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CHLORHEXIDINE-IMPREGNATED DRESSING FOR PREVENTION OF CATHETER-RELATED BLOODSTREAM INFECTION: A META-ANALYSIS

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Abstract

Background—Catheter related bloodstream infections (CRBSI) are associated with significant morbidity and mortality and effective methods for their prevention are needed.

Objective—To assess the efficacy of a chlorhexidine-impregnated dressing for prevention of central venous catheter-related colonization and CRBSI using meta-analysis.

Data Sources—Multiple computerized database searches supplemented by manual searches including relevant conference proceedings.

Study Selection—Randomized controlled trials (RCT) evaluating the efficacy of a chlorhexidine-impregnated dressing compared with conventional dressings for prevention of catheter colonization and CRBSI.

Data Extraction—Data were extracted on patient and catheter characteristics and outcomes.

Data Synthesis—Pooled estimates of the relative risk (RR) and 95% confidence intervals (CI) were obtained using the DerSimonian and Laird random effects model and the Mantel-Haenszel

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fixed effects model. Heterogeneity was assessed using the Cochran Q statistic and I^2. Subgroup analyses were used to explore heterogeneity.

Results—Nine RCTs met the inclusion criteria. Use of a chlorhexidine-impregnated dressing resulted in a reduced incidence of CRBSI (random effects RR 0.57, 95% CI 0.42–0.79, P=0.002). The incidence of catheter colonization was also markedly reduced in the chlorhexidine-impregnated dressing group (random effects RR 0.51, 95% CI 0.39–0.67, P< 0.001). There was significant benefit for prevention of catheter colonization and CRBSI, including arterial catheters used for hemodynamic monitoring. Other than in low birth weight infants, adverse effects were rare and minor.

Conclusions—Our analysis shows that a chlorhexidine-impregnated dressing is beneficial in preventing catheter colonization and, more importantly, CRBSI and warrants routine use in patients at high risk of CRBSI and CVC or arterial catheter colonization in ICUs.

Keywords

chlorhexidine; catheter-related infection; nosocomial infection; critical care

INTRODUCTION

Modern medical care relies on effective intravascular access for the management of a broad spectrum of acute and chronic conditions. Intravascular catheters are often needed in patients of all ages requiring intensive care, parenteral alimentation, cancer chemotherapy, organ transplantation, home antibiotic therapy, or hemodialysis(1–3). An estimated 5 million U.S. patients require either short-term or prolonged central venous access each year(4–7).

Although vital to care, these devices are associated with a risk of catheter-related bloodstream infection (CRBSI)(3, 6, 7). CRBSIs directly increase antibiotic exposure, length of stay and healthcare costs. Many studies suggest increased mortality as well(8–11). CRBSI is increasingly recognized as a preventable health care associated infection(12). As of October 2008, the United States Centers for Medicare and Medicaid Services has ceased to reimburse healthcare institutions for these complications, driving home the need for effective strategies to prevent CRBSI(13, 14).

Microorganisms cause CRBSI by one of three ways: at insertion, during use, or by spread from remote infection. The most common is at insertion when skin organisms invade the percutaneous tract extraluminally via capillary action. During regular use, contamination of the hub and lumen can occur whenever an infusion is started, or when the CVC is manipulated with a guidewire. Finally organisms can be carried hematogenously to the implanted device from remote sources of infection, e.g. pneumonia or urinary tract infection(15–19).

Understanding CRBSI pathogenesis has led to the development of preventative strategies, including the creation of best practice guidelines and the implementation of evidence-based “bundles” such as those developed by the Institute for Healthcare Improvement(4, 20, 21). These strategies are focused on hand hygiene, the use of full-barrier precautions during catheter insertion, skin antisepsis using chlorhexidine, preferential use of the subclavian/

internal jugular sites for non-tunneled catheters, and daily evaluation of catheter necessity with prompt removal of unnecessary lines(4, 20).

Strict adherence to evidence based best practices clearly reduces CRBSI rates(3, 12, 22–26). However, individual interventions that can make CRBSI prevention simpler, more effective and more cost effective merit investigation. A promising intervention directed at reducing the extraluminal route of infection is a chlorhexidine gluconate-impregnated dressing placed at the time of CVC insertion(27–29). The dressing releases chlorhexidine onto the skin for a 10-day period(30). Studies on the efficacy of a chlorhexidine impregnated dressing for reducing CRBSI have had conflicting results(31–38). We undertook a meta-analysis to examine the efficacy of a chlorhexidine-impregnated dressing compared with conventional site care for prevention of CRBSI and catheter colonization.

METHODS

Search Strategy

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)(39). Databases including PUBMED (including MEDLINE), EMBASE, Web of Science, CinAHL and clinicaltrials.gov were searched using the keywords “chlorhexidine, dressing, sponge, central venous catheter, arterial catheter, bacteremia, bloodstream infection” through October of 2012. No date range or language restrictions were applied. References to relevant studies were manually inspected for additional studies. A librarian assisted in performing the search. Abstracts from relevant proceedings and conferences including the Interscience Conference on Antimicrobial Agents and Chemotherapy, Infectious Diseases Society of America, Society for Healthcare Epidemiology of America, Society for Pediatric Research, American Society of Hematology, and European Congress of Clinical Microbiology and Infectious Diseases were also searched using the keyword “chlorhexidine.” The search was repeated with the same keywords using Google scholar search engine (http://scholar.google.com).

Inclusion criteria

Included studies were prospective randomized trials comparing a chlorhexidine-impregnated dressing with conventional site care. Studies had to provide standardized microbiologically based definitions for CRBSI and had to systematically report the incidence of CRBSI with sufficient information to allow calculation of a risk ratio, either in the article or after contact with authors. Case-control, case reports, reviews; retrospective studies and nonrandomized prospective trials were excluded.

Outcome measures

The primary outcome measure was CRBSI. Catheter colonization was identified as a secondary outcome. The definitions of CRBSI and catheter colonization were as provided by the individual studies.

Data Extraction

Three investigators (NS, AG, JO) independently abstracted data on the size of the study sample, patient population, type of vascular devices, dressing, cutaneous antiseptic used, device use duration, incidence of catheter colonization, and incidence of CRBSI. The authors of studies that did not report incidence data for relative risk calculations were contacted for additional information.

We evaluated the included studies for methodological quality using the recommendations outlined in the *Cochrane Handbook of Systematic Reviews*.(40) The risk of bias in each study was assigned as either low or high. Three authors (NS, AG, JO) independently reviewed each report identified by the above mentioned search strategy. Disagreements among abstracters regarding values or analysis assignments were resolved by discussion.

Statistical analysis

Pooled estimates of the RR and 95% CI were obtained using the DerSimonian and Laird random effects model and the Mantel-Haenszel fixed effects model(41, 42). Some studies included patients who had more than one vascular catheter during the study period. For these studies, we inflated the variance of the risk ratio to adjust for within-patient correlation(43, 44).

Heterogeneity was assessed using the Cochran Q statistic and I^2, $100\% \times \left[\frac{Q - df}{Q}\right]$, where Q is Cochran's Q statistic and df is degrees of freedom.(40) Degrees of freedom are equal to *k*-1 where *k* is the number of studies. Negative values of I^2 are conventionally equal to 0% so I^2 values can range between 0 and 100%. 0% indicates no observed heterogeneity and larger values indicate increasing heterogeneity. Subgroup analyses were used to explore possible reasons for heterogeneity. Publication bias was assessed using a funnel plot and Eggers statistical test(45, 46). Statistical analyses were performed using Stats Direct (2002, Cheshire, U.K.) and Review Manager software(47).

RESULTS

Study selection

The database search retrieved 505 unique citations of which 7 met our inclusion criteria (Figure 1)(31, 33–38). Manual search identified 2 additional studies(32, 48). Excluded studies fell into one or more of the following exclusionary categories: nonrandomized trial (n=8), chlorhexidine solution or impregnated catheters rather than dressing (n=108), chlorhexidine for indications other than intravascular devices (n=126), review article (n=42), editorial or letter (n=13), study population or outcome not meeting selection criteria (n=7), or unrelated to intravascular device use (n=194).

Study Characteristics

The 9 trials enrolled 6067 patients with a total of 11214 catheterizations; 5586 catheters in 2984 patients received a chlorhexidine-impregnated dressing and 5628 catheters in 3083 patients received conventional site care. Two large studies accounted for more than half the

patient population(35, 48). Two studies were conducted in neonates, infants or children(31, 33), two in adult patients with malignancy(34, 37), and five in adult medical-surgical and cardiothoracic intensive care units (ICUs)(32, 35, 36, 38, 48).

The characteristics of the 9 randomized controlled trials are summarized in Table 1. Five studies(32, 34, 36, 38, 48) recorded catheter colonization and CRBSI using the catheter as the unit of analysis, while three of the included trials(31, 33, 37) reported the data using the patient as the unit of analysis. One study(35) reported the outcome measures for both patients and catheters.

The mean duration of catheterization varied between the studies but was similar within the control and intervention groups of each individual trial. These are reported in Table 2.

Details of catheter care were provided in all studies. Insertion was performed by either medical or surgical ICU staff in five studies.(32, 35, 36, 38)(48). In one study neonatologists and nurse practitioners inserted the catheters(31). Two studies exclusively used anesthesiologist-inserted catheters in the operating room setting(33, 37). Radiologists inserted the catheters in one study(34).

All studies used standard aseptic technique in inserting lines, including cutaneous antisepsis. The different topical antisepsis agents are summarized in Table 1. One study used different skin preparations for the comparator (povidone-iodine) and treatment (70% isopropyl alcohol) arms(31).

The subclavian or internal jugular sites were the preferred central venous access site in most studies(32, 33, 35, 37, 48). Only one study used the femoral site predominantly(36), and one used primarily peripherally inserted central catheters (PICCs)(31). Two studies did not specify the sites used.(34, 38) The trial by Maki et al included central venous, peripherally inserted central catheters (PICCs), pulmonary artery, and peripheral arterial catheterizations(32).

With the exception of one study that used no dressing(34), all the other trials used occlusive dressings as the comparator. Dressing changes were conducted at seven day intervals in three studies(31, 33, 37), 3 day intervals for one studies(36), and 5 day intervals for one study(38). One study varied the interval by assignment, with 7 day changes in the experimental group, and 2 day intervals in the control group(32), and another two randomized patients into 3- and – day dressing changes(35, 48).

The majority of patients analyzed in this meta-analysis were patients in ICUs, both pediatric and adult patients in 7 of the 9 included trials(31–33, 35, 36, 38, 48). Duration of catheterization ranged from 5.6 days(33) to 71.5 days(34).

Details of randomization

Block randomization was used in seven trials(31–33, 35–37, 48). In the remaining two studies, the method of randomization was not given(34, 38). Single blind methodology was employed in review of cultures and/or data in four studies(33, 35, 36, 48).

Intention to treat analysis was described in 5 trials(31, 32, 34, 35, 48)

Study quality

Two of the included studies were determined to have a high risk of bias,(34, 37) while the remaining 7 studies were classified as low risk. The risk assessments of the individual studies are listed in Table 1.

Diagnosis of catheter colonization and catheter-related bloodstream infection (CRBSI)

The authors used various definitions for catheter colonization and CRBSI in the included studies (Table 1). One study provided no definition for catheter colonization, other studies defined it as catheter-tip culture yielding >15 colonies or ≥1000 colony-forming units per milliliter (CFU/mL). Another used a lower cutoff of 100 CFU/mL(48). Roberts defined catheter colonization non-quantitatively as isolation of the same organism from exit site and catheter tip without obvious signs of infection(38).

CRBSI was defined by Chambers et al as positive blood cultures drawn in the presence of fever with no other recognized focus of infection, causing premature removal of the catheter and the catheter tip, yielding >15 CFU/mL of the same organism(34). Similar definitions were used in the studies by Arvaniti, Garland, Levy and Maki(31–33, 36). Roberts identified CRBSI as any infection yielding the same organism from the CVC tip/exit site and a blood culture isolate, and associated with fever and elevated white cell count(38). Ruschulte et al used blood cultures drawn both percutaneously and from the catheter, with a differential time to positivity of > 2 hours(37). Timsit et al used the following definition: positive blood cultures sampled 48 hours before or 48 hours after catheter removal with a quantitative catheter tip culture yielding the same microorganisms or a differential time to positivity of blood cultures ≥ 2 hours, without any other focus of infection(35).

Incidence of catheter colonization

Overall, 362/5581 (6.5%) catheters were colonized in the chlorhexidine-impregnated dressing group compared with 743/5200 (13.2%) in the comparator arm. The chlorhexidine-impregnated dressing was associated with a RR of 0.51 (random effects model, 95% CI 0.39–0.67). This is illustrated as a forest plot in Figure 2.

Incidence of CRBSI

Overall, 1.2% (67/5639) of patients developed CRBSI in the treatment group compared with 2.3% (127/5608) of patients in the comparator group. Six of the nine trials had results favoring the chlorhexidine-impregnated dressing for reducing CRBSI. The relative risk (RR) for CRBSI comparing the chlorhexidine and comparator groups in the meta-analysis was 0.57 (random effects model, 95% CI 0.42–0.79, P=0.002).

Publication bias

Funnel plots (Fig. 4) did not indicate publication bias to be likely. Eggers test was not statistically significant (P= 0.15).

Assessment of heterogeneity

There was substantial clinical heterogeneity in the included studies with differing patient populations, protocols for catheter care, and definitions of CRBSI. Using the Cochran Q statistic, we did not find statistical heterogeneity (P= 0.35). An alternate test for heterogeneity, I^2 was 10% indicating low statistical heterogeneity. I^2 for colonization was moderate at 64%.

Only two studies failed to demonstrate a reduction in colonization with impregnated sponges. The first had a small sample size, and authors stated the study was not adequately powered to make a definitive statement about chlorhexidine dressing efficacy.(38) The second study attributed the lack of effect to avoidance of femoral catheterization sites, smaller percentage of trauma patients and use of povidone-iodine skin antisepsis prior to cannulation.(36)

Subgroup analysis

To explore the reasons for heterogeneity, we undertook three subgroup analyses limited to studies assessing the efficacy of the chlorhexidine-impregnated dressing for 1) prevention of CRBSI in patients with malignancy, 2) in adult ICU patients only and 3) in pediatric ICU patients only.

Using a random effects model to analyze data from the two studies in patients with hematologic malignancy,(34, 37) we found a statistically significant benefit with the use of use of chlorhexidine-impregnated dressing. The RR was 0.52 (Random effects model, 95% CI 0.31–0.86, P=0.01).

Five studies were limited to adult ICU populations(32, 35, 36, 38, 48) and the chlorhexidine impregnated dressing was associated with a RR of 0.45 (Random effects model 95% CI 0.28–0.72). In the pediatric population, the chlorhexidine impregnated dressing was not associated with a statistically significant reduction in BSI (random effects RR 1.21, 0.60–2.44)(31, 33).

Cost of chlorhexidine-impregnated dressing

One study(35) had a formal evaluation of cost effectiveness published in a separate manuscript in 2012. Comparing the costs of CRBSI (ICU length of stay, diagnostic tests, antibiotics) against the costs of chlorhexidine dressings ($9.73 for the dressing itself, cost of changing catheter if patient develops dermatitis) against various rates of CRBSI, the study found chlorhexidine impregnated dressings cost effective even at very low rates of CRBSI, saving $88 for each catheter at incidence rate of 0.35 infections/1000 catheter days.(49) Two studies estimated the costs of chlorhexidine-impregnated dressings(35, 37). Ruschulte et al estimated the cost at €6 each, with the cost of preventing one CRBSI approximately €342 for a catheter left in place for 16 days (June 2, 2009: approximately equal to US $9.90 and $564.30, respectively). Using the estimate of Warren et al for treatment of CRBSI (US $11,971), a chlorhexidine-impregnated dressing was concluded to be cost-effective(50). In the study by Timsit et al, the number needed to treat with chlorhexidine-impregnated dressings in order to prevent one CRBSI was 117 catheters (95% CI, 86–1020). The authors

estimated that treatment for 10 days would require 3 dressings, each of which cost US $6 (2007 dollars), and the cost of preventing a single episode of major CRBSI was estimated at $2106 (95% CI, $1518-$18,360). The authors concluded that the cost of managing a single case of major CRBSI ranged from US $8000-$28,000, indicating that the use of chlorhexidine-impregnated dressing was cost saving [35].

Microbiology and resistance to chlorhexidine

Staphylococcus epidermidis was the most common organism isolated, followed by *Staphylococcus aureus*, other Gram-positive cocci and *Escherichia coli*. None of the studies reported incidence of resistance to chlorhexidine. However, routine surveillance by Chambers et al before and after catheterization grew one isolate of micrococcus at one month in 0.01% chlorhexidine broth but did not grow at subsequent concentrations(34).

Adverse effects of chlorhexidine

Contact dermatitis from the chlorhexidine-impregnated dressing was the most common adverse effect reported in studies(31, 35, 48). Timsit et al found the incidence of severe contact dermatitis requiring catheter removal to be 5.3 per 1000 catheters(35). Garland reported a much higher incidence of 19 (5.7%) of 335 neonates(31). Birth weight of all 7 neonates who developed contact dermatitis in the initial 15 months of the study was 880g or less with a gestational age less than 27 weeks with CVCs placed on day 8 of life or earlier. The observation of an adverse reaction in premature babies with extremely low birth weights led to a change in the inclusion criteria for the study and thereafter, infants <26 weeks of gestation were enrolled in the study only if CVC was inserted after the first week of life. Overall, in the treatment group, 15 (15%) of 98 neonates with birth weight <1000g developed contact dermatitis versus 4 (1.5%) of 237 neonates ≥1000g ($p<0.0001$). Garland et al also reported pressure necrosis in 2 cases. No systemic reactions to chlorhexidine were observed.

DISCUSSION

In this meta-analysis, a chlorhexidine-impregnated dressing was significantly more effective than traditional site care for preventing vascular catheter colonization and CRBSI. The RRR was 45% for CRBSI and 48% for catheter colonization. The pooled absolute risk reduction in CRBSI was 1.3%, making the number needed to treat 77.

Our findings suggest that a chlorhexidine-impregnated dressing can provide considerable value in reducing the risk of CRBSI in patients with central vascular catheters. A chlorhexidine-impregnated dressing is expected to be of greatest benefit in a setting where the extraluminal route of infection is expected to predominant such as short-term catheters. Garland et al, in a sub-cohort analysis, found that the differences in catheter tip colonization, an accepted surrogate for CRBSI, between the treatment and control groups were most evident for neonates whose catheters were in situ less than or equal to 14 days (11% vs. 25%, $p=0.0007$); and there were no differences between the treatment and control groups when the catheter was in situ longer than 14 days (23% vs. 20%, $p=0.53$).(3) This analysis suggests that there may be little or no advantage to using a chlorhexidine-impregnated

dressing on a catheter in place beyond 14 days. This likely corresponds to a change in the pathogenesis of CRBSI from the extraluminal route,(27) associated with short-term CVCs, to the intraluminal route(17). The benefits of chlorhexidine-impregnated dressings would not be expected to have as much impact CRBSI rates when the intraluminal route is the primary source of infection, as is the case with long-term devices and any CVC after the first or second week of insertion with routine dressing changes.

Most studies in our analysis used a chlorhexidine-impregnated sponge dressing (Biopatch™, Johnson and Johnson, New Brunswick, New Jersey), and one study used an integrated chlorhexidine dressing (3M™ Tegaderm™ CHG Dressing, 3M, St Paul, Minnesota). We included both types in our analyses as the mechanism of activity would be expected to be similar. The Biopatch™ dressing comes as a round sponge which is placed circumferentially around the insertion site. Errors in placement and dressing disruption have been well described with a sponge dressing(51). At our institution, we have been using the foam dressing for over a decade and continue to witness wrong placement of the sponge dressing. An integrated chlorhexidine dressing obviates this problem.

To our knowledge, ours is the first meta-analysis to examine the impact of a chlorhexidine dressing including both a sponge dressing and an integrated dressing. Ho et al previously demonstrated a non-statistically significant trend toward reduction in CRBSI with the use of chlorhexidine-impregnated sponge dressings.(52) This analysis includes 7 studies evaluated by this previous analysis, and includes 2 additional, recently published large studies. This study excluded one included in Ho et al, which evaluated skin colonization as its endpoint., as it did not evaluate catheter colonization or CRBSI, the main outcomes for this analysis(53).

Chlorhexidine impregnated dressings must be viewed as an adjunct to the sum total of essential preventive measures shown to reduce CRBSI and do not replace insertion and maintenance best practices. But even if a high rate of compliance with best practices has been achieved, two of the most recent trials found a substantial and highly statistically significant reduction in CRBSI with a very low baseline rate of CRBSI.

There was significant heterogeneity in the populations studied including neonates, pediatric cardiothoracic ICU, adult ICU and cancer patients. Exploring heterogeneity by subgroup analyses, we found that the beneficial effect of chlorhexidine-impregnated dressing use was pronounced in patients with malignancy. However, no definitive recommendations regarding the use of chlorhexidine-impregnated dressings in patients with malignancy can be made based on this analysis due to limitations in the designs of the two included trials of cancer patients.

It is important to ascertain whether the benefit of the chlorhexidine-impregnated dressing is confined to a particular type of vascular catheter. In the three studies that included arterial catheters(32, 35, 48), the beneficial effect of the chlorhexidine-impregnated dressing extended also to peripheral arterial catheters, suggesting that use of the chlorhexidine-impregnated dressing on arterial catheters warrants consideration.

Consideration of adverse effects of topical prolonged exposure to chlorhexidine is essential and adverse effects were explicitly addressed in three published clinical trials included in our meta-analysis(31, 35, 48). Reported adverse effects of cutaneous use of chlorhexidine include contact dermatitis and pressure necrosis. These adverse reactions were encountered in approximately 15% of cases in a randomized trial of a chlorhexidine-impregnated sponge dressing in premature neonates with birth weight <1000g and suggest that a chlorhexidine-impregnated dressing should be used with caution in this population. Generally, chlorhexidine-impregnated dressings for prevention of CRBSI appear to be safe and well tolerated; however clinicians should remain vigilant for erythema and dermatitis at the site of the chlorhexidine-impregnated dressing.

Another potential concern associated with the prolonged use of antiseptic agents is the emergence of microbial resistance(54). Frequent exposure to chlorhexidine may result in development of resistance to biocides(55, 56). However, in clinical trials of chlorhexidine-impregnated vascular devices, resistance to chlorhexidine has not been detected(57, 58). A recent well-designed trial comparing a second-generation central venous catheter impregnated with chlorhexidine and silver sulfadiazine to a standard uncoated catheter for prevention of CRBSI included rigorous efforts to detect antiseptic resistance(57). The investigators found that the zones of inhibition to chlorhexidine were similar for organisms recovered from both the antiseptic and control catheters. However, *in vitro* studies of *Pseudomonas stutzeri* exposed to slowly increasing concentrations of chlorhexidine found emergence of resistance to chlorhexidine and several classes of therapeutic antimicrobial agents(59). None of the published clinical trials included in our analysis adequately assessed emergence of resistance to chlorhexidine among isolates recovered from blood or catheter segments. Although low level bacterial chlorhexidine resistance(60) and resistance genes encoding chlorhexidine resistance(61) have been identified, there have no reports of clinically relevant chlorhexidine resistance to date(61, 62), despite the very wide use of chlorhexidine for cutaneous disinfection vascular access sites and surgical sites and in recent years, total body bathing of patients in critical care units(63–65). The increasing use of chlorhexidine makes continued surveillance for developing resistance important(61), but, as the microbial populations beneath a chlorhexidine dressing are minute following cutaneous disinfection, it seems unlikely that the use of chlorhexidine sponge dressings for prevention of vascular catheter-related BSI will contribute materially to the emergence and spread of chlorhexidine-resistant nosocomial pathogens.

Cost-effectiveness analyses have been limited to the chlorhexidine sponge dressing. A cost-effectiveness analysis by Crawford et al found that chlorhexidine-impregnated sponge dressing use has the potential for an estimated annual savings of US $275 million to $1.97 billion and a decrease of 329 to 3906 deaths.(66) However, this analysis was based on data obtained from a single randomized trial, highlighting the need for further cost-effectiveness analysis using differing patient populations and a broader range of efficacy estimates. A more recent study used using computer models based on average effectiveness data and CRBSI rates found that in a hypothetical 400 bed hospital, consistent use of a chlorhexidine sponge dressing would be expected to prevent 35 CRBSI events and save a net of $895,000 annually(51).

There are several limitations to our analyses that warrant consideration. Although one of the studies blinded the investigators evaluating the data(32), and two blinded assessors(35, 48), none of the included studies were truly double blind, increasing risk of bias. Two studies reported that blinded laboratory personnel performed cultures, and one study utilized a blinded case report review, however, the influence of the presence of the dressing on the clinician's suspicion and decision to investigate CRBSI is unknown(33, 35). Only two studies performed a comprehensive epidemiologic evaluation of the CRBSI source by sampling the catheter hub and performing molecular identification of isolated coagulase negative staphylococci (CoNS) to establish concordance between strains found in the blood, catheter tip and hub(31, 32). Additional limitations include the varied populations, settings, catheter types and reasons for use, as well as differences in standard practices for the prevention of CRBSI.

These limitations notwithstanding, our results have important implications for clinicians involved in the care of patients with intravascular catheters and highly support the use of a chlorhexidine-impregnated dressing. Our analyses support the routine use of a chlorhexidine-impregnated dressing for the prevention of CRBSI as part of a comprehensive approach to reducing CRBSI. Future research needs to undertake comparative effectiveness and cost-effectiveness studies to determine which of the available multiple novel technologies and prevention strategies, alone or in combination, provide the most impact for reducing CRBSI and better identify subgroups of patients most likely to benefit.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

REFERENCES

1. Climo M, Diekema D, Warren DK, et al. Prevalence of the use of central venous access devices within and outside of the intensive care unit: results of a survey among hospitals in the prevention epicenter program of the Centers for Disease Control and Prevention. Infect Control Hosp Epidemiol. 2003; 24(12):942–945. [PubMed: 14700410]
2. Shlaes DM, Gerding DN, John JF Jr, et al. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. Clin Infect Dis. 1997; 25(3):584–599. [PubMed: 9314444]
3. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009; 49(1):1–45. [PubMed: 19489710]
4. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. Am J Infect Control. 2002; 30(8):476–489. [PubMed: 12461511]
5. Mermel LA, Farr BM, Sherertz RJ, et al. Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis. 2001; 32(9):1249–1272. [PubMed: 11303260]
6. Safdar N, Crnich CJ, Maki DG. The pathogenesis of ventilator-associated pneumonia: its relevance to developing effective strategies for prevention. Respir Care. 2005; 50(6):725–739. discussion 739–741. [PubMed: 15913465]
7. Safdar N, Crnich CJ, Maki DG. Nosocomial Infections in the Intensive Care Unit Associated with Invasive Medical Devices. Curr Infect Dis Rep. 2001; 3(6):487–495. [PubMed: 11722804]

8. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. Jama. 1994; 271(20):1598–1601. [PubMed: 8182812]
9. Arnow PM, Quimosing EM, Beach M. Consequences of intravascular catheter sepsis. Clin Infect Dis. 1993; 16(6):778–784. [PubMed: 8329510]
10. Collignon PJ. Intravascular catheter associated sepsis: a common problem. The Australian Study on Intravascular Catheter Associated Sepsis. Med J Aust. 1994; 161(6):374–378. [PubMed: 8090116]
11. Rello J, Ochagavia A, Sabanes E, et al. Evaluation of outcome of intravenous catheter-related infections in critically ill patients. Am J Respir Crit Care Med. 2000; 162(3 Pt 1):1027–1030. [PubMed: 10988125]
12. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med. 2006; 355(26):2725–2732. [PubMed: 17192537]
13. Mattie AS, Webster BL. Centers for Medicare and Medicaid Services' "never events": an analysis and recommendations to hospitals. Health Care Manag (Frederick). 2008; 27(4):338–349. [PubMed: 19011417]
14. Clancy CM. CMS's hospital-acquired condition lists link hospital payment, patient safety. Am J Med Qual. 2009; 24(2):166–168. [PubMed: 19228892]
15. Marrie TJ, Costerton JW. Scanning and transmission electron microscopy of in situ bacterial colonization of intravenous and intraarterial catheters. J Clin Microbiol. 1984; 19(5):687–693. [PubMed: 6429190]
16. Cooper GL, Schiller AL, Hopkins CC. Possible role of capillary action in pathogenesis of experimental catheter-associated dermal tunnel infections. J Clin Microbiol. 1988; 26(1):8–12. [PubMed: 3343317]
17. Sitges-Serra A, Linares J, Garau J. Catheter sepsis: the clue is the hub. Surgery. 1985; 97(3):355–357. [PubMed: 3919458]
18. Maki DG, Jarrett F, Sarafin HW. A semiquantitative culture method for identification of catheter-related infection in the burn patient. J Surg Res. 1977; 22(5):513–520. [PubMed: 323579]
19. Crnich CJ, Maki DG. The promise of novel technology for the prevention of intravascular device-related bloodstream infection. II. Long-term devices. Clin Infect Dis. 2002; 34(10):1362–1368. [PubMed: 11981732]
20. Haraden, CP. What is a bundle?. 2006. http://www.ihi.org/IHI/Topics/CriticalCare/IntensiveCare/ImprovementStories/WhatIsaBundle.htmhttp://www.ihi.org/IHI/Topics/CriticalCare/IntensiveCare/ImprovementStories/WhatIsaBundle.htm[cited 2008 August 8]Available from
21. Yokoe DS, Mermel LA, Anderson DJ, et al. A compendium of strategies to prevent healthcare-associated infections in acute care hospitals. Infect Control Hosp Epidemiol. 2008; 29(Suppl 1):S12–S21. [PubMed: 18840084]
22. Eggimann P, Harbarth S, Constantin MN, et al. Impact of a prevention strategy targeted at vascular-access care on incidence of infections acquired in intensive care. Lancet. 2000; 355(9218):1864–1868. [PubMed: 10866442]
23. Berenholtz SM, Pronovost PJ, Lipsett PA, et al. Eliminating catheter-related bloodstream infections in the intensive care unit. Crit Care Med. 2004; 32(10):2014–2020. [PubMed: 15483409]
24. Zingg W, Imhof A, Maggiorini M, et al. Impact of a prevention strategy targeting hand hygiene and catheter care on the incidence of catheter-related bloodstream infections. Crit Care Med. 2009; 37(7):2167–2173. quiz 2180. [PubMed: 19487942]
25. Warren DK, Zack JE, Mayfield JL, et al. The effect of an education program on the incidence of central venous catheter-associated bloodstream infection in a medical ICU. Chest. 2004; 126(5):1612–1618. [PubMed: 15539735]
26. Coopersmith CM, Zack JE, Ward MR, et al. The impact of bedside behavior on catheter-related bacteremia in the intensive care unit. Arch Surg. 2004; 139(2):131–136. [PubMed: 14769568]
27. Safdar N, Maki DG. The pathogenesis of catheter-related bloodstream infection with noncuffed short-term central venous catheters. Intensive Care Med. 2004; 30(1):62–67. [PubMed: 14647886]

28. Mermel LA, McCormick RD, Springman SR, et al. The pathogenesis and epidemiology of catheter-related infection with pulmonary artery Swan-Ganz catheters: a prospective study utilizing molecular subtyping. Am J Med. 1991; 91(3B):197S–205S. [PubMed: 1928165]
29. Bjornson HS, Colley R, Bower RH, et al. Association between microorganism growth at the catheter insertion site and colonization of the catheter in patients receiving total parenteral nutrition. Surgery. 1982; 92(4):720–727. [PubMed: 6812229]
30. Banton J. Techniques to prevent central venous catheter infections: products, research, and recommendations. Nutr Clin Pract. 2006; 21(1):56–61. [PubMed: 16439770]
31. Garland JS, Alex CP, Mueller CD, et al. A randomized trial comparing povidone-iodine to a chlorhexidine gluconate-impregnated dressing for prevention of central venous catheter infections in neonates. Pediatrics. 2001; 107(6):1431–1436. [PubMed: 11389271]
32. Maki D, Mermel L, Kluger D, et al. The efficacy of a chlorhexidine impregnated sponge (Biopatch) for the prevention of intravascular catheter-related infection-a prospective randomized controlled multicenter study. 2000 2000.
33. Levy I, Katz J, Solter E, et al. Chlorhexidine-impregnated dressing for prevention of colonization of central venous catheters in infants and children - A randomized controlled study. Pediatric Infectious Disease Journal. 2005; 24(8):676–679. [PubMed: 16094219]
34. Chambers ST, Sanders J, Patton WN, et al. 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. 2005; 61(1):53–61. [PubMed: 16002181]
35. Timsit JF, Schwebel C, Bouadma L, et al. Chlorhexidine-impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults: a randomized controlled trial. Jama. 2009; 301(12):1231–1241. [PubMed: 19318651]
36. Arvaniti K, Lathyris D, Clouva-Molyvdas P, et al. 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. Critical care medicine. 2012; 40(2):420–429. [PubMed: 21926583]
37. Ruschulte H, Franke M, Gastmeier P, et al. Prevention of central venous catheter related infections with chlorhexidine gluconate impregnated wound dressings: a randomized controlled trial. Ann Hematol. 2009; 88(3):267–272. [PubMed: 18679683]
38. Roberts BL, Cheung D. BIOPATCH -- a new concept in antimicrobial dressings for invasive devices. Australian Critical Care. 1998; 11(1):16–19. [PubMed: 9708081]
39. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 2009; 151(4):W65–94. [PubMed: 19622512]
40. Saint S, Higgins LA, Nallamothu BK, et al. Do physicians examine patients in contact isolation less frequently? A brief report. Am J Infect Control. 2003; 31(6):354–356. [PubMed: 14608302]
41. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7(3):177–188. [PubMed: 3802833]
42. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959; 22(4):719–748. [PubMed: 13655060]
43. Donner, A.; Klar, N. Design and Analysis of Cluster Randomization Trials in Health Research. London: 2000.
44. Chaiyakunapruk N, Veenstra DL, Lipsky BA, et al. Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care: a meta-analysis. Ann Intern Med. 2002; 136(11):792–801. [PubMed: 12044127]
45. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997; 315(7109):629–634. [PubMed: 9310563]
46. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol. 2001; 54(10):1046–1055. [PubMed: 11576817]
47. Review Manager. 5.0 ed. Nordic Cochrane Review Centre;

48. Timsit JF, Mimoz O, Mourvillier B, et al. Randomized Controlled Trial of Chlorhexidine Dressing and Highly Adhesive Dressing for Preventing Catheter-Related Infections in Critically Ill Adults. American journal of respiratory and critical care medicine. 2012

49. Schwebel C, Lucet JC, Vesin A, et al. Economic evaluation of chlorhexidine-impregnated sponges for preventing catheter-related infections in critically ill adults in the Dressing Study. Critical care medicine. 2012; 40(1):11–17. [PubMed: 21926570]

50. Warren DK, Quadir WW, Hollenbeak CS, et al. Attributable cost of catheter-associated bloodstream infections among intensive care patients in a nonteaching hospital. Crit Care Med. 2006; 34(8):2084–2089. [PubMed: 16763511]

51. Ye X, Rupnow M, Bastide P, et al. Economic impact of use of chlorhexidine-impregnated sponge dressing for prevention of central line-associated infections in the United States. American journal of infection control. 2011; 39(8):647–654. [PubMed: 21641681]

52. Ho KM. Comment on: Use of chlorhexidine-impregnated dressing to prevent vascular and epidural catheter colonization and infection: a meta-analysis. The Journal of antimicrobial chemotherapy. 2010; 65(4):811–814. [PubMed: 20142265]

53. Hanazaki K, Shingu K, Adachi W, et al. Chlorhexidine dressing for reduction in microbial colonization of the skin with central venous catheters: a prospective randomized controlled trial. J Hosp Infect. 1999; 42(2):165–168. [PubMed: 10389070]

54. Tambe SM, Sampath L, Modak SM. In vitro evaluation of the risk of developing bacterial resistance to antiseptics and antibiotics used in medical devices. J Antimicrob Chemother. 2001; 47(5):589–598. [PubMed: 11328769]

55. McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action, and resistance. Clin Microbiol Rev. 1999; 12(1):147–179. [PubMed: 9880479]

56. Penna TC, Mazzola PG, Silva Martins AM. The efficacy of chemical agents in cleaning and disinfection programs. BMC Infect Dis. 2001; 1:16. [PubMed: 11591223]

57. Rupp ME, Lisco SJ, Lipsett PA, et al. Effect of a second-generation venous catheter impregnated with chlorhexidine and silver sulfadiazine on central catheter - Related infections - A randomized, controlled trial. Annals of Internal Medicine. 2005; 143(8):570–580. [PubMed: 16230723]

58. Maki DG, Stolz SM, Wheeler S, et al. Prevention of central venous catheterrelated bloodstream infection by use of an antiseptic-impregnated catheter. A randomized, controlled trial. Ann Intern Med. 1997; 127(4):257–266. [PubMed: 9265424]

59. Tattawasart U, Maillard JY, Furr JR, et al. Development of resistance to chlorhexidine diacetate and cetylpyridinium chloride in Pseudomonas stutzeri and changes in antibiotic susceptibility. J Hosp Infect. 1999; 42(3):219–229. [PubMed: 10439995]

60. Cookson BD, Bolton MC, Platt JH. Chlorhexidine resistance in methicillin-resistant Staphylococcus aureus or just an elevated MIC? An in vitro and in vivo assessment. Antimicrob Agents Chemother. 1991; 35(10):1997–2002. [PubMed: 1759820]

61. Horner C, Mawer D, Wilcox M. Reduced susceptibility to chlorhexidine in staphylococci: is it increasing and does it matter? The Journal of antimicrobial chemotherapy. 2012; 67(11):2547–2559. [PubMed: 22833635]

62. Johnson MD, Schlett CD, Grandits GA, et al. Chlorhexidine does not select for resistance in Staphylococcus aureus isolates in a community setting. Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America. 2012; 33(10):1061–1063.

63. O'Horo JC, Silva GL, Munoz-Price LS, et al. The efficacy of daily bathing with chlorhexidine for reducing healthcare-associated bloodstream infections: a meta-analysis. Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America. 2012; 33(3):257–267.

64. Derde LP, Dautzenberg MJ, Bonten MJ. Chlorhexidine body washing to control antimicrobial-resistant bacteria in intensive care units: a systematic review. Intensive Care Med. 2012; 38(6): 931–939. [PubMed: 22527065]

65. Climo MW, Sepkowitz KA, Zuccotti G, et al. The effect of daily bathing with chlorhexidine on the acquisition of methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus,

and healthcare-associated bloodstream infections: results of a quasi-experimental multicenter trial. Crit Care Med. 2009; 37(6):1858–1865. [PubMed: 19384220]

66. Crawford AG, Fuhr JP, Rao B. Cost-benefit analysis of chlorhexidine gluconate dressing in the prevention of catheter related bloodstream infections. Infection Control and Hospital Epidemiology. 2004; 25(8):668–674. [PubMed: 15357159]

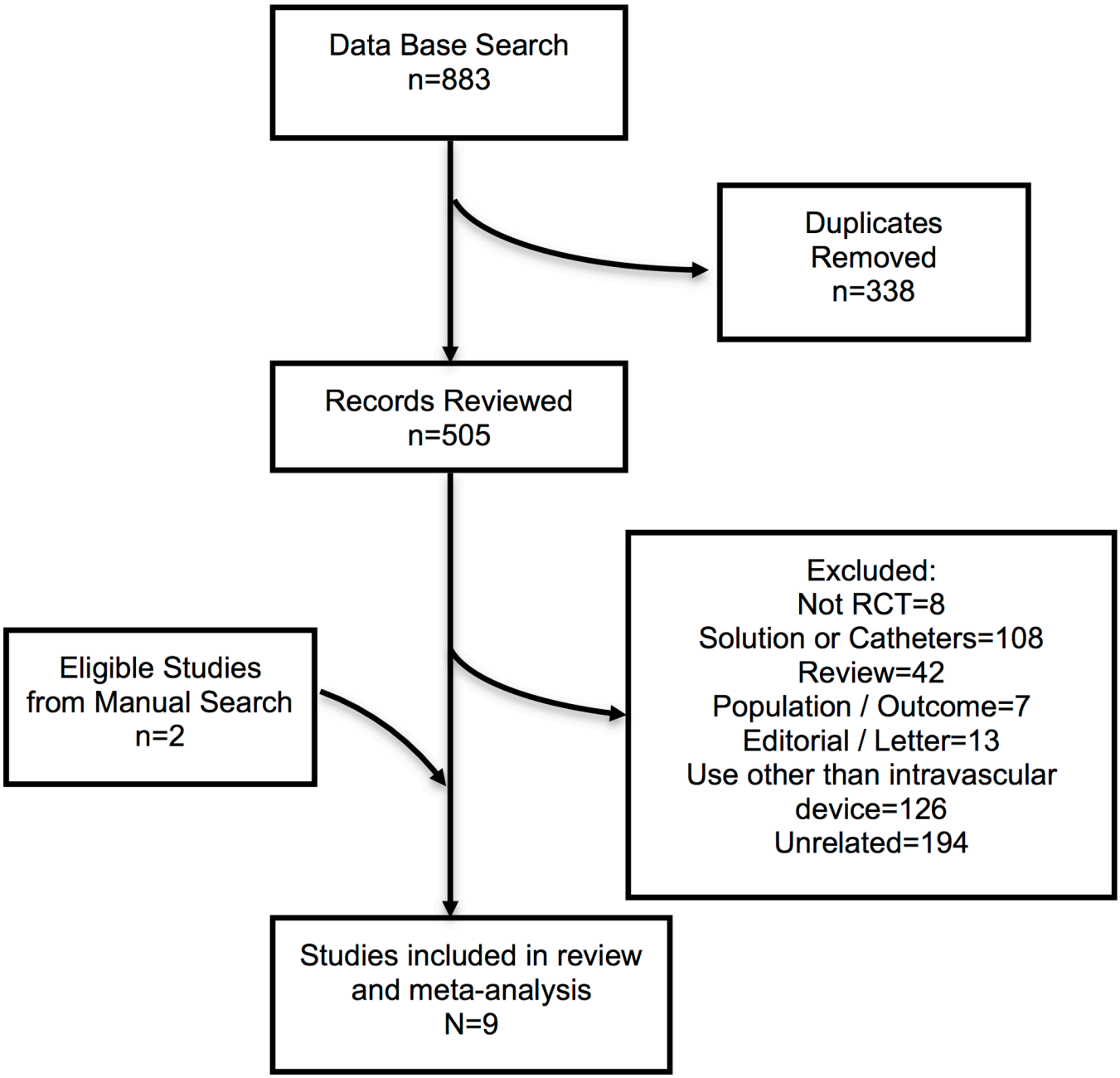

Figure 1.
Literature search and selection of studies

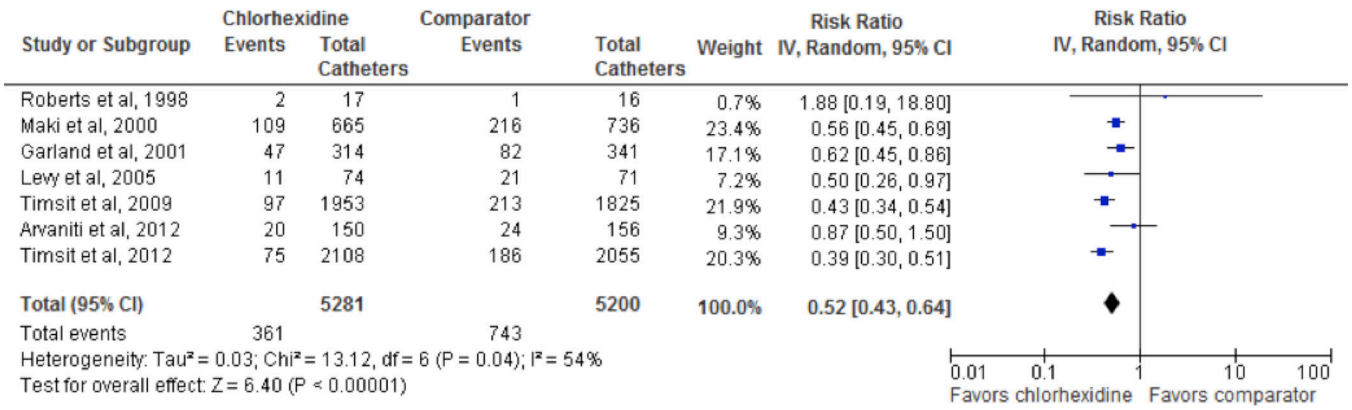

Figure 2.

Relative risk of catheter colonization with chlorhexidine-impregnated dressing and comparator using a random effects model.

I will redo the charts to provide the correct reference number after the name for each when we have the rest edited as the numbers may shift

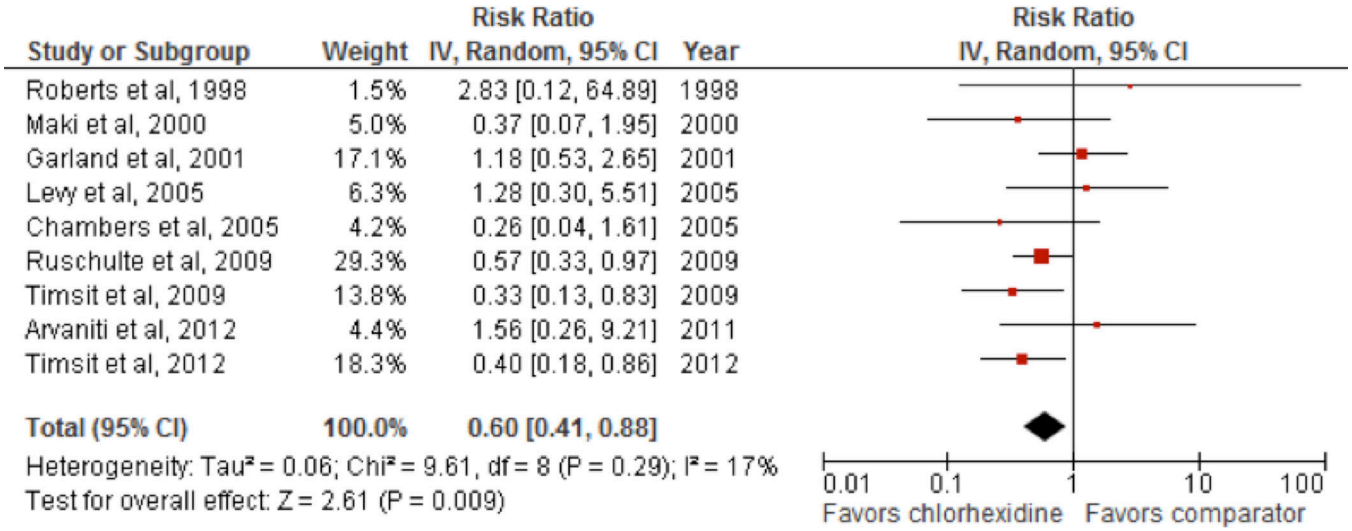

Figure 3.

Relative risk of CRBSI with chlorhexidine-impregnated dressing and comparator using a random effects model.

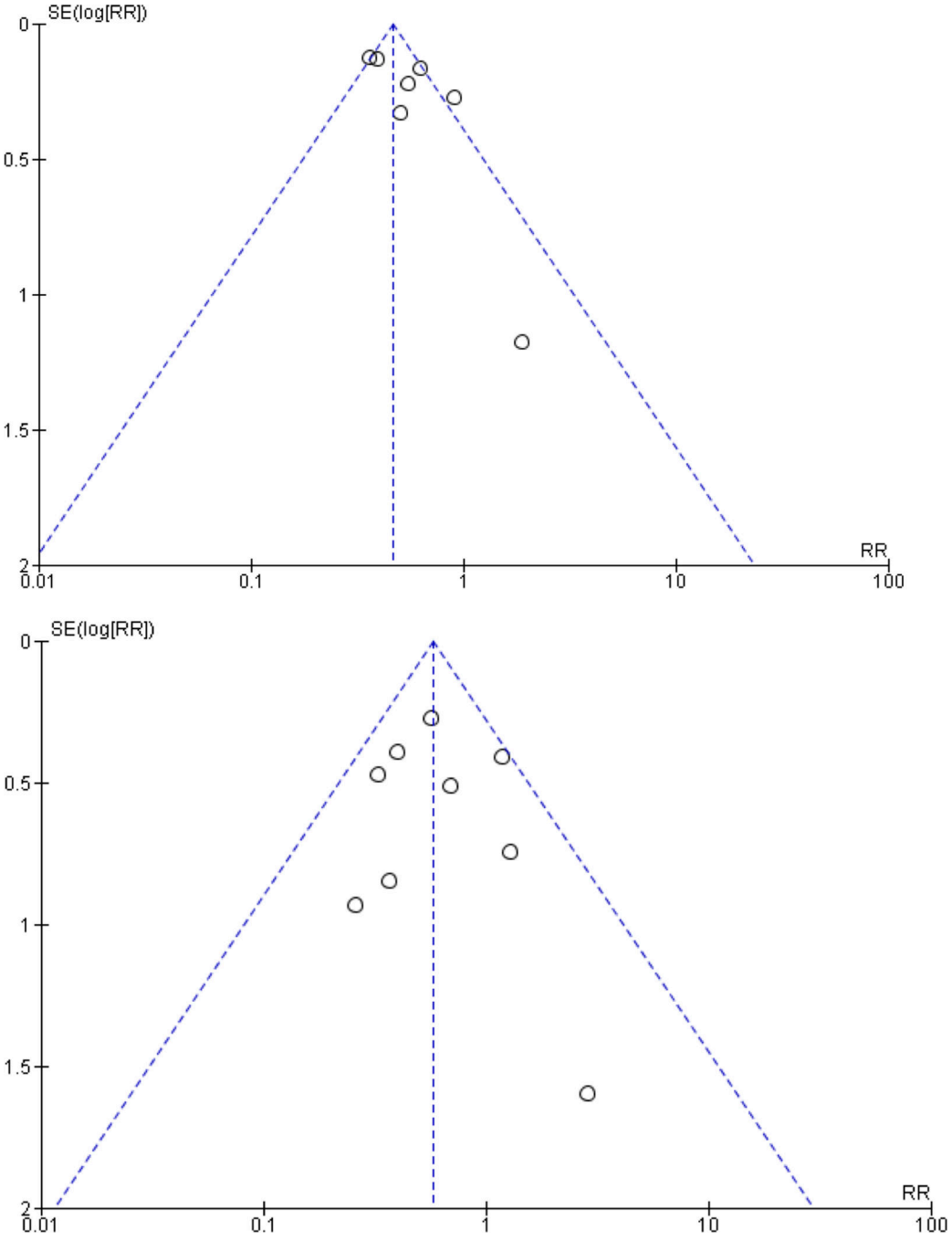

Figure 4.

Funnel plot to evaluate for publication bias for colonization (left) and CRBSI (right). Publication bias is not evident.

Table 1

Characteristics of included studies

Author, year	Population Setting and inclusion criteria	Catheter Type	Definition of catheter colonization	Definition of CRBSI	Skin antiseptic	Dressing replacement interval	Risk of Bias, Comments
Roberts et al, 1998(38)	Adult ICU patients requiring CVC during a 7 week period	CVC	Same organism from CVC tip and exit site, no clinical infection	Clinical infection with same organism isolated from catheter tip (and/or exit site) and blood	Chlorhexidine 0.5% in 70% alcohol	Every 5 days or as needed	LOW RISK -Underpowered to detect differences in catheter colonization and CRBSI between groups
Maki et al, 2000(32)	Adult patients requiring CVC, pulmonary artery or peripheral arterial catheters	CVC, pulmonary artery, or peripheral arterial catheter	>15 CFUs by roll plate method	Isolation of the same organism from peripheral blood and catheter tip, hub or infusate	NR	Control: Every 2 days Treatment group: Every 7 days	LOW RISK -Abstract only -Additional information (catheterization duration, CVC insertion site) obtained by reviewing publications based on the same study population and from study author
Garland et al, 2001(31)	Neonates admitted to level III ICU with CVC expected to remain in place a minimum of 48 hours	CVC, and tunneled (Broviac) CVC	Semi-quantitative catheter colony count >15 CFU	Clinical infection with same organism isolated from catheter tip and blood	Control group: 10% povidone-iodine Treatment group: 70% alcohol	Every 7 days (Twice weekly in surgically placed CVC with control dressing)	LOW RISK -Study halted before recruitment goal met (funding constraints and low CRBSI rates) -Different skin anti-sepsis used in two groups -Underpowered to detect difference in CRBSI between groups
Chambers et al, 2005(34)	Adult patients in hematology unit undergoing chemotherapy	Long-term, tunneled, cuffed CVC	NR	Fever and positive blood cultures without alternative infection source, and catheter tip culture with >15 colonies of the same organism	Alcohol-povidone-iodine 10%	Treatment group: weekly or as needed Control group: no dressing	HIGH RISK -Control group had no dressing once exit site dry / free of ooze: -This may not represent a healed site and could increase risk of tunnel and exit site infection, and ultimately increased risk for CRBSI, in control group
Levy et al, 2005(33)	Pediatric cardiac intensive care unit patients requiring CVC for minimum of 48 hours	Short-term, non-tunneled CVC	>15 CFU by the roll-plate technique, no signs of infection	Bacteremia with isolation of the same organism from CVC tip nd blood	Chlorhexidine	As needed	LOW RISK -No established interval for dressing change -Underpowered to detect CRBSI difference

Author, year	Population Setting and inclusion criteria	Catheter Type	Definition of catheter colonization	Definition of CRBSI	Skin antiseptic	Dressing replacement interval	Risk of Bias, Comments
Ruschulte et al, 2009(37)	Adults with hematologic or oncologic malignancy with catheter expected for minimum of 5 days	Short-term, non-tunneled catheter impregnated on the exterior surface with silver sulfadiazine-chlorhexidine	NR	Clinical evidence of infection and time-to-positivity method used with CVC and peripherally drawn blood cultures	Alcohol spray	Every other week or as needed	HIGH RISK -High baseline rate of infection -Short-term rather than long term CVCs used in population of oncologic patients -81% of CVC placed in internal jugular rather than subclavian site -Alcohol spray used as skin antiseptic -62% of CRBSI caused by CoNS without molecular epidemiology to confirm source
Timsit et al, 2009(35)	Adult ICU patients requiring catheter minimum of 48 hours	CVC and/or arterial catheter	Quantitative CVC tip culture ≥1000 CFUs/mL	Clinical infection without alternative source, peripheral blood drawn immediately prior to or within 48 hours following catheter removal and quantitative catheter tip culture isolating the same organism, or confirmed using differential time to positivity test	4% aqueous povidone-iodine scrub solution followed by 5% povidone-iodine in 70% alcohol solution	Every 3 days or every 7 days (Based on randomized group assignment)	LOW RISK -Modified ITT analysis: those who withdrew consent after randomization were not included in denominator of ITT analysis -60% of CVCs were at jugular or femoral sites, 41% of peripheral arterial catheters were at femoral site
Arvaniti et al, 2012(36)	Adult ICU patients requiring catheter at least 72 hours	CVC	Quantitative CVC tip culture with >1000 CFU/mL and no systemic signs of sepsis	Quantitative CVC tip culture with >1000 CFU/mL with systemic signs of sepsis	NR	Every 3 days or as needed	LOW RISK -Had third arm (antibiotic impregnated catheters) excluded for this analysis
Timsit et al, 2012(48)	Adult ICU patients expected to require catheter for at least 48 hours	CVC	Quantitative CVC tip culture >1000 CFU/mL and no systemic signs of sepsis	Correlation between peripheral blood culture and quantitative tip culture without other likely source	Alcohol-povidone or alcohol chlorhexidine	Every 3–7 days or as needed	LOW RISK -Randomized control trial using intention to treat analysis

CFU, Colony Forming Units; CoNS, coagulase-negative staphylococci; CRBSI, catheter-related bloodstream infection; CVC, central venous catheter; ICU, intensive care unit; NR, not reported

Table 2

Incidence of catheter colonization and CRBSI with chlorhexidine-impregnated dressing

Author, year	Number of patients/catheters		Mean duration of catheterization (days)		Catheter Colonization n/N (%)			CRBSI n/N (%)		
	CHG dressing	control	CHG dressing	Control	CHG dressing	Control	RR (95% CI)	CHG dressing	Control	RR (95% CI)
Roberts et al, 1998(38)	17/17	16/16	7	6	2/17 (12)	1/16 (6)	1.88 (0.19–18.80)	1/17 (5)	0/16 (0)	2.83 (0.12–64.89)
Maki et al, 2000(32)	301/665	366/736	NR	NR	109/665 (16)	216/736 (29)	0.55 (0.36–0.85)[a]	8/665 (1)	24/736 (3)	0.37 (0.07–1.95)[a]
Garland et al, 2001(31)*	335/335	370/370	17.7	17.4	47/314 (15)	82/341 (24)	0.62 (0.45–0.86)	12 /314 (4)	11/341 (3)	1.18 (0.53–2.65)
Chambers et al, 2005(34)	52/58	43/54	71.5	62.5	NR	NR	NR	2/58 (3)	7/54 (13)	0.27 (0.06–1.22)[a]
Levy et al, 2005(33)	74/74	71/71	5.75	5.6	11/74 (15)	21/71 (29)	0.50 (0.26–0.97)	4/74 (5)	3/71 (4)	1.28 (0.30–5.51)
Ruschulte et al, 2009(37)	300/300	301/301	16.62	15.76	NR	NR	NR	19/300 (6)	34/301 (11)	0.56 (0.33–0.96)
Timsit et al, 2009(35)	817/1953	819/1825	6[c]	6[c]	97/1953 (4)	213/1825 (12)	0.36 (0.28–0.46)[b]	6/1953 (0)	17/1825 (0)	0.33 (0.13–0.83)[b]
Arvaniti et al, 2012(36)	150/150	156/156	7.03	7.38	21/156 (14)	24/156 (15)	0.91 (0.53–1.56)	6/150 (4)	9/156 (6)	0.69 (0.25–1.90)
Timsit et al, 2012(48)	938/2108	941/2055	8.21	8.29	75/2108 (3.5)	186/2055 (9.0)	0.39 (0.30–0.51)	9/2108 (0.4)	22/2055 (1.0)	0.40 (0.18–0.86)
Total	2984/5586	3083/5628			362/5281	743/5200	0.51 (0.39–0.67)	67/5639	127/5608	0.57 (0.42–0.79)

[a] variance estimate inflated to adjust for correlation

[b] as reported in the study after adjusting for correlation

[c] Median reported in place of mean

CHG, chlorhexidine-impregnated dressing; CRBSI, catheter-related bloodstream infection; CVC, central venous catheter

* 21 chlorhexidine-dressed catheters, and 56 control catheters were not cultured, and were excluded from the analyses