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

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

Study Selection: Randomized controlled trials evaluating the efficacy of a chlorhexidine-impregnated dressing compared with conventional dressings for prevention of catheter colonization and catheter-related bloodstream infection.

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

Data Synthesis: Nine randomized controlled trials met the inclusion criteria. Use of a chlorhexidine-impregnated dressing resulted in a reduced prevalence of catheter-related bloodstream infection (random effects relative risk, 0.60; 95% CI, 0.41–0.88, \( p = 0.009 \)). The prevalence of catheter colonization was also markedly reduced in the chlorhexidine-impregnated dressing group (random effects relative risk, 0.52; 95% CI, 0.43–0.64; \( p < 0.001 \)). There was significant benefit for prevention of catheter colonization and catheter-related bloodstream infection, 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, catheter-related bloodstream infection and warrants routine use in patients at high risk of catheter-related bloodstream infection and central venous catheter or arterial catheter colonization. (Crit Care Med 2014; XX:00–00)

Key Words: catheter-related infection; chlorhexidine; nosocomial infection

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 risk of catheter-related bloodstream infection (CRBSI) (3, 6, 7). CRBSIs directly increase antibiotic exposure, length of stay, and healthcare costs and may increase mortality (8–11). CRBSI is increasingly recognized as a preventable healthcare-associated infection (12), prompting the United States Centers for Medicare and Medicaid Service to cease reimbursing healthcare institutions for these complications as of October 2008. There is an urgent need for effective strategies to prevent CRBSI (13, 14).

The most common route of infection occurs 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 the
catheter is manipulated, such as when an infusion is started, or when the central venous catheter (CVC) is manipulated with a guidewire. Finally, organisms can be carried hematogenously to the implanted device from remote sources of infection, for example, pneumonia or urinary tract infection (15–19).

Understanding these mechanisms of CRBSI, pathogenesis has led to specific preventive strategies, including the creation of best practice guidelines and evidence-based “bundles” such as those developed by the Institute for Healthcare Improvement (4, 20, 21). These include an emphasis 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 nontunneled catheters, and daily evaluation of catheter necessity with prompt removal of unnecessary catheters (4, 20).

Strict adherence to evidence-based best practices clearly reduces CRBSI rates (3, 12, 22–26). Individual interventions that can make CRBSI prevention simpler and more cost effective merit further 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), which 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 (39). The search strategy was developed with the assistance of an expert librarian (for search details, see online supplementary material, Supplemental Digital Content 1, http://links.lww.com/CCM/A880).

Inclusion Criteria
Included studies were prospective randomized trials comparing a chlorhexidine-impregnated dressing with conventional site care. Included studies had to provide microbiologically based definitions for CRBSI and systematically report the prevalence of CRBSI in both comparator and control arms. Authors of potentially relevant studies were contacted for further information if some of these data were unpublished. 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 (N.S., A.G., J.O.) independently abstracted data on the size of the study sample, patient population, type of vascular devices, dressing, cutaneous antiseptic used, device use duration, prevalence of catheter colonization, and prevalence of CRBSI. The authors of studies that did not report prevalence data for analysis were contacted for additional information.

We evaluated the included studies for methodological quality using the recommendations outlined in the Cochrane Handbook of Systematic Review (40). The risk of bias in each study was assigned as either low or high. Three authors (N.S., A.G., J.O.) 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 relative risk (RR) and 95% CI were obtained using the DerSimonian and Laird random effects model (41). 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 (42, 43). Heterogeneity was assessed using the Cochran Q statistic and I² (40). Negative values of I² are conventionally equal to 0% so I² values can range between 0% and 100%. Zero percent 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 (44, 45). Statistical analyses were performed using Stats Direct (2002, Cheshire, United Kingdom) and Review Manager software (2008, Nordic Cochrane Center).

RESULTS

Study Selection
The database search retrieved 505 unique citations of which seven met our inclusion criteria, described in Figure 1 (31, 33–38). Manual search of references of included studies identified two additional studies (32, 46). 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 nine trials enrolled 6,067 patients with a total of 11,214 catheterizations; 5,586 catheters in 2,984 patients received a
The characteristics of the nine randomized controlled trials are summarized in Table 1. Five studies (32, 34, 36, 38, 46) 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 reported the outcome measures for both patients and catheters (35).

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.

All studies used standard aseptic technique in inserting catheters, 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, 46). 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 (32) included central venous, PICCs, and five in adult medical-surgical and cardiothoracic ICUs (32, 35, 36, 38, 46).

The majority of patients analyzed in this meta-analysis were patients in ICUs, both pediatric and adult patients in seven of the nine included trials (31–33, 35, 36, 38, 46). Duration of catheterization ranged from 5.6 (33) to 71.5 days (34).

Details of Randomization
Block randomization was used in seven trials (31–33, 35–37, 46). 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, 46). Intention-to-treat analysis was described in five trials (31, 32, 34, 35, 46).

Study Quality
Two of the included studies were determined to have a high risk of bias due to high baseline infections and nonstandard infection control practices (34, 37), whereas the remaining seven studies were classified as low risk. The risk assessments of the individual studies are listed in Table 1.

Three large studies (32, 35, 47) accounted for 83% of the included patients. All three of these studies were designated as having a low risk of bias.

Diagnosis of Catheter Colonization and 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 greater than 15 colonies or greater than or equal to 1,000 colony-forming units per milliliter (CFU/mL). Another two used a lower cutoff of 100 CFU/mL using the Sherertz technique (35, 46). Roberts and Cheung (38) defined catheter colonization nonquantitatively as isolation of the same organism from exit site and catheter tip without obvious signs of infection.

CRBSI was defined by Chambers et al (34) 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 greater than 15 CFU/mL of the same organism. Similar definitions were used in the studies by Arvaniti et al (36), Garland et al (31), Levy et al (33), and Maki et al (32). Roberts and Cheung (38) 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 WBC count. Ruschulte et al (37) used blood cultures drawn both percutaneously and from the catheter, with a differential time to positivity of greater than 2 hours. Timsit et al (35, 47) 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 greater than or equal to 2 hours, without any other focus of infection.
### TABLE 1. Descriptive Characteristics of the Nine Included Studies

<table>
<thead>
<tr>
<th>References</th>
<th>Population, Setting, and Inclusion Criteria</th>
<th>Catheter Type</th>
<th>Definition of Catheter Colonization</th>
<th>Definition of CRBSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roberts and Cheung (38)</td>
<td>Adult ICU patients requiring CVC during a 7-wk period</td>
<td>CVC</td>
<td>Same organism from CVC tip and exit site, no clinical infection</td>
<td>Clinical infection with same organism isolated from catheter tip (and/or exit site) and blood</td>
</tr>
<tr>
<td>Maki et al (32)</td>
<td>Adult patients requiring CVC, pulmonary artery or peripheral arterial catheters</td>
<td>CVC, pulmonary artery, or peripheral arterial catheter</td>
<td>&gt; 15 CFUs by roll plate method</td>
<td>Isolation of the same organism from peripheral blood and catheter tip, hub, or infusion</td>
</tr>
<tr>
<td>Garland et al (31)</td>
<td>Neonates admitted to level III ICU with CVC expected to remain in place a minimum of 48 hr</td>
<td>CVC and tunneled (Broviac) CVC</td>
<td>Semiquantitative catheter colony count &gt; 15 CFU</td>
<td>Clinical infection with same organism isolated from catheter tip and blood</td>
</tr>
<tr>
<td>Chambers et al (34)</td>
<td>Adult patients in hematology unit undergoing chemotherapy</td>
<td>Long-term, tunneled, cuffed CVC</td>
<td>NR</td>
<td>Fever and positive blood cultures without alternative infection source and catheter tip culture with &gt; 15 colonies of the same organism</td>
</tr>
<tr>
<td>Levy et al (39)</td>
<td>Pediatric cardiac ICU patients requiring CVC for minimum of 48 hr</td>
<td>Short-term, nontunneled CVC</td>
<td>&gt; 15 CFU by the roll-plate technique, no signs of infection</td>
<td>Bacteremia with isolation of the same organism from CVC tip and blood</td>
</tr>
<tr>
<td>Ruschulte et al (37)</td>
<td>Adults with hematologic or oncologic malignancy with catheter expected for minimum of 5 d</td>
<td>Short-term, nontunneled catheter impregnated on the exterior surface with silver sulfadiazine-chlorhexidine</td>
<td>NR</td>
<td>Clinical evidence of infection and time-to-positivity method used with CVC and peripherally drawn blood cultures</td>
</tr>
<tr>
<td>Timsit et al (35)</td>
<td>Adult ICU patients requiring catheter minimum of 48 hr</td>
<td>CVC and/or arterial catheter</td>
<td>Quantitative CVC tip culture ≥ 1,000 CFUs/mL</td>
<td>Clinical infection without alternative source, peripheral blood drawn immediately prior to or within 48 hr following catheter removal and quantitative catheter tip culture isolating the same organism, or confirmed using differential time to positivity test</td>
</tr>
<tr>
<td>Arvaniti et al (36)</td>
<td>Adult ICU patients requiring catheter at least 72 hr</td>
<td>CVC</td>
<td>Quantitative CVC tip culture with &gt; 1,000 CFU/mL and no systemic signs of sepsis</td>
<td>Quantitative CVC tip culture with &gt; 1,000 CFU/mL with systemic signs of sepsis</td>
</tr>
<tr>
<td>Timsit et al (47)</td>
<td>Adult ICU patients expected to require catheter for at least 48 hr</td>
<td>CVC</td>
<td>Quantitative CVC tip culture &gt; 1,000 CFU/mL and no systemic signs of sepsis</td>
<td>Correlation between peripheral blood culture and quantitative tip culture without other likely source</td>
</tr>
</tbody>
</table>

CRBSI = catheter-related bloodstream infection, CVC = central venous catheter, CFU = colony-forming units, NR = not reported, ITT = intention to treat.
<table>
<thead>
<tr>
<th>Skin Antiseptic</th>
<th>Dressing Replacement Interval</th>
<th>Risk of Bias and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorhexidine 0.5% in 70% alcohol</td>
<td>Every 5 d or as needed</td>
<td>Low risk Underpowered to detect differences in catheter colonization and CRBSI between groups</td>
</tr>
<tr>
<td>NR</td>
<td>Control: every 2 d Treatment group: every 7 d</td>
<td>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</td>
</tr>
<tr>
<td>Control group: 10% povidone-iodine</td>
<td>Every 7 d (twice weekly in surgically placed CVC with control dressing)</td>
<td>Low risk Study halted before recruitment goal met (funding constraints and low CRBSI rates) Different skin antiseptic used in two groups Underpowered to detect difference in CRBSI between groups</td>
</tr>
<tr>
<td>Treatment group: 70% alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol-povidone-iodine 10%</td>
<td>Treatment group: weekly or as needed Control group: no dressing</td>
<td>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</td>
</tr>
<tr>
<td>Chlorhexidine</td>
<td>As needed</td>
<td>Low risk No established interval for dressing change Underpowered to detect CRBSI difference</td>
</tr>
<tr>
<td>Alcohol spray</td>
<td>Every other week or as needed</td>
<td>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 coagulase-negative staphylococci without molecular epidemiology to confirm source</td>
</tr>
<tr>
<td>4% aqueous povidone-iodine scrub solution followed by 5% povidone-iodine in 70% alcohol solution</td>
<td>Every 3 d or every 7 d (based on randomized group assignment)</td>
<td>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</td>
</tr>
<tr>
<td>NR</td>
<td>Every 3 d or as needed</td>
<td>Low risk Had third arm (antibiotic-impregnated catheters) excluded for this analysis</td>
</tr>
<tr>
<td>Alcohol-povidone or alcohol chlorhexidine</td>
<td>Every 3–7 d according to center/assignment or as needed</td>
<td>Low risk Randomized control trial using intention-to-treat analysis</td>
</tr>
</tbody>
</table>
Prevalence of Catheter Colonization

Seven of the nine studies provided data on colonization (31–33, 35, 36, 38, 46). Overall, 361 of 5,281 catheters (6.8%) were colonized in the chlorhexidine-impregnated dressing group compared with 743 of 5,200 (14.3%) in the comparator arm. The chlorhexidine-impregnated dressing was associated with an RR of 0.52 (95% CI, 0.43–0.64; \( p < 0.001 \)). This is illustrated as a forest plot in Figure 2.

Prevalence of CRBSI

Overall, 1.1% of patients (64 of 5,639) developed CRBSI in the treatment group compared with 2.1% of patients (120 of 5,608) in the comparator group. Six of the nine trials had results favoring the chlorhexidine-impregnated dressing for reducing CRBSI. The RR for CRBSI comparing the chlorhexidine and comparator groups in the meta-analysis was 0.60 (95% CI, 0.41–0.88; \( p = 0.009 \)), depicted as a forest plot in Figure 3.

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 colonization. \( I^2 \) for colonization was moderate at 54%. For CRBSI, heterogeneity was low (\( I^2 = 17\% \)).

Only two studies failed to demonstrate a reduction in colonization with impregnated sponges. The first had a small sample size, and authors stated that 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 PICU 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 chlorhexidine-impregnated dressing. The RR was 0.53 (95% CI, 0.32–0.89; \( p = 0.02 \)).

Five studies were limited to adult ICU populations (32, 35, 36, 38, 46) and the chlorhexidine-impregnated dressing was associated with an RR of 0.45 (95% CI, 0.28–0.72). In the pediatric population, the chlorhexidine-impregnated dressing was not associated with a statistically significant reduction in bloodstream infection (BSI) (RR, 1.21; 95% CI, 0.60–2.44) (31, 33).

Duration of catheterization was reported in all but two studies. Catheterization averaged longer than 2 weeks in three studies (31, 34, 37). In that subgroup, there was not an appreciable impact on rates...
of BSI (RR = 0.68; 95% CI, 0.36–1.30). In the remaining five studies (33, 35, 36, 38, 46), the benefit of chlorhexidine dressings was more pronounced (RR = 0.52; 95% CI, 0.30–0.90).

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 prevalence of resistance to chlorhexidine. However, routine surveillance by Chambers et al (34) before and after catheterization grew one isolate of micrococcus at 1 month in 0.01% chlorhexidine broth but did not grow at subsequent concentrations.

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 relative risk reduction 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
TABLE 2. Prevalence of Catheter Colonization and Catheter-Related Bloodstream Infection With Chlorhexidine-Impregnated Dressing

<table>
<thead>
<tr>
<th>References</th>
<th>No. of Patients/Catheters</th>
<th>Mean Duration of Catheterization (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHG Dressing</td>
<td>Control</td>
</tr>
<tr>
<td>Roberts and Cheung (38)</td>
<td>17/17</td>
<td>16/16</td>
</tr>
<tr>
<td>Maki et al (32)</td>
<td>301/665</td>
<td>366/736</td>
</tr>
<tr>
<td>Garland et al (31)</td>
<td>335/335</td>
<td>370/370</td>
</tr>
<tr>
<td>Chambers et al (34)</td>
<td>52/58</td>
<td>43/54</td>
</tr>
<tr>
<td>Levy et al (33)</td>
<td>74/74</td>
<td>71/71</td>
</tr>
<tr>
<td>Ruschulte et al (37)</td>
<td>300/300</td>
<td>301/301</td>
</tr>
<tr>
<td>Timsit et al (35)</td>
<td>817/1,953</td>
<td>819/1,825</td>
</tr>
<tr>
<td>Arvaniti et al (36)</td>
<td>150/150</td>
<td>156/156</td>
</tr>
<tr>
<td>Timsit et al (47)</td>
<td>938/2,108</td>
<td>941/2,065</td>
</tr>
<tr>
<td>Total</td>
<td>2,984/5,586</td>
<td>3,083/5,628</td>
</tr>
</tbody>
</table>

CHG = chlorhexidine-impregnated dressing, RR = relative risk, NR = not reported.

*Variance estimate inflated to adjust for correlation.

†21 chlorhexidine-dressed catheters and 56 control catheters were not cultured and were excluded from the analyses.

*Median reported in place of mean.

As reported in the study after adjusting for correlation.

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 predominate such as short-term catheters. Garland et al, in a subcohort 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%; \( p = 0.0007 \)); 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 on 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, NJ), and one study used an integrated chlorhexidine dressing (3M Tegaderm Chlorhexidine Dressing, 3M, St Paul, MN) (46). 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 that is placed circumferentially around the insertion site. Errors in placement and dressing disruption have been well described with a sponge dressing (48). At our institution, we have been using the sponge dressing for over a decade and continue to witness wrong placement of the dressing. An integrated chlorhexidine dressing obviates this problem but may have its own limitations such as difficulty in removal.

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 (49) previously demonstrated a nonstatistically significant trend toward reduction in CRBSI with the use of chlorhexidine-impregnated sponge dressings. This analysis includes seven studies evaluated by this previous analysis and includes two additional, recently published large studies. This study excluded one included in Ho et al (49), which evaluated skin colonization as its endpoint, because it did not evaluate catheter colonization or CRBSI, the main outcomes for this analysis.

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.

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, 46), 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, 46). 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 less than 1,000 g 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 (50). Frequent exposure to chlorhexidine may result in development of resistance to biocides (51, 52). However, in clinical trials of chlorhexidine-impregnated vascular devices, resistance to chlorhexidine has not been detected (53, 54). A recent well-designed trial comparing a second-generation CVC impregnated with chlorhexidine and silver sulfadiazine with a standard uncoated catheter for prevention of CRBSI included rigorous efforts to detect antiseptic resistance (53). 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 (55). 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 (56) and resistance genes encoding chlorhexidine resistance (57) have been identified, there have been no reports of clinically relevant chlorhexidine resistance to date (57, 58), despite the widespread 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 (59–61). The increasing use of chlorhexidine makes continued surveillance for developing resistance important (57), 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.

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, 46), 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 used 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 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.

Another significant limitation is the variable rates of catheter-related infections seen across studies, with control-group CRBSI rates ranging from 0% to 13%. Differences in local practice and prevention guideline implementation over time may account for this difference.

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.

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