chemotherapy patients No analysis for CoNS
Timsit *et al*. (2009) Prospective, randomized, multicenter	1,636 critically ill adults requiring an arterial or central venous catheter≥48 h	Treatment povidone iodine antisepsis +chlorhexidine disc Controls povidone iodine antisepsis + no disc	Catheter colonization Major catheter -related infection CRBSIs	Catheter colonization Treatment: 6.3/1,000 days Controls: 15.8/1,000 days RR 0.36, 95% CI 90.28-0.46 Major catheter-related infection Treatment: 0.6/1,000 days Controls: 1.4/1,000 days RR 0.39, 95% CI 0.16-0.93 CRBSIs Treatment: 0.4/1,000 days Controls: 1.3/1,000 days RR 0.24, 95% CI 0.09-0.65	Chlorhexidine-impregnated discs decrease the incidence of catheter colonization, CRBSIs, and major catheter-related infections in critically ill adults High risk population Inconsistent definition of catheter colonization
Arvaniti *et al*. (2011) Prospective, randomized, multicenter	465 critically ill adults requiring a multilumen central venous catheter	Treatment: chlorhexidine disc or silver -impregnated catheter Control: standard catheter	Catheter colonization Catheter infection with/without bacteremia	Catheter colonization Disc: 19.9/1,000 days Control: 20.9/1,000 days OR, 1.21; 95% CI 0.6-2.6 Infection without bacteremia Disc: 5.7/1,000 days Control: 8.8/1,000 days OR, 0.65; 95% CI, 0.23-1.85 Infection with bacteremia Disc: 2.8/1,000 days Control: 1.4/1,000 days OR, 1.65; 95% CI, 0.3-10.0	Chlorhexidine-impregnated discs do not decrease the rate of catheter colonization or CRBSIs in critically ill adults Low study power (62%) No collection of dressing change frequency or compliance

CRBSI, Catheter-Related Bloodstream Infection; RR, Relative Risk; OR, Odds Ratio

The primary outcome was the proportion of patients developing CRBSIs. Overall, 601 patients were included in the analysis. In the control group, 34/301 (11.3%) patients developed CRBSIs, whereas, 19/300 (6.3%) patients in the treatment group developed these infections (RR, 0.54; 95% CI, 0.31-0.94). The authors concluded that chlorhexidine-impregnated discs decrease the incidence of CRBSIs in oncology patients receiving chemotherapy.

Overall, this was a well-designed study with a large population of patients. This population differs from other large trials, in which the patients were mostly critically ill patients admitted for treatment of other medical problems. This is the first study to evaluate the effectiveness of these discs in oncology patients and is also the first study to use supplemental prophylactic agents (antimicrobial-impregnated catheters) other than skin antisepsis alone. This study demonstrated that the use of both impregnated discs and catheters, in combination, are effective in oncology patients, who are inherently at higher risk for infection due to their immunocompromised state and long duration of catheterization. This study also has some limitations. The investigators did not indicate whether there was any additional analysis performed on CoNS isolates to determine concordance between the strains isolated from the catheter and the blood; therefore, we are unsure if their rate of CRBSIs is overestimated.

The largest study to date evaluating the effectiveness of chlorhexidine-impregnated discs was published by Timsit and colleagues (Timsit *et al*., 2009). This study was a prospective, randomized, controlled, multicenter trial that evaluated critically ill adults who required an arterial or central venous catheter at least 48 h. Patients were randomized to receive the chlorhexidine-impregnated disc (treatment) or no disc (controls) changed at either three or seven days; therefore, four treatment groups were formed (disc + three-day interval, disc + seven-day interval, no disc + three day-interval and no disc + seven-day interval). The primary outcomes of this study were the incidence of patients who developed catheter colonization, a CRBSI, or a major catheter-related infection defined as either a CRBSI or catheter-related sepsis without a bloodstream infection. This study also evaluated whether changing dressings every seven days increased infection rates compared to three-day dressing change intervals. Overall, 3,778 catheters were included in the analysis. Patients randomized to the treatment group experienced lower incidence rates per 1,000 catheter-days of catheter colonization (HR, 0.36; 95% CI, 0.28-0.46), CRBSIs (HR, 0.24; 95% CI, 0.09-0.63) and major catheter-related infections (HR, 0.39; 95% CI, 0.16-0.93). This study also demonstrated that a seven-day dressing change interval did not increase the incidence per 1,000 catheter-days of catheter colonization (HR, 0.99; 95% CI, 0.77-1.28), CRBSIs (HR, 1.26; 95% CI, 0.47-3.34) and major catheter-related infections (HR, 1.16; 95% CI, 0.5-2.69). The authors concluded that the use of chlorhexidine-impregnated discs reduce the incidence of catheter colonization, CRBSIs and major catheter-related infections in critically ill patients and that reducing the dressing change interval to seven days does not increase the risk of infection.

The study by Timsit *et al*. (2009) is one of the first to demonstrate the non-inferiority of a longer duration dressing change interval. This conclusion is limited due to the fact that patients in both dressing change interval arms had similar durations between dressing changes due to the necessity to change soiled dressings. This study had a strong study design and the investigators performed additional analysis on CoNS isolates, so it is likely that the incidence of catheter-related infections is accurate. This is also one of the only studies to determine if chlorhexidine-impregnated discs decrease the incidence of major catheter-related infections; however, catheter-related sepsis without a bloodstream infection may be difficult to diagnose and difficult to attribute specifically to the catheter, especially in critically ill adults.

Finally, the most recent study evaluating chlorhexidine-impregnated discs was conducted Arvaniti *et al*. (2011). This study was a prospective, randomized, multicenter trial in five centers in Greece. This study included adult patients requiring multi-lumen central venous catheters in the intensive care unit. The primary outcomes of interest included catheter colonization and CRBSIs. Patients were randomly assigned to a standard catheter (n = 156), a chlorhexidine-impregnated disc (n = 150), or a silver-impregnated catheter (Oligon®) (n = 159). Catheter colonization occurred at similar rates in all three groups: standard catheter (15.4%), chlorhexidine-impregnated disc (14%) and silver-impregnated catheter (15.7%) (p = 0.35). No differences in catheter-related infections with or without bacteremia were noted in the active treatment arms compared to the standard catheter group (HR, 0.65; p = 0.42). The authors concluded that neither the chlorhexidine-impregnated disc nor silver-impregnated catheter decreased the rate of catheter colonization or infection with or without bacteremia in this critically ill population.

Arvaniti *et al*. (2011) conducted one of the first studies comparing two active treatments for prevention of catheter infections in critically ill, hospitalized patients. The authors were unable, however, to

demonstrate significant improvements in catheter colonization and infections rates likely secondary to the low study power (62%). The investigators were also un-blinded, which could lead to investigator bias. Finally, the number or dressing changes and compliance with infection control procedures were not recorded, both of which could adversely affect infection rates. Although this study is limited by these factors, it is also one of the first studies to demonstrate the lack of effectiveness of these two interventions.

Other studies have also evaluated these outcomes in different populations of hospitalized patients. Studies by Garland *et al*. (2001); Levy *et al*. (2005) and Onder *et al*. (2009) specifically evaluated pediatric patients, each of which evaluated the effectiveness of chlorhexidine-impregnated discs versus no discs. Garland *et al*. (2001) performed a prospective, randomized, controlled, multicenter study, which evaluated critically ill neonates requiring a CVC at least 48 hours (n = 705). This study demonstrated a significant reduction in catheter colonization with use of the chlorhexidine-impregnated discs (9% reduction; 95% CI, 0.5-0.9), but a non-significant reduction in CRBSIs (0.6% reduction; 95% CI, 0.5-2.7). This study was unique in that the mean duration of catheterization was 17 days, meaning that the use of chlorhexidine-impregnated discs may not be effective in long-term catheterization. Levy and colleagues (Levy *et al*., 2005) performed a randomized controlled trial in critically ill pediatric patients (n = 145) post-cardiac surgery. This study demonstrated significant reductions in catheter colonization (14.2% reduction, p = 0.04), but no reduction in CRBSIs in the chlorhexidine-impregnated disc group (p = 1). Onder *et al*. (2009) performed a retrospective observational cohort study of pediatric hemodialysis patients (n = 78). This study evaluated exit site infections and CRBSIs. Although exit site infections were significantly reduced in the chlorhexidine-impregnated disc group (16% reduction, $p<0.05$), CRBSIs were non-significantly reduced (4% reduction, $p>0.05$). Chambers *et al*. (2005) performed a randomized controlled trial in neutropenic oncology adult patients (n = 114 catheters) receiving chemotherapy via tunneled CVCs. This study only evaluated the proportion of patients acquiring exit site infections and tunnel infections. The study demonstrated reductions in both of these outcomes (34% reduction; 95% CI, 0.04-0.37); however, CRBSIs were not evaluated.

To summarize, chlorhexidine-impregnated discs are effective prophylactic agents for the prevention of catheter colonization and other local infections in hospitalized patients; however, effectiveness in preventing CRBSIs may be limited to critically ill patients.

Cost-effectiveness of chlorhexidine-impregnated discs in hospitalized patients: A cost-benefit analysis was performed by Crawford *et al*. (2004) using data from the Maki trial. The primary outcomes of interest were the cost of chlorhexidine-impregnated discs versus standard dressings, the averted cost of treating local infections and CRBSIs and mortality attributable to CRBSIs. Multiple sensitivity analyses were performed by varying the rate of CRBSIs (5-6%), cost of treating a CRBSI ($8,000-$25,000), number of catheters used annually in the U.S. (3 million to 5 million) and attributable mortality (1-5%). The investigators demonstrated that the cost of preventing one CRBSI with the use of chlorhexidine-impregnated discs could save $238-$965 per patient and the net benefit of treating all catheterized patients could save $275 million to $1.97 billion per year. Also, use of chlorhexidine-impregnated discs could prevent 329-3,906 deaths per year. The authors concluded that not only do these discs reduce catheter-related infections, they also reduce costs and mortality.

This cost-benefit analysis is one of two studies to provide national estimates of the potential financial impact of chlorhexidine-impregnated discs. The authors performed multiple sensitivity analyses to determine the possible range of the impact; however, the financial estimates in this study were determined using data from the Maki trial, which has its own inherent limitations. Also, higher rates of mortality have been reported with CRBSIs and costs may be slightly outdated.

A second cost-effectiveness was conducted by Schwebel *et al*. (2012) in based on the results of the Timsit study. This analysis estimated the direct costs of catheter-related infections and additional hospital length of stay due to these infections. The cost-effectiveness of chlorhexidine-impregnated discs were assessed using the overall cost of a catheter-related infection ($24,090/episode), the cost of a dressing ($9.08) and the cost of the disc ($9.73). Assuming a baseline infection rate of 1.4%, chlorhexidine-impregnated discs saved $197 or $83 per patient based on a three-day change regimen and seven-day change regimen, respectively. A sensitivity analysis was conducted by varying the rate of infection (0.35%) and cost of a catheter-related infection ($44,000). Using these values, the chlorhexidine-impregnated dressing remained cost-effective, saving and estimated $164 per patient.

This analysis by Schwebel and colleagues provides further data supporting the cost-effectiveness of chlorhexidine-impregnated discs in critically ill patients. This study is strengthened by the use of results from a well-designed, peer-reviewed trial and the use of multiple sensitivity analyses. Chlorhexidine-impregnated

discs appear to be a cost-effective prophylactic agent for the prevention of catheter-related infections.

Effectiveness of chlorhexidine-impregnated discs in outpatients and patients with epidural catheters: Other studies have evaluated the effectiveness of chlorhexidine-impregnated discs in outpatients and patients with epidural catheters. Two randomized controlled trials demonstrated a reduction in catheter colonization when chlorhexidine-impregnated discs were used in adult patients with epidural catheters. Mann *et al*. (2001) demonstrated a colonization rate of 42.3% in controls versus 3.45% in patients randomized to the chlorhexidine disc ($p = 0.001$). Shapiro *et al*. (1990) produced similar results (29.0% VS 3.8%; $p<0.05$). CRBSIs were not evaluated in these studies. A recent study by Camins *et al*. (2010) and colleagues is one of the first to evaluate the effectiveness of chlorhexidine-impregnated discs in outpatients. This was a prospective observational cohort study in a population of 121 adults undergoing outpatient hemodialysis through tunneled CVCs. A reduction in the incidence of CRBSIs was demonstrated in the chlorhexidine-impregnated disc group compared to the control group; however, this was a non-significant reduction (RR, 1.22; $p = 0.46$).

Ho and Litton (2006) published a meta-analysis in 2006 evaluating studies with the objective of determining the effectiveness of chlorhexidine-impregnated discs for the prevention of catheter colonization and CRBSIs in patients with epidural and intravenous catheters. This study demonstrated significant reductions in catheter colonization (OR, 0.4; 95% CI, 0.34-0.65), but only a trend in decreasing CRBSIs in patients who used the chlorhexidine-impregnated disc compared to control groups (OR, 0.58; 95% CI, 0.29-1.14). This original meta-analysis did not include the studies by Timsit *et al*. (2009) and Ruschulte *et al*. (2009). The authors of this meta-analysis have published a revised analysis of the original data to include these two studies. Because these two studies were large, the addition of these studies provided sufficient sample size to show a significant reduction in CRBSIs with use of chlorhexidine-impregnated discs compared to control groups (OR, 0.55; 95% CI, 0.35-0.86). It is important to note the limitations of this meta-analysis though. Each of the included studies was comprised of different patient populations, comparison groups and outcomes; therefore, the overall meta-analysis had significant heterogeneity ($I^2 = 30.2\%$).

Effectiveness of PHMB-impregnated discs: To date, there have been no published studies evaluating the effectiveness of PHMB-impregnated discs for the prevention of catheter-related infections; however, there may be value in using this agent. PHMB is in the same biguanide class of antiseptics as chlorhexidine, with the same mechanism of action and antimicrobial spectrum. PHMB has been shown to be equally effective as chlorhexidine in the treatment of other infections, like acanthamoeba keratitis (Lim *et al*., 2008). PHMB also has a slightly higher biocompatibility index (1.36 VS. 0.98), meaning that the ratio of antibacterial activity to cytotoxicity is higher with PHMB (Muller and Kramer, 2008). In vitro data suggest that PHMB is active against organisms at lower concentrations (lower minimum inhibitory concentrations and minimum bactericidal concentrations) and PHMB-impregnated gauze and foam wound dressings have also been used to prevent infection and promote wound healing in other types of wounds (e.g., surgical site infections, traumatic wounds, ulcers) (Roth *et al*., 2007; Andriessen and Eberlein, 2008; Valenzuela and Perucho, 2008; Penn *et al*., 2006; Timmons and Leak, 2010). The cost of PHMB discs is lower than chlorhexidine discs (~$5.00/disc VS. $7.50/disc, respectively); therefore, the use of PHMB discs may prove to be a more cost-effective alternative than chlorhexidine-impregnated discs.

Chlorhexidine-impregnated discs are effective in preventing catheter colonization in hospitalized patients and outpatients; however, effectiveness in preventing CRBSIs may be limited to hospitalized, critically ill patients. These agents should be utilized for the duration of catheterization in high risk, critically ill patients and in hospitals where catheter-related infection rates are persistently high despite other preventative strategies.

Although many studies have evaluated the effectiveness of several pharmaceutical agents for the prevention of catheter-related infections, there are still significant gaps in the literature regarding these infections, including the effectiveness of PHMB-impregnated discs and the cost-effectiveness of PHMB-impregnated discs compared to chlorhexidine-impregnated discs. It is also unclear if antimicrobial-impregnated discs are effective in specific populations, like in outpatients, patients at high risk compared to low risk patients and patients with long-term catheters.

CONCLUSION

Chlorhexidine-impregnated discs should be utilized for the duration of catheterization in high risk, critically ill patients and in hospitals where catheter-related infection rates are persistently high despite other preventative strategies. Futher investigation of the effectiveness of these discs in other populations and of other antimicrobial-impregnated discs is needed.

ACKNOWLEDGEMENT

No funding was provided for the conduct of this review or the preparation of this study. CRF is supported by the U.S. National Institutes of Health (NIH) in the form of a NIH/KL2 career development award (3UL1RR025767). CRF has also received research grants and/or served as a scientific consultant/advisor for AstraZeneca, Forest, Ortho McNeil Janssen Pharmaceuticals and Pfizer. KRD declares no competing interests.

REFERENCES

Andriessen, A.E. and T. Eberlein, 2008. Original research assessment of a wound cleansing solution in the treatment of problem wounds. Wounds, 20: 171-175.

Armstrong, C.W., C.G. Mayhall, K.B. Miller, H.H. Newsome Jr and H.J. Sugerman *et al*., 1990. Clinical predictors of infection of central venous catheters used for total parenteral nutrition. Infect. Control Hosp. Epidemiol., 11: 71-78. PMID: 2107249

Arvaniti, K., D. Lathyris, P. Clouva-Molyvdas, A.B. Haidich and E. Mouloudi *et al*., 2011. Comparison of Oligon catheters and chlorhexidine-impregnated sponges with standard multilumen central venous catheters for prevention of associated colonization and infections in intensive care unit patients: A multicenter, randomized, controlled study. Crit Care Med., 40: 420-429. PMID: 21926583

Beyersmann, J., P. Gastmeier, H. Grundmann, S. Barwolff and C. Geffers *et al*., 2006. Use of multistate models to assess prolongation of intensive care unit stay due to nosocomial infection. Infect. Control Hosp. Epidemiol., 27: 493-499. PMID: 16671031

Bjornson, H.S., R. Colley, R.H. Bower, V.P. Duty and J.T. Schwartz-Fulton *et al*., 1982. Association between microorganism growth at the catheter insertion site and colonization of the catheter in patients receiving total parenteral nutrition. Surgery, 92: 720-727. PMID: 6812229

Camins, B.C., A.M. Richmond, K.L. Dyer, H.N. Zimmerman and D.W. Coyne *et al*., 2010. A crossover intervention trial evaluating the efficacy of a chlorhexidine-impregnated sponge in reducing catheter-related bloodstream infections among patients undergoing hemodialysis. Infect. Control Hosp. Epidemiol., 31: 1118-1123. PMID: 20879855

Carrico, R., 2009. APIC Text of Infection Control And Epidemiology. 3rd Edn., Association Professionals Infections Control Epidemiology, Washington, DC., ISBN: 1933013443, pp: 1700.

Chambers, S.T., J. Sanders, W.N. Patton, P. Ganly and M. Birch *et al*., 2005. Reduction of exit-site infections of tunnelled intravascular catheters among neutropenic patients by sustained-release chlorhexidine dressings: results from a prospective randomized controlled trial. J. Hosp. Infect., 61: 53-61. PMID: 16002181

Cleri, D.J., M.L. Corrado and S.J. Seligman, 1980. Quantitative culture of intravenous catheters and other intravascular inserts. J. Infect. Dis.,141: 781-786. PMID: 6993589

Crawford, A.G., J.P. Fuhr and B. Rao, 2004. Cost-benefit analysis of chlorhexidine gluconate dressing in the prevention of catheter-related bloodstream infections. Infect. Control Hosp. Epidemiol., 25: 668-674. PMID: 15357159

Garland, J.S., C.P. Alex, C.D. Mueller, D. Otten and C. Shivpuri *et al*., 2001. A randomized trial comparing povidone-iodine to a chlorhexidine gluconate-impregnated dressing for prevention of central venous catheter infections in neonates. Pediatrics., 107: 1431-1436. DOI: 10.1542/peds.107.6.1431

Ho, K.M. and E. Litton, 2006. Use of chlorhexidine-impregnated dressing to prevent vascular and epidural catheter colonization and infection: a meta-analysis. J. Antimicrob. Chemother., 58: 281-287. DOI: 10.1093/jac/dkl234

Jones, V. and T. Milton, 2000. When and how to use foam dressings. Nurs. Times, 96: 2-3.

Kautz, O., H. Schumann, F. Degerbeck, L. Venemalm and T. Jakob, 2010. Severe anaphylaxis to the antiseptic polyhexanide. Allergy 65: 1068-1070. PMID: 20102357

Klevens, R.M., J.R. Edwards, C.L. Richards, T.C. Horan and R.P. Gaynes *et al*., 2007. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Public. Health Rep., 122: 160-166. PMID: 17357358

Kluger, D.M. and D.G. Maki, 1999. The relative risk of intravascular device related bloodstream infections in adults. San Francisco, CA.

Krautheim, A.B., T.H. Jermann and A.J. Bircher, 2004. Chlorhexidine anaphylaxis: Case report and review of the literature. Contact Dermatitis, 50: 113-116. PMID: 15153122

Laura, R., M. Degl'Innocenti, M. Mocali, F. Alberani and S. Boschi *et al*., 2000. Comparison of two different time interval protocols for central venous catheter dressing in bone marrow transplant patients: Results of a randomized, multicenter study. The Italian Nurse Bone Marrow Transplant Group (GITMO). Haematologica, 85: 275-279. PMID: 10702816

Levy, I., J. Katz, E. Solter, Z. Samra and B. Vidne *et al*., 2005. Chlorhexidine-impregnated dressing for prevention of colonization of central venous catheters in infants and children: A randomized controlled study. Pediatr. Infect. Dis. J., 24: 676-679. PMID: 16094219

Lim, N., D. Goh, C. Bunce, W. Xing and G. Fraenkel *et al*., 2008. Comparison of polyhexamethylene biguanide and chlorhexidine as monotherapy agents in the treatment of Acanthamoeba keratitis. Am. J. Ophthalmol, 145: 130-135. PMID: 17996208

Maki, D.G., 1981. Nosocomial bacteremia. An epidemiologic overview. Am. J. Med., 70: 719-732. PMID: 7211906

Maki, D.G., C.E. Weise and H.W. Sarafin, 1977. A semiquantitative culture method for identifying intravenous-catheter-related infection. N. Engl. J. Med., 296: 1305-1309. PMID: 323710

Maki, D.G., L.Mermel, D. Kluger, L. Narans and V. Knasinski *et al*., 2000. The efficacy of chlorhexidine-impregnated sponge (Biopatch) for the prevention of intravascular catheter-related infection-a prospective, randomized, controlled, multicenter study. Programs and abstracts of the 40th Interscience Conference of Antimicrobial Agents and Chemotherapy, Washington, DC.

Mann, T.J., C.E. Orlikowski, L.C. Gurrin and A.D. Keil, 2001. The effect of the biopatch, a chlorhexidine impregnated dressing, on bacterial colonization of epidural catheter exit sites. Anaesth. Intensive Care., 29: 600-603. PMID: 11771602

McGhee, D., D. Bade and C.B. Shah, 2009. Activity of antimicrobial dressings using clinically relevant organisms MRSA, VRE and *P. aeruginosa*. Mansfield, MA: Covidien.

Mermel, L.A., R.D. McCormick, S.R. Springman and D.G. Maki, 1991. The pathogenesis and epidemiology of catheter-related infection with pulmonary artery Swan-Ganz catheters: A prospective study utilizing molecular subtyping. Am. J. Med., 91: 197S-205S. PMID: 1928165

Muller, G. and A. Kramer, 2008. Biocompatibility index of antiseptic agents by parallel assessment of antimicrobial activity and cellular cytotoxicity. J. Antimicrob. Chemother, 61: 1281-1287. PMID: 18364400

Onder, A.M., J. Chandar, A. Billings, R. Diaz and D. Francoeur *et al*., 2009. Chlorhexidine-based antiseptic solutions effectively reduce catheter-related bacteremia. Pediatr. Nephrol, 24: 1741-1747. PMID: 19296135

Pearson, M.L., 1996. Guideline for prevention of intravascular device-related infections. Hospital Infection Control Practices Advisory Committee. Infect. Control Hosp. Epidemiol., 17: 438-473. PMID: 8839803

Penn, R.G., S.K. Vyhlidal, S. Roberts and S. Miller, 2006. The reduction of vascular surgical site infection with the use of antimicrobial gauze. Am. J. Infect. Control., 34: 131-132.

Perencevich, E.N., P.W. Stone, S.B. Wright, Y. Carmeli and D.N. Fisman *et al*., 2007. Raising standards while watching the bottom line: Making a business case for infection control. Infect. Control Hosp. Epidemiol., 28: 1121-1133. PMID: 17933084

Raad, I., J. Umphrey, A. Khan, L.J. Truett and G.P. Bodey, 1993. The duration of placement as a predictor of peripheral and pulmonary arterial catheter infections. J. Hosp. Infect., 23: 17-26. PMID: 8095944

Raad, I., S. Davis and M. Becker, *et al*., 1993. Low infection rate and long durability of nontunneled silastic catheters. A safe and cost-effective alternative for long-term venous access. Arch. Intern. Med., 153: 1791-1796. PMID:

Roth, B., O. Assadian, F. Wurmitzer and A. Kramer, 2007. Surgical site infections after primary antiseptic cleansing of dirty-contaminated wounds by polihexanide, PVP iodine resp. hydrogen peroxide. GMS Krankenhaushyg Interdiszip, 2: Doc58- Doc58.

Ruschulte, H., M. Franke, P. Gastmeier, S. Zenz and K.H. Mahr *et al*., 2009. Prevention of central venous catheter related infections with chlorhexidine gluconate impregnated wound dressings: A randomized controlled trial. Ann. Hematol., 88: 267-272. PMID: 18679683

Schwebel, C., J.C. Lucet, A. Vesin, X. Arrault and S. Calvino-Gunther *et al*., 2012. Economic evaluation of chlorhexidine-impregnated sponges for preventing catheter-related infections in critically ill adults in the Dressing Study. Crit. Care Med., 40: 11-17. DOI: 10.1097/CCM.0b013e31822f0604

Shapiro, J.M., E.L. Bond and J.K. Garman, 1990. Use of a chlorhexidine dressing to reduce microbial colonization of epidural catheters. Anesthesiology, 73: 625-631. PMID: 2121070

Sherertz, R.J., I.I. Raad, A. Belani, L.C. Koo and D.L. Pickett *et al*., 1990. Three-year experience with sonicated vascular catheter cultures in a clinical microbiology laboratory. J. Clin. Microbiol., 28: 76-82.

Syndman, D.R., H.F. Gorgea, B.R. Pober, J.A. Majka and S.A. Murray *et al*., 1982. Predictive value of surveillance skin cultures in total-parenteral-nutrition-related infection. Lancet, 2: 1385-1388. PMID: 6129473

Timmons, J. and K. Leak, 2010. PHMB: The role of Kendall AMD Antimicrobial Foam Dressings (0.5% PHMB) in the treatment of wounds. Covidien, Mansfield, MA.

Timsit, J.F., C. Schwebel, L. Bouadma, A. Geffroy and M. Garrouste-Orgeas *et al*., 2009. Chlorhexidine-impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults: a randomized controlled trial. JAMA., 301: 1231-1241. PMID: 19318651

Valenzuela, A. and N.S. Perucho, 2008. The effectiveness of a 0.1% polihexanide gel. Rev. Endferm., 31: 7-12.

Wisplinghoff, H., T. Bischoff, S.M. Tallent, H. Seifert and R.P. Wenzel *et al*., 2004. Nosocomial bloodstream infections in US hospitals: Analysis of 24,179 cases from a prospective nationwide surveillance study. Clin. Infect. Dis., 39: 309-317. PMID: 15306996