Strategies for the prevention of central venous catheter infections: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review

Eunice Y. Huang, Catherine Chen, Fizan Abdullah, Gudrun Aspelund, Douglas C. Barnhart, Casey M. Calkins, Robert A. Cowles, Cynthia D. Downard, Adam B. Goldin, Steven L. Lee, Shawn D. St. Peter, Marjorie J. Arca

For the 2011 American Pediatric Surgical Association Outcomes and Clinical Trials Committee

Abstract

Purpose: The aim of this study is to review the current evidence-based data regarding strategies for prevention of central venous catheter (CVC) infections at the time of catheter insertion and as a part of routine care.

Methods: We conducted a PubMed search from January 1990 to November 2010 using the following keywords: central venous catheter, clinical trials, pediatric, infection, prevention, antibiotic, chlorhexidine, dressing, antiseptic impregnated catheters, ethanol lock, impregnated cuff, insertion site infection, and Cochrane systematic review. Seven questions, selected by the American Pediatric Surgical Association Outcomes and Clinical Trials Committee, were addressed.

Results: Thirty-six studies were selected for detailed review based on the strength of their study design and relevance to our 7 questions. These studies provide evidence that (1) chlorhexidine skin prep and chlorhexidine-impregnated dressing can decrease CVC colonization and bloodstream infection, (2) use of heparin and antibiotic-impregnated CVCs can decrease CVC colonization and bloodstream infec-
The use of central venous catheters (CVCs) is indispensable in contemporary medical care, particularly in pediatric patients with debilitating chronic disease. Nevertheless, complications arising from the use of CVCs, the most common being catheter-related infections, have contributed significantly to patient morbidity and health care costs [1]. In the recent past, many strategies have been studied to identify processes or devices that can effectively reduce the risk of CVC-related infections. Most of these studies have been performed in the adult population, but many studies have also included pediatric patients. At times, conclusions for pediatric patients are extrapolated from evidence provided by adult patient series. The goal of the present study is to review the current evidence regarding strategies for prevention of CVC infections at the time of catheter insertion and as a part of routine care.

1. Material and methods

Members of the 2011 American Pediatric Surgical Association Outcomes and Clinical Trials Committee delineated issues pertinent to the practice of pediatric surgery with regard to preventing CVC infections. Seven questions were identified relating to the process of CVC insertion and routine catheter care. These questions were

1. Is chlorhexidine a more effective cutaneous antiseptic agent than povidone-iodine for CVC insertion and care?
2. Is administration of perioperative antibiotics necessary at the time of CVC insertion?
3. Does the use of antimicrobial or antiseptic-impregnated catheters and/or cuffs affect the risk of catheter colonization (CC) and/or catheter-related bloodstream infections (CRBSIs)?
4. Does the site of insertion influence subsequent risk for CC and/or CRBSI?
5. Does the placement of a chlorhexidine-impregnated sponge (Biopatch; Ethicon Inc, Cincinnati, OH) at the CVC insertion site decrease the risk of CC and/or CRBSI?
6. Are antibiotic or ethanol lock therapies effective in decreasing CC and/or CRBSI? and
7. Are there differing strategies for the management of CRBSI in short- vs long-term CVCs?

A computerized search of PubMed, MEDLINE, and the Cochrane Library databases from January 1990 to November 2010 was performed with the search limits of human and English language. Search keywords included central venous catheter, clinical trials, pediatric, infection, prevention, antibiotic, chlorhexidine, dressing, antiseptic impregnated catheters, ethanol lock, impregnated cuff, insertion site infection, and Cochrane systematic review.

Searches were conducted in 2 stages. First, all titles and abstracts relevant to the above-stated questions were examined. Based on this analysis, all potentially relevant studies were extracted, and full articles, assessed. Selection for inclusion in our final review article followed the hierarchy below:

1. All consensus guidelines, systematic reviews, and/or meta-analyses of randomized clinical trials (RCTs) were reviewed and included, if appropriate;
2. Individual RCTs were added if they were of good quality, especially if they were not included in the meta-analyses;
3. If minimal RCT data were available, prospective observational studies were included; and
4. If minimal data were available from observational studies, then retrospective studies, including case-control studies, case reports, or expert opinions, were included.

Levels of Evidence and Grades of Recommendation published by the Oxford Centre for Evidence-based Medicine was used as a guideline for evidence grading (Fig. 1) [2].

Because the referenced studies covered a broad range of topics and because they span a 20-year period, definitions associated with standard terminology were not always exactly the same across studies. Any significant differences in definition will be noted in the appropriate subsections. The following general definitions were used in the referenced studies and in this review:

1) Catheter colonization was defined as quantitative catheter tip culture resulting in 10³ colony-forming units or more or semiquantitative culture (roll-plate technique) resulting in more than 15 colony-forming units.
2) Catheter-related bloodstream infection was defined as isolation of the same organism from the colonized catheter and from at least 1 cultured peripheral blood sample drawn 48 hours before or after catheter removal and clinical manifestations of infection without another source of infection; or isolation of same organism from a peripheral blood culture and a semiquantitative or quantitative culture of a catheter segment and clinical manifestations of infection without another source of infection; or per 2009 Infectious Diseases Society of America guidelines, positivity of a catheter-drawn culture at least

Conclusion: Grade A and B recommendations can be made based on available evidence in adult and limited pediatric studies for multiple components of proper CVC insertion practices and subsequent management. These strategies can minimize the risk of CVC infections in pediatric patients.
© 2011 Elsevier Inc. All rights reserved.
STRATEGIES FOR PREVENTION OF CVC INFECTIONS

1) Is chlorhexidine a more effective cutaneous antiseptic agent than povidone-iodine for CVC insertion and care?

**Grade A/B recommendation:** Extrapolating from studies on adult subjects, use of chlorhexidine with alcohol as cutaneous antisepsis decreases the risk of CC and CRBSI when compared to 10% povidone-iodine. Care should be taken in using chlorhexidine in neonates and premature infants because of increased risk of skin irritation and systemic absorption.

2) Is administration of perioperative antibiotics necessary at the time of CVC insertion?

**Grade A/B recommendation:** Benefit of systemic prophylactic antibiotic at the time of CVC insertion is currently unclear. The most recent consensus guideline does not recommend systemic antibiotic prophylaxis at time of catheter insertion; however, this differs from a previous CDC guideline. Antibiotic prophylaxis may be beneficial in certain subpopulations. Additional large randomized pediatric trials addressing this question will be beneficial.

3) Does the use of antimicrobial or antiseptic impregnated catheters and/or cuffs affect the risk of CC and/or CRBSI?

**Grade A recommendation:** In studies performed mostly in adult subjects, heparin coated and antibiotic impregnated CVCs were associated with significant and substantial reductions in CRBSI with significant but weaker effects on CC. Use of chlorhexidine-silver sulfadiazine catheters reduced the risk of CC with minimal effects on CRBSI.

4) Does the site of insertion influence subsequent risk for CC and/or CRBSI?

**Grade B recommendation:** In adult studies, no difference is noted in CRBSI between subclavian, internal jugular, and femoral sites, although CC may be lower at subclavian sites.

5) Does the placement of a chlorhexidine impregnated sponge (Biopatch®) at the CVC insertion site decrease the risk of CC and/or CRBSI?

**Grade A recommendation:** Use of a chlorhexidine impregnated sponge (Biopatch®) at the CVC insertion site decreases the risk of catheter related infections in pediatric and adult patients. Chlorhexidine sponges may cause contact dermatitis in neonates and extremely premature infants and should not be utilized in this patient population.

6) Are antibiotic or ethanol lock therapies effective in decreasing CC and/or CRBSI?

**Grades A/B recommendation:** Ethanol lock therapy for silicone CVCs can be administered safely and can effectively reduce the incidence of catheter related infections. Prophylactic use of vancomycin heparin lock solution reduces the incidence of CC in adults, but not shown to promote vancomycin resistance, but is associated with asymptomatic hypoglycemia.

7) Are there differing strategies for the management of CRBSI in short-term versus long-term CVCs?

**Grades A/B recommendation:** Patients with an uncomplicated CRBSI and a short-term CVC should undergo catheter removal and treatment with systemic antibiotics for at least 7 to 14 days based on the pathogen. Patients with a long-term CVC and an uncomplicated CRBSI due to coagulase-negative staphylococcus or enterococcus may retain the CVC and complete a course of systemic antibiotics with the use of antibiotic lock therapy. Removal of the CVC is required if there is clinical deterioration, or persisting or relapsing bacteremia. Infections with *Staphylococcus aureus*, *gram-negative bacilli*, or *Candida* require immediate removal of the infected CVC and a defined course of systemic antibiotic therapy, except in rare circumstances when no alternate venous access is available. Pediatric patients treated without catheter removal should be closely monitored with clinical evaluation, additional blood cultures, and the use of antibiotic lock therapy with systemic therapy for catheter salvage.

---

Fig. 1 Summary of systematic review of strategies for the prevention of CVC-related infections.
Central venous catheter

Tunneled CVC

Chlorhexidine-based cutaneous antisepsis strongly support the use of chlorhexidine in decreasing CC and possibly CRBSI when used at the time of CVC insertion and for CVC care. Additional recent evidence, again, in adult subjects, has further shown that chlorhexidine is more effective than povidone-iodine in the prevention of skin-based surgical site infections.

Data showing benefit of chlorhexidine use as skin antisepsis for CVC insertion and care in the pediatric population are lacking. The only neonatal study to have shown increased efficacy of chlorhexidine over povidone-iodine in decreasing CC was published by Garland et al [11] in 1995 looking at PICCs. This study was limited by a lack of randomization and by the fact that the 2 treatments occurred over different periods, but the results show improvement of CC with use of 0.5% chlorhexidine plus 70% isopropyl alcohol.

In consideration of the known risk for systemic absorption of chlorhexidine and the possibility of contact dermatitis, particularly in premature infants, recent pediatric studies have focused more on addressing these 2 adverse events rather than on CRBSI. Garland et al [12] reported a pilot trial in neonates receiving PICCs, evaluating incidence of contact dermatitis from skin prep containing 2% chlorhexidine vs 10% povidone-iodine. The goal of this trial was to enroll 150 neonates older than 7 days and weighing more than 1500 g. The trial was terminated early because of low enrollment. In the 48 neonates who were enrolled, there were no differences in CC or CRBSI between the 2 groups, and no severe dermatitis was seen in the chlorhexidine group. Ten infants underwent measurement of serum chlorhexidine after application, of which 5 had measurable concentrations. Visscher et al [13] reported their results evaluating skin conditions on 40 neonatal intensive care unit (NICU) patients (gestational age, <40 weeks) receiving 2% chlorhexidine with 70% alcohol as skin prep at PICC sites. They concluded that the skin erythema and dryness seen in the treated patients resulted not specifically from chlorhexidine but from a combination of chlorhexidine and adhesive dressings. In a time sequence trial to evaluate a multifactorial approach to reducing CRBSI, Andersen et al [14] reported that 4 (11%) of 36 study neonates less than 1000 g developed contact dermatitis after a 2% chlorhexidine (without alcohol) scrub, and no contact dermatitis was seen in 49 study neonates who were 1000 g or more. Although the available studies show a low incidence of skin complications from use of chlorhexidine skin prep in premature infants more than 1500 g, additional studies will be needed to further characterize this risk. It should be noted that the ChloraPrep label recommends against using the product in children younger than 2 months because of the potential for excessive skin irritation and increased drug absorption.

### 2.1.2. Is administration of perioperative antibiotics necessary at the time of CVC insertion?

In the 2002 consensus guidelines published in *Pediatrics* from the Healthcare Infection Control Practices Advisory Committee of the Centers for Disease Control (CDC) and...
<table>
<thead>
<tr>
<th>Study, year</th>
<th>Design</th>
<th>Population</th>
<th>n</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Results (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mimoz et al [4], 2007</td>
<td>RCT</td>
<td>Adult, ICU, CVC</td>
<td>481</td>
<td>Bisepine b</td>
<td>CC</td>
<td>IR: Bs, b 11.6%; PI, 22.2%</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CRBSI</td>
<td>IR: Bs, b 1.7%; PI, 4.2%</td>
<td>.09</td>
</tr>
<tr>
<td>Langgartner et al [9], 2004</td>
<td>RCT</td>
<td>Adult, ward + ICU, CVC</td>
<td>140</td>
<td>Skinsept c + PI vs Skinsept c vs PI</td>
<td>CC</td>
<td>IR: Sk c + PI, 4.7%; Sk c 24.4%; PI, 30.8%</td>
<td>.006</td>
</tr>
<tr>
<td>Chaiyakunapruk et al [5], 2002</td>
<td>Meta-analysis</td>
<td>8 RCTs, all adult, included CVC, peripheral, arterial</td>
<td>4143</td>
<td>ChloraPrep d, 0.5% CH, Bisepine b</td>
<td>RR</td>
<td>0.49 (0.31-0.71)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Humar et al [6], 2000</td>
<td>RCT</td>
<td>Adult, ICU, CVC</td>
<td>242</td>
<td>0.5% CH</td>
<td>RR</td>
<td>0.49 (0.28-0.88)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Mimoz et al [7], 1996</td>
<td>RCT</td>
<td>Adult, ICU, CVC</td>
<td>158</td>
<td>Bisepine b</td>
<td>RR</td>
<td>0.3 (0.1-1.0)</td>
<td>.03</td>
</tr>
<tr>
<td>Maki et al [8], 1991</td>
<td>RCT</td>
<td>Adult, ICU, CVC</td>
<td>144</td>
<td>2% CH</td>
<td>RR</td>
<td>0.3 (0.1-1.0)</td>
<td>.02</td>
</tr>
<tr>
<td>Garland et al [11], 1995</td>
<td>PNT</td>
<td>Pediatric, NICU, PICC</td>
<td>826</td>
<td>0.5% CH + 70% isopropyl alcohol</td>
<td>OR</td>
<td>0.26 (0.07-0.91)</td>
<td>.18</td>
</tr>
<tr>
<td>Darouiche et al [10], 2010</td>
<td>RCT</td>
<td>Adult, clean-contaminated surgery</td>
<td>897</td>
<td>ChloraPrep d</td>
<td>OR</td>
<td>0.59 (0.41-0.85)</td>
<td>.004</td>
</tr>
</tbody>
</table>

ICU indicates intensive care unit; IR, infection rate; RR, relative risk; PI, povidone-iodine; CH, chlorhexidine; PNT, prospective, nonrandomized trial (first 6 months used povidone-iodine, second 6 months used 0.5% chlorhexidine + 70% isopropyl alcohol); SSI, surgical site infection.

- Control is 10% povidone-iodine aqueous solution.
- Bisepine (Bs): 0.25% chlorhexidine, 0.025% benzalkonium chloride, 4% benzyl alcohol.
- Skinsept (Sk): 0.5% chlorhexidine, 70% isopropyl alcohol.
- ChloraPrep: 2% chlorhexidine, 70% isopropyl alcohol.
other professional organizations, the authors did not recommend routine systemic antibiotic prophylaxis for CVC infection prevention. This recommendation was based on 3 randomized adult studies (published in 1985, 1990, and 1997) that demonstrated no difference in the incidence of CRBSI with systemic antibiotic administration at the time of catheter insertion [15]. Two of these studies investigated vancomycin, and the other investigated teicoplanin. The working group also cited 2 studies assessing efficacy of continuous low-dose vancomycin infusion in preventing CVC infections in infants; both demonstrated a statistically significant reduction in CRBSI but no reduction in mortality. Because of the potential risk for development of vancomycin-resistant organisms from continuous prophylactic use, the authors did not recommend prophylactic vancomycin for the prevention of CVC infection. In a separate Cochrane review focusing on neonates, 3 studies were combined to evaluate the use of postinsertion prophylactic systemic antibiotics to reduce morbidity and mortality in neonates with CVCs, including PICCs, of which 2 evaluated vancomycin, and 1, amoxicillin [16]. The authors concluded that although the use of postinsertion systemic antibiotic prophylaxis in neonates with CVC reduced sepsis rates, no difference was seen in overall mortality. In addition, data were lacking on neurodevelopmental outcomes and on the potential for selection of resistant organisms.

In summary, neither of these reviews recommended routine use of prophylactic antibiotics either before or after CVC insertion. Additional studies focusing specifically on short-term perioperative antibiotics in the pediatric population will likely be informative.

Prophylactic antibiotic therapy administered as catheter flushes may be beneficial in oncologic patients. In another Cochrane review focusing on prevention of CC-positive CVC infections in oncology patients, 9 trials were included [17]. Four reported on efficacy of perioperative vancomycin or teicoplanin use for infection prevention in adult oncology patients. These studies showed that administering an antibiotic before tunneled CVC insertion decreased the risk of catheter-related sepsis, but the effect was not significant (odds ratio [OR], 0.42; 95% confidence interval [CI], 0.13-1.31). Five studies (3 in pediatric patients and 2 included adult and pediatric patients) reported on efficacy of using a vancomycin-heparin lock solution vs a heparin flush. These studies showed a significant decrease in catheter-related sepsis with this therapy (OR, 0.43; 95% CI, 0.21-0.87). The authors concluded that, in patients where risk of catheter-related infection rate is high, current data did not support benefit of prophylactic intravenous antibiotics before tunneled CVC placement. However, using an antibiotic heparin lock therapy to prevent tunneled CVC infection may be justified.

Of note, the 1999 Guideline for Prevention of Surgical Site Infection drafted by the CDC recommends surgical antimicrobial prophylaxis for operations where “intravascular prosthetic material or a prosthetic joint will be inserted” [18].

2.1.3. Does the use of antimicrobial or antiseptic-impregnated catheters and/or cuffs affect the risk of CC and/or CRBSI?

There are several catheters that have been designed to potentially decrease the incidence of CC and CRBSI. Long-term indwelling silicone catheters are available, with an attached silver-impregnated cuff located next to the tissue ingrowth cuff. In addition, multiple types of coated or impregnated CVCs are available, including heparin, chlorhexidine-silver sulfadiazine, antibiotic (the most common being minocycline and rifampicin), silver, and 5-fluorouracil. In 2008, Gilbert and Harden [19] performed a review of 37 RCTs comparing the effectiveness of impregnated CVCs (Table 2). In this review, 3 studies included patients younger than 18 years, but only 1 focused exclusively on pediatric patients with 200 children randomized to standard vs heparin-bonded nontunneled CVCs in a pediatric intensive care unit [20]. The relative risk for CRBSI in that study was 0.06 (95% CI, 0.01-0.41) for the heparin-bonded catheters. In the remaining 36 studies, compared with standard catheters, significant reductions in CRBSI were found for heparin-coated and antibiotic-impregnated CVCs [19]. Although pooled relative risks for CC were also decreased in heparin-coated, antibiotic-impregnated, and chlorhexidine-silver sulfadiazine–impregnated CVCs, there was significant heterogeneity in the pooled CC data for the antibiotic and chlorhexidine-silver sulfadiazine groups, which may reflect the weakness of using CC as a surrogate for determining risk for CVC-related infections. No impregnated CVCs exist for neonates weighing less than 3 kg. Adult data using 5-fluorouracil–impregnated catheters show similar colonization, local infection, and CRBSI rates when compared with chlorhexidine-silver sulfadiazine–impregnated catheters [21]. Only 1 RCT has compared standard cuffed central catheters with similar catheters with a second silver-impregnated cuff in primarily adult patients [22]. There was no effect of a silver-impregnated cuff in decreasing the incidence of CRBSI [22].

In summary, in studies performed mostly in adult subjects, heparin-coated and antibiotic-impregnated CVCs were associated with significant and substantial reductions in CRBSI with significant but weaker effects on CC. 5-fluorouracil–coated CVCs are a safe and effective alternative to chlorhexidine-silver sulfadiazine catheters in critically ill adult patients.

2.1.4. Does the site of insertion influence subsequent risk for CC and/or CRBSI?

When comparing subclavian, internal jugular, and femoral venous sites in the adult population, 2 prospective observational studies found that CC was lowest at the subclavian site, but there was no difference in CRBSI among the 3 sites [23,24] (Table 3). A single-center retrospective review in the neonatal population, however, found an infection rate nearly 6 times higher in the neck/subclavian
sites (12.5%) when compared with the groin site (2.04%) with tunneled silicone CVCs [25]. This study also reported higher rates of other complications, including dislodgement, pneumothorax, and pleural and pericardial effusions in the neck/subclavian cohort.

2.2. Practices during routine CVC care

2.2.1. Does the placement of a chlorhexidine-impregnated sponge (Biopatch) at the CVC insertion site decrease the risk of CC and/or CRBSI?

Five RCTs [26-30] and 1 meta-analysis [31] comparing chlorhexidine-impregnated sponge “antiseptic” dressing (Biopatch, Ethicon Inc) to a standard dressing were identified in the literature (Table 4). The meta-analysis [31] included the studies by Chambers et al [28], Levy et al [29], and Garland et al [30] as well as 1 study published in abstract form, 1 study published as a letter to the editor, and 1 small Australian study. There was 1 neonatal and 1 pediatric study included in this meta-analysis. The analysis concluded that use of a chlorhexidine-impregnated dressing resulted in a statistically significant decrease in CC but not in CRBSI. More recently, 2 large adult RCTs [26,27] have shown that chlorhexidine-impregnated dressings decrease the incidence not only of CC but also of CRBSI.

In the study by Garland et al [30] in 2001, 15 (15%) of 98 neonates less than 1000 g and 4 (1.5%) of 237 neonates 1000 g or more treated with the antiseptic sponge developed contact dermatitis. None of the control group (10% povidone-iodine skin scrub) developed contact dermatitis. The authors, therefore, concluded that this complication limits its use in the extremely premature neonatal population. It should be noted that the Biopatch label states that this dressing should not be used on premature infants.

2.2.2. Are antibiotic or ethanol lock therapies effective in decreasing CC and/or CRBSI?

Four studies were found evaluating ethanol lock therapy for the prevention of CVC infections, including 1 adult RCT [32], 2 pediatric retrospective studies [33,34], and 1 pediatric prospective single-armed study [35] (Table 5). Because most catheters in these studies were salvaged, identifying CVC that strictly satisfied the CRBSI definition was difficult. As a result, the outcome measure most commonly used was bloodstream infections likely associated with CVC. The adult RCT as well as the 2 retrospective pediatric studies showed benefit of ethanol lock therapy [32-34]. The prospective pediatric study by Kayton et al [35] was the only one that used this therapy on patients with Mediports, and it terminated early because of a high incidence of catheter thrombosis. It is important to note some concerns with ethanol lock therapy: (1) ethanol is not compatible with heparin and will precipitate if exposed to heparinized saline [36], (2) ethanol may weaken silicone CVC and is not recommended for use in polyurethane CVC because of risk of catheter disruption.

Table 2

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Design</th>
<th>Population</th>
<th>n</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Results (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walz et al [21], 2010</td>
<td>RCT, noninferiority</td>
<td>Adult, ICU (25 centers), CVC up to 28 d</td>
<td>960 catheters</td>
<td>5-FU CVC vs CH-SS CVC</td>
<td>CC</td>
<td>IR: 5-FU, 2.9%; CH-SS, 5.3% (−2.6% to −0.13%)</td>
</tr>
<tr>
<td>Gilbert and Harden [19], 2008</td>
<td>Meta-analysis</td>
<td>37 RCTs (6 studies with patients age &lt;18 y, 2 studies on tunneled antibiotic-impregnated silicone CVC)</td>
<td>11,586 patients</td>
<td>4 types of impregnated or coated CVC: heparin, CH-SS, CH-SS, antibiotic, silver</td>
<td>CC</td>
<td>RR: heparin, 0.42 (0.18-0.99) .05</td>
</tr>
<tr>
<td>Groeger et al [22], 1993</td>
<td>RCT</td>
<td>Cancer patients, median age 29 and 32 y, tunneled cuffed CVC</td>
<td>200 patients</td>
<td>Standard CVC vs same CVC with second more proximal subcutaneous silver-impregnated cuff (silver)</td>
<td>CRBSI</td>
<td>Hazard rate: standard, 0.0027 (0.0014-0.0040); silver, 0.0022 (0.0014-0.0030); silver-impregnated cuff (silver)</td>
</tr>
</tbody>
</table>

5-FU indicates 5-fluorouracil; CH-SS, chlorhexidine and silver sulfadiazine; NS, not significant.
Table 3  Summary of studies reviewing the relationship between insertion sites and CC and CRBSI

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Design</th>
<th>Population</th>
<th>n</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Results (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gowardman et al [23], 2008</td>
<td>Prospective observational study</td>
<td>Adult, ICU, CVC, and PICC</td>
<td>410 patients, 605 catheters</td>
<td>3 insertion sites: subclavian, IJ, femoral</td>
<td>CC</td>
<td>HR: subclavian, 1.00 HR: IJ, 3.64 (1.32-10.03) HR: Femoral, 5.15 (1.82-14.51)</td>
<td>.004</td>
</tr>
<tr>
<td>Norwood et al [24], 2000</td>
<td>Prospective observational study</td>
<td>Pediatric and adult trauma patients, age 9-90 y, CH-SS CVC</td>
<td>324 patients, 460 catheters</td>
<td>3 insertion sites: subclavian, IJ, femoral</td>
<td>CC</td>
<td>IR: subclavian, 3% IR: IJ, 10% IR: femoral, 9%</td>
<td>.03</td>
</tr>
</tbody>
</table>

IJ indicates internal jugular; HR, hazard ratio.

Table 4  Summary of studies evaluating the use of chlorhexidine-impregnated sponge at the catheter insertion site

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Design</th>
<th>Population</th>
<th>n</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Results (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timsit et al [26], 2009</td>
<td>RCT</td>
<td>Adult, ICU, CVC, or arterial</td>
<td>1636 patients, 3778 catheters</td>
<td>Chlorhexidine-impregnated sponge (Biopatch)</td>
<td>CC</td>
<td>HR, 0.36 (0.28-0.46)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ruschulte et al [27], 2009</td>
<td>RCT</td>
<td>Adult, heme/oncology, CVC</td>
<td>601 patients</td>
<td>6 RCTs (2 pediatric), CVC/tunneled CVC/PA/artificial</td>
<td>CC</td>
<td>OR, 0.47 (0.34-0.65)</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td>Ho and Litton [31], 2006</td>
<td>Meta-analysis</td>
<td>Adult, heme/oncology, tunneled CVC</td>
<td>2446 catheters</td>
<td>CVC/tunneled CVC/PA/artificial</td>
<td>CRBSI</td>
<td>OR, 0.61 (0.30-1.26)</td>
<td>.19</td>
</tr>
<tr>
<td>Chambers et al [28], 2005</td>
<td>RCT</td>
<td>Adult, heme/oncology, tunneled CVC</td>
<td>112 catheters</td>
<td>Exit-site/tunnel/tip infections</td>
<td>CRBSI</td>
<td>OR, 0.13 (0.04-0.37)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Levy et al [29], 2005</td>
<td>RCT</td>
<td>Age 0-18 y, pediatric cardiac ICU, CVC</td>
<td>145 patients</td>
<td></td>
<td>CC</td>
<td>RR, 0.61 (0.37-1.0)</td>
<td>.04</td>
</tr>
<tr>
<td>Garland et al [30], 2001</td>
<td>RCT</td>
<td>NICU, PICC, and tunneled CVC</td>
<td>705 neonates</td>
<td></td>
<td>CC</td>
<td>RR, 1.2 (0.5-2.7)</td>
<td>.65</td>
</tr>
</tbody>
</table>
Table 5  Summary of studies evaluating the use of ethanol lock and antibiotic lock therapy as an adjunct to decreasing CC and CRBSI

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Design</th>
<th>Population</th>
<th>n</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Results</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cober et al [33], 2011</td>
<td>Retrospective review</td>
<td>Patients &lt;25 y old and ≥5 kg, high risk for CVC infection, with silicone-based CVC</td>
<td>15 patients</td>
<td>70% ethanol lock solution instilled daily for ≥2 h, historical control</td>
<td>Bloodstream infection&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pre-EtOH lock, 8.0 ± 5.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CVC repair (leak or disruption)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Post-EtOH lock, 1.3 ± 3.0</td>
<td>.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Post-EtOH lock, 3.1 ± 5.2</td>
<td></td>
</tr>
<tr>
<td>Kayton et al [35], 2010</td>
<td>Prospective phase I single-armed clinical trial</td>
<td>Pediatric patients receiving antibody treatments for neuroblastoma (all Mediports)</td>
<td>12 patients, 123 ethanol locks</td>
<td>On 4/5 days of antibody cycle, 70% ethanol administered to dwell overnight</td>
<td>Blood EtOH&lt;sup&gt;b&lt;/sup&gt; (+) cultures</td>
<td>Less than “legal limit” for ethanol intoxication</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1/12 patients (8%)—Streptococcus pneumoniae</td>
<td></td>
</tr>
<tr>
<td>Jones et al [34], 2010</td>
<td>Retrospective review</td>
<td>TPN-dependent intestinal failure children; age 3 mo to 18 y; ≥5 kg; silicone CVC and PICC</td>
<td>23 patients</td>
<td>70% ethanol lock instilled 3 times per week for 4 h</td>
<td>Median CVC IR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pre-EtOH lock, 9.9 (IQR, 4.4-16.0)</td>
<td>.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median catheter change rate&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Post-EtOH lock, 2.1 (IQR, 0.0-7.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Post-EtOH lock, 8.2 (IQR, 4.6-11.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Post-EtOH lock, 0.0 (IQR, 0.0-4.7)</td>
<td>.008</td>
</tr>
<tr>
<td>Sanders et al [32], 2008</td>
<td>RCT</td>
<td>Adult inpatients receiving intensive chemotherapy, dual-lumen tunneled CVC</td>
<td>64 patients</td>
<td>70% ethanol lock instilled daily for 2 h vs heparinized saline</td>
<td>Combined definite and probable CRBSI&lt;sup&gt;e&lt;/sup&gt;</td>
<td>RR, 0.16 (95% CI, 0.04-0.66)</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OR, 0.18 (95% CI, 0.05-0.65)</td>
<td></td>
</tr>
<tr>
<td>Garland et al [38], 2005</td>
<td>RCT</td>
<td>NICU, PICC</td>
<td>85 patients</td>
<td>Vancomycin-heparinized saline</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; TPN, total parenteral nutrition; CABSI, catheter-associated bloodstream infection.

<sup>a</sup> Expressed as mean occurrences per 1000 catheter days ± SD.

<sup>b</sup> Central venous catheter infection rate: positive blood culture from the CVC in the absence of another confirmed source of infection, expressed as number of infections per 1000 catheter days; each patient acted as his own control, and median rates of catheter infections pre- and postethanol lock therapy initiation were compared.

<sup>c</sup> Catheter change rate: a confirmed removal of one catheter and replacement by another, expressed as occurrence per 1000 catheter days.

<sup>d</sup> The occurrence of a bloodstream infection in a patient with a CVC whose catheter was in use within the preceding 48 hours.

<sup>e</sup> Definite CRBSI: positive peripheral blood culture with concordant colonization of the catheter hub or catheter tip, clonal concordance confirmed by DNA subtyping for coagulase-negative staphylococci. Probable CRBSI: positive peripheral blood and colonization of catheter, but DNA subtyping was not done.
[37], and (3) systemic instillation of ethanol can theoretically result in ethanol intoxication, although none of the aforementioned studies reported this effect.

One published RCT evaluated vancomycin lock therapy in the neonatal population [38]. The authors compared a vancomycin-heparinized saline lock 2 or 3 times a day for 20 minutes in neonates on parenteral nutrition and for 60 minutes in enterally fed neonates vs standard heparinized saline. This study reported significant benefit of vancomycin lock therapy on decreasing CRBSI. Of interest, no vancomycin-resistant microorganisms were detected in skin or rectal surveillance cultures in any study participants during this study. Only 1 neonate in the vancomycin lock group had a detectable serum level of vancomycin, but the specimen was drawn 24 hours after intravenous vancomycin had been discontinued. Hypoglycemia was noted in 31% of the study participants at approximately 20 minutes into the dwell. No neonates were clinically symptomatic when hypoglycemic, and blood glucose concentrations promptly corrected after glucose infusion.

2.3. Are there differing strategies for the management of CRBSI in short-term vs long-term CVCs?

In the 2009 update by the Infectious Diseases Society of America, the authors outline approaches to the management of CRBSI in patients with short- and long-term CVCs, citing grade A and B sources as the basis for their recommendations [3]. Short-term catheters were defined as devices that were in situ for less than 14 days. Although not specifically defined, the authors included tunneled silicone catheters and catheters with subcutaneously implanted port reservoirs in their discussion on long-term catheters. Patients were categorized as either having an uncomplicated CRBSI (defined as bloodstream infection and fever resolving within 72 hours of start of antibiotic therapy; no intravascular hardware; no evidence of endocarditis or suppurative thrombophlebitis; and, for *Staphylococcus aureus*, no active malignancy or ongoing immunosuppression) or a complicated CRBSI (defined as those with persistent bacteremia 72 hours after treatment, with suppurative thrombophlebitis, endocarditis, osteomyelitis, or possible metastatic seeding). Patients with an uncomplicated CRBSI with a short-term CVC were recommended to undergo catheter removal and treatment with systemic antibiotics based on the pathogen for at least 7 to 14 days. Patients with a long-term CVC and uncomplicated CRBSI with coagulase-negative *Staphylococcus* or *Enterococcus* may retain the CVC and complete a course of systemic antibiotics with use of antibiotic lock therapy. Removal of the CVC is required if there is clinical deterioration or persisting or relapsing bacteremia. Patients with a long-term CVC and an uncomplicated CRBSI with *S aureus*, Gram-negative bacilli, or *Candida* require immediate removal of the infected CVC and a defined course of systemic antibiotic therapy, except in rare circumstances when no alternate venous access is available. All patients with complicated CRBSI should have the catheter removed immediately and receive prolonged intravenous antibiotic therapy based on the pathogen. A unique aspect of pediatric patients with CRBSI is the need to weigh the benefit of catheter removal with the difficulty of obtaining alternate venous access for an individual patient. Children treated for CRBSI without catheter removal should be closely monitored with clinical evaluation, additional blood cultures, and use of antibiotic lock therapy combined with systemic therapy for catheter salvage.

3. Summary of findings

1. Extrapolating from studies on adult subjects, use of chlorhexidine with alcohol as cutaneous antisepsis decreases the risk of CC and CRBSI when compared with 10% povidone-iodine. Care should be taken in using chlorhexidine in neonates and premature infants because of increased risk of skin irritation and systemic absorption (grade A/B evidence).

2. Benefit of systemic prophylactic antibiotic at the time of CVC insertion is currently unclear. The most recent consensus guideline does not recommend systemic antibiotic prophylaxis at the time of catheter insertion (grade A/B evidence); however, this differs from a previous CDC guideline. Antibiotic prophylaxis may be beneficial in certain subpopulations. Additional large randomized pediatric trials addressing this question will be beneficial.

3. In studies performed mostly in adult subjects, heparin-coated and antibiotic-impregnated CVCs were associated with significant and substantial reductions in CRBSI with significant but weaker effects on CC. Use of chlorhexidine-silver sulfadiazine catheters reduced the risk of CC with minimal effects on CRBSI (grade A evidence).

4. In adult studies, no difference is noted in CRBSI between subclavian, internal jugular, and femoral sites, although CC may be lower at subclavian sites (grade B recommendation).

5. Use of a chlorhexidine-impregnated sponge (Biopatch) at the CVC insertion site decreases the risk of catheter-related infections in pediatric and adult patients. Chlorhexidine sponges may cause contact dermatitis in neonates and extremely premature infants and should not be used in this patient population (grade A evidence).

6. Ethanol lock therapy for silicone CVCs can be administered safely and can effectively reduce the incidence of catheter-related infections. Prophylactic use of vancomycin-heparin lock solution reduces the incidence of CRBSI, has not been shown to promote vancomycin resistance, but is associated with asymptomatic hypoglycemia (grade A/B evidence).
7. Patients with an uncomplicated CRBSI and a short-term CVC should undergo catheter removal and treatment with systemic antibiotics for at least 7 to 14 days based on the pathogen. Patients with a long-term CVC and an uncomplicated CRBSI because of coagulase-negative Staphylococcus or Enterococcus may retain the CVC and complete a course of systemic antibiotics with the use of antibiotic lock therapy. Removal of the CVC is required if there is clinical deterioration or persisting or relapsing bacteremia. Infections with Staphylococcus aureus, Gram-negative bacilli, or Candida require immediate removal of the infected CVC and a defined course of systemic antibiotic therapy, except in rare circumstances when no alternate venous access is available. Pediatric patients treated without catheter removal should be closely monitored with clinical evaluation, additional blood cultures, and the use of antibiotic lock therapy with systemic therapy for catheter salvage (grade A/B evidence).

4. Conclusion

Although robust evidence exists to support many of the components of good clinical practice for prevention of CVC infections, additional pediatric studies are necessary in some areas to confirm findings noted in the adult population. Questions that may benefit from future prospective trials focusing on pediatric patients include

1. Is chlorhexidine a more effective cutaneous antisepsis than povidone-iodine at time of CVC insertion?
2. Is systemic antibiotic necessary at time of CVC insertion?
3. What is the optimal site for CVC insertion?
4. Is ethanol lock therapy safe to use in Mediports? and
5. Is ethanol lock therapy effective in decreasing risk of CVC infections?

Multicenter prospective trials will be necessary to answer these questions. Cooperation within the American Pediatric Surgical Association community will greatly enhance our ability to accomplish these goals.

References


