This is an Accepted Manuscript for *Infection Control & Hospital Epidemiology* as part of the Cambridge Coronavirus Collection.
DOI: 10.1017/ice.2022.53

SHEA White Paper

SHEA neonatal intensive care unit (NICU) white paper series: Practical approaches for the prevention of central line-associated bloodstream infections

Martha Muller, MD[1], Kristina A. Bryant, MD[2], Claudia Espinosa, MD, MSC[3], Jill A. Jones, MS, APRN, NNP-BC[4], Caroline Quach, MD, MSc, FRCPC[5], Jessica R. Rindels, MBA, BSN, RN, CIC[6], Dan L. Stewart, MD[7], Kenneth M. Zangwill, MD[8], Pablo J. Sánchez, MD[9]

[1]Pediatric Infectious Disease, University of New Mexico School of Medicine and UNM Health Sciences, Albuquerque, NM
[2]Pediatric Infectious Diseases, University of Louisville and Norton Children's, Louisville, KY
[3]Pediatric Infectious Diseases, University of South Florida Morsani College of Medicine, Tampa, FL
[4] Nationwide Children's Hospital, Columbus, Ohio
[5]Departments of Microbiology, Infectious Diseases and Immunology and Pediatrics, University of Montreal, Clinical Department of Laboratory Medicine, CHU Sainte-Justine (QC, Canada) - ORCID: 0000-0002-1170-9475
[6]Children's Mercy Hospital, Kansas City, MO; ORCID 0000-0002-2428-8462
[7]Norton Children's Hospital and the University of Louisville School of Medicine, Louisville, KY
[8]Division of Pediatric Infectious Diseases and Department of Infection Prevention and Control, Harbor-UCLA Medical Center, Torrance, CA - ORCID: 0000-0002-5026-4368
[9]Department of Pediatrics, Divisions of Neonatology and Pediatric Infectious Diseases, Nationwide Children's Hospital, Abigail Wexner Research Institute at Nationwide Children's Hospital, Center for Perinatal Research, The Ohio State University College of Medicine, Columbus, OH 43205; ORCID 0000-0003-2437-1247

Corresponding author: Kristina A. Bryant, MD, Pediatric Infectious Diseases, University of Louisville and Norton Children's, Louisville, KY, kristina.bryant@louisville.edu

Introduction

Central line-associated bloodstream infections (CLABSIs) are among the most frequent invasive infections among infants in the NICU and contribute to substantial morbidity and mortality. Infants who survive CLABSIs have prolonged hospitalization resulting in increased healthcare costs and suffer greater comorbidities including worse neurodevelopmental and growth outcomes (1-3). A bundled approach to central line care practices in the NICU has reduced CLABSI rates significantly (4-6), but challenges remain. A cross-sectional study using 2013-2018 Centers for Disease Control and Prevention (CDC) surveillance data from 132 NICUs that report to the National Healthcare Safety Network (NHSN) suggested that previous improvements in CLABSI rates have plateaued (7). During the study period, CLABSI rates remained stable, with mean rates of 1.56 CLABSIs per 1000 central catheter-days in NICU patients with birth weight ≤1500 g and 0.72 per 1000 central catheter-days for those with birth weight >1500 g. Infants in the NICU have certain unmodifiable risk factors for infection such as an immature immune system and requirement for life-sustaining invasive procedures such as endotracheal intubation and umbilical, central venous and arterial catheterization that are essential for respiratory and nutritional support. Importantly, these infants often suffer from disruption in skin and intestinal integrity that may contribute to translocation of pathogens resulting in a diagnosis of CLABSI. Nevertheless, it is clear that adherence to proper insertion techniques and management of the CVC can reduce CLABSI even in the highest risk infants. CDC has recommended elements of insertion and maintenance bundles for all patients, although the nuances of care for NICU patients are not included (see **Table 3**) (8). This white paper provides clinicians with practical guidance on the implementation of strategies to prevent CLABSI in NICU patients, including those above and beyond the elements suggested by CDC.

Intended use

The Society for Healthcare Epidemiology of America (SHEA) intends for this document to serve as a companion to the CDC Healthcare Infection Control Practices Advisory Committee (HICPAC) *Guideline for Prevention of Infections in Neonatal Intensive Care Unit Patients* (9), and to provide practical, expert opinion, and/or evidence-based answers to frequently asked questions about CLABSI detection and prevention in the NICU. This document is not a comprehensive compilation of infection prevention strategies recommended for NICUs. Hand

hygiene, environmental cleaning and disinfection, infection prevention education for family members/caregivers and other core practices recommended by the CDC for all healthcare settings are essential to CLABSI prevention and are detailed elsewhere.

The published literature related to the questions presented herein is not sufficient to meet Grading of Recommendations Assessment, Development and Evaluation (GRADE) standards (9, 10); therefore, the authors provide no evidence grading and answers incorporate experts' clinical experience. No guideline, expert guidance, or white paper can anticipate all situations. This document is meant to serve as an adjunct to individual judgment by qualified professionals. In general, these recommendations apply to non-outbreak settings. Healthcare personnel (HCP) may implement additional measures during an outbreak or other special clinical scenarios.

Methods

This document has been authored by pediatric infectious diseases specialists, neonatologists, advanced practice nurse practitioners, infection preventionists, members of the HICPAC guideline-writing panel, and members of the SHEA Pediatric Leadership Council to identify and address practical questions anticipated from practitioners and infection prevention professionals. This document is part of the "SHEA neonatal intensive care unit (NICU) white paper series." Two documents in the series precede this one: "Practical approaches to *Clostridioides difficile* prevention" published in August 2018 (11) and "Practical approaches to *Staphylococcus aureus* prevention," published in September 2020 (12).

Unlike the SHEA expert guidance format, this document is not based on a systematic literature search. Instead, for the selected topic areas, the authors provide practical approaches in question-and-answer format, with answers based on consensus expert opinion within the context of the literature search conducted for the companion HICPAC document and supplemented by other published information retrieved by the authors.

The full white paper series is overseen by a group of experts in pediatrics, including pediatric infectious diseases specialists, neonatologists, advanced practice nurse practitioners, and infection preventionists, convened by SHEA, called the NICU Advisory Panel (see **Acknowledgements**). The NICU Advisory Panel members serve as representatives for the following organizations: the American Hospital Association (AHA), the American Academy of Pediatrics (AAP), the Association for Professionals in Infection Control and Epidemiology

(APIC), the Infectious Diseases Society of America (IDSA), The Joint Commission, the National Association of Neonatal Nurses (NANN), the Pediatric Infectious Diseases Society (PIDS), and the Vermont Oxford Network (VON). This document was reviewed by the NICU Advisory Panel member organizations, the SHEA Guidelines Committee, the SHEA Publications Committee.

It was endorsed by the Society for Healthcare Epidemiology of America (SHEA), the National Association of Neonatal Nurses (NANN), the Pediatric Infectious Diseases Society (PIDS).

A list of abbreviations, to include organizations' acronyms, is provided in **Table 1**.

Authors

The authors include current and past members of the SHEA Guidelines Committee and the SHEA Pediatric Leadership Council. All authors served as volunteers. At their respective institutions, authors are directly involved or provide an advisory role in the development of policies pertaining to pediatric and/or neonatal infection prevention in the NICU.

The NICU Advisory Panel (see **Acknowledgements**), a collaborative group of pediatric and pathogen-specific experts convened by SHEA, provided oversight and review of the draft document.

Practical approaches: Questions and Answers

The list of questions and recommendations are listed in **Table 2**.

Question 1: Which NICU patients are likely to benefit from use of chlorhexidine (CHG) skin antisepsis for CVC insertion and maintenance?

Answer 1:

- Skin antisepsis should occur for all infants in the NICU, and optimally should be performed with a CHG-containing product.
- For infants ≥8 weeks of age or older, 2% CHG in 70% alcohol should be used.
- For infants <8 weeks of age, the authors' clinical experience shows that a CHG-containing product may be used safely. Additionally, the U.S. Food and Drug Administration (FDA) has stated that CHG may be "[used] with care in premature infants or infants under 2 months of age" (13).

- For infants born at <28 weeks' gestation, especially when ≤7 days of age, NICUs may consider use of aqueous 2% CHG for skin antisepsis.

A variety of antiseptics, containing differing amounts of CHG, with and without alcohol (aqueous CHG), are available. The use of a CHG-containing skin antiseptic, in combination with alcohol, for CVC insertion and maintenance is preferred, based on its efficacy in reducing CLABSI in populations outside of the NICU. In the NICU, the optimal concentration of CHG-containing agent has not been determined. Although the FDA has stated CHG may be "[used] with care in premature infants or infants under 2 months of age," (13), the authors' clinical experience shows that it may be used safely. Figure 1, from the Centre Hospitalier Universitaire (CHU) Sainte-Justine Hospital in Montreal, Canada details how one hospital has operationalized options for antisepsis for various procedures commonly performed in the NICU setting. While more detailed than the recommendations provided in this document, it could serve as a useful model for NICUs seeking to implement the use of CHG. Infants (≥8 weeks of age) may benefit from a higher CHG concentration (i.e., 2%) (14) (see **Figure 1**). For CVC insertion, some centers use 2% aqueous rather than alcohol-based CHG in extremely preterm infants (<28 weeks' gestation), but recommend that, once dried, CHG should be rinsed off the skin with sterile water to prevent burns. However, Garland et al. showed that the application of 2% CHG in 70% isopropyl alcohol for skin antisepsis before CVC placement and with each weekly dressing change in infants weighing ≥1500 grams and ≥7 days of age was not associated with dermatitis although cutaneous absorption of CHG occurred in 15% of infants (15).

As an alternative to alcohol-based CHG solutions that may potentiate skin irritation and cutaneous CHG absorption, some NICUs use 1% or 2% aqueous CHG for skin antisepsis. In a randomized, blinded, non-100 inferiority trial of 308 infants who were 26 to 42 weeks' gestation, the use of 1% aqueous CHG for skin antisepsis was comparable to a 2% aqueous CHG solution when assessed by the proportion of negative skin swab cultures after skin antisepsis (14). Overall, 93% of swabs were sterile in the 1% CHG group compared with 95.6% in the 2% CHG group (risk difference -2.7%, 95% CI -6.2 - +0.8%). The lower bound of the 95% CI crossed the prespecified absolute non-inferiority limit of 5%. Mild dermatitis was identified in 2.3% of infants in each group, with the worst being transient slightly pink discoloration of the skin without edema. Percutaneous absorption of chlorhexidine occurred in all 59 sampled infants but did not differ by the concentration of the aqueous preparation with the median CHG

concentration at 24 hours being 19.6 ng/ml and 12.6 ng/ml in the 1% and 2% aqueous CHG group, respectively (14). Therefore, use of the lower CHG concentration does not offer any substantial safety advantage.

CHG skin antisepsis is commonly used in many NICUs. In 2016, a survey of 58 academic NICUs in the United States found that CHG was used by 86% of centers, mostly for skin antisepsis at the time of CVC insertion, CVC dressing changes, CVC maintenance, and peripheral intravenous catheter insertion. In NICUs where CHG was restricted by age or weight, the most common requirements for CHG use were gestational age >28 weeks and weight >1000 grams.

CHG-based skin antisepsis has demonstrated superiority compared to povidone-iodine in settings outside of the NICU (16). Limited data from clinical trials in the NICU have failed to demonstrate superiority of either product from a safety and efficacy standpoint, although the use of povidone-iodine was associated with an increased risk of high thyroid stimulating hormone level requiring treatment (15, 17). Recent guidelines from CDC for the prevention of CLABSIs in NICU patients advise to "consider the use of alcohol-containing chlorhexidine for skin antisepsis to prevent central line-associated blood stream infection (CLABSI) in neonatal intensive care unit (NICU) patients in whom the benefits are judged to outweigh the potential risks" (9). The consensus of the authors is that CHG-based skin antisepsis and not an iodine-based product is optimal for all infants regardless of gestational age and birth weight.

Frequent inspection of the skin site where CHG has been applied is important to detect and manage cutaneous adverse effects including chemical burns (18). To decrease their occurrence, only the minimum amount of CHG-containing solution should be used, with removal of any excess solution, as well as any soaked materials or drapes from the skin. Parents should be informed of the potential for CHG to cause skin irritation at the time consent for CVC placement is obtained (19). When severe dermatitis or chemical burns occur, temporary use of povidone-iodine or a lower concentration of aqueous CHG may be needed until the skin injury is healed. Consultation with the NICU wound team or other specialists such as burn and plastic surgeons may be necessary.

Question 2: How often should CVC dressings be changed in NICU infants?

Answer 2:

- To reduce skin barrier breakdown and the risk for dislodgement of the CVC, CVC dressings should be changed only if soiled, damp, or loose, regardless of gestational age (and not according to a specific interval of time, e.g., every 7 days).
- The integrity of the CVC dressing should be inspected by designated HCP at least daily.

Transparent CVC dressings have been recommended to be changed every 7 days, and more frequently if soiled, damp, or loose (20); however, it also is likely that in extremely preterm infants in particular (<28 weeks' gestation), each dressing removal may result in skin barrier breakdown leading to an increased risk of CLABSI. Some NICUs will only change a transparent dressing if soiled, damp, or loose, and this is the authors' consensus recommendation for all NICU patients regardless of gestational or chronologic age or weight. While acknowledging that this is different than the CDC recommendation (see **Table 3**), deferring changing dressings of NICU patients if they are intact has been recommended by other experts (21-23). Daily inspection of the dressing's integrity, preferably by a dedicated team or trained bedside nurse, is recommended.

Very limited data suggest that use of cyanoacrylate glue at the CVC insertion site may decrease bleeding and thus increase the time between dressing changes in extremely preterm infants. In one NICU the addition of cyanoacrylate glue to the insertion bundle for percutaneously placed CVCs significantly reduced accidental catheter dislodgement and anecdotally reduced bleeding at the insertion site (24).

Question 3: In which NICU patients should CHG-impregnated sponges or other CHG-impregnated dressings be used?

Answer 3:

- CHG-impregnated dressings are associated with an increased risk of contact dermatitis in NICU infants. Benefits have not been demonstrated in NICU infants and these products are not recommended by the authors (25).
- If other interventions have failed to reduce CLABSI in an infant in the NICU, or if there is an increase in the NICU's baseline CLABSI rates, CHG-impregnated dressings may be considered in infants ≥28 weeks' gestation and ≥7 days of age.

There are several types of dressings that incorporate chlorhexidine including CHG-impregnated sponges, transparent dressings, and films. A CHG-impregnated sponge, also called a patch or disk, is a device composed of sterile polyurethane foam impregnated with CHG. It is intended to be applied at the insertion site of a central line before a sterile, transparent dressing is placed. This device is designed to provide continuous protection from skin re-colonization by slowly releasing CHG while also absorbing and drawing fluids away from the site (26). The use of CHG-impregnated sponges (e.g., Biopatch® Protective Disk with CHG, Ethicon Inc., Raritan, NJ) has been shown to reduce CLABSIs in adults, but the benefits are less clear in pediatric patients (27). The National Health Service (NHS UK), recommends that if used, CHG-impregnated sponges should be restricted to infants ≥28 weeks' gestation and ≥7 days of age and that pressure over the sponge be avoided to prevent skin necrosis (28). Adverse skin reactions, including dermatitis and cellulitis at the insertion site, may occur and not be visible under the sponge, and this may be a deterrent to their use in some infants.

Dressings impregnated with antiseptics or antibiotics (i.e., antimicrobial dressings) have also been studied in NICU infants (8, 29). A Cochrane review evaluated the effectiveness and safety of antimicrobial dressings used at the time of CVC insertion in reducing CLABSIs in the NICU. Compared to polyurethane dressing/povidone-iodine cleansing, CHG sponges/alcohol cleansing reduced catheter colonization (RR 0.62, 95% CI 0.45-0.86) but did not change the important outcomes of bloodstream infection (BSI) (RR 1.18, 95% CI 0.53-2.65) or sepsis (RR 1.06, 95% CI 0.75-1.52) (29). In addition, the use of CHG-impregnated dressings was associated with contact dermatitis in preterm infants (RR 43.06 95%CI 2.61-710.44) (29). Use of a silver-alginate patch appeared safe, but there was insufficient evidence of benefit.

CDC does not recommend the use of CHG-impregnated dressings (including sponges) to protect the sites of short-term, non-tunneled CVCs for premature infants due to the risk of serious adverse skin reactions. The use of such dressings is considered an unresolved issue in all patients less than 18 years of age (8), including NICU infants, due to the lack of sufficient evidence from published, high-quality studies about efficacy in this age group.

Some NICUs utilize CHG dressings for selected infants. Twenty percent (10/50) of neonatology training program directors in the US who responded to a 2014 survey reported using impregnated dressings or disks (the survey did not differentiate between the products) (30). A survey of SHEA Pediatric Leadership Council members in April 2014 revealed that 5 of 26 NICUs (19%)

used a "CHG dressing" on infants with surgically placed CVCs but the criteria for use were variable and included infants who were >28 weeks' gestation and weighing >1000 grams, ≥34 weeks' corrected age, or >2 months chronologic age. Only 3 of 27 (11%) NICUs used CHG dressings on similar infants with peripherally inserted central catheters (PICCs, also called percutaneously inserted CVCs) (31). The survey did not differentiate between sponges and impregnated dressings.

Question 4: Should alcohol disinfectant caps be used in the NICU?

Answer 4:

- NICUs may consider use of disinfectant caps as an additional intervention to reduce CLABSI rates when other interventions have failed.

Access of pathogenic organisms to the bloodstream via a CVC is prevented in part by careful disinfection of the catheter hub. The manual "scrub-the-hub" process is time-consuming and thus compliance by HCP may be suboptimal. Disinfectant caps containing 70% isopropyl alcohol placed over intravenous needleless connectors act as antiseptic barriers by passive disinfection, decreasing hub colonization (32). Two in vitro studies found leakage of alcohol through the hub membrane (33, 34) but the potential clinical significance of this is unknown. Adverse effects resulting from alcohol leakage in a clinical setting have not been identified. In vitro, alcohol leakage can vary by cap manufacturer and may be reduced by allowing the hub membrane to dry for 30 seconds prior to an infusion and limiting the number of days that the cap remains in place (<7 days).

In pediatric patients, disinfectant caps have been used in many hospitals, usually as part of a bundle, with subsequent reduction in CLABSIs. In 2019, the National Institute of Health and Care Excellence (NICE) cited disinfectant caps as a potential intervention to reduce CLABSIs, but due to insufficient evidence, further research to assess their clinical benefit was recommended (35). A systematic review that included nine studies comparing the effects of disinfectant caps (Curos™ and SwabCap®) with manual disinfection in multiple US and UK hospital settings (including one pediatric hospital) found disinfectant caps effectively reduced CLABSIs (Incidence Rate Ratio=0.59, 95% CI 0.45-0.77, p<0.001) and were cost-saving (36, 37). In a prospective, single center, pre- and post-observational study conducted in the pediatric and neonatal intensive care units, CLABSI rates decreased by 22% with the use of disinfectant caps compared to the manual scrub-the-hub method, but the difference was not statistically

significant (95% CI -34%-55%; p=0.368) (37). Among ambulatory pediatric oncologic patients, a randomized controlled trial evaluating disinfectant caps did not demonstrate a significant reduction in CLABSI incidence (38).

Despite the lack of supportive evidence in pediatrics, many NICUs utilize disinfectant caps without reporting clinically significant adverse effects. A survey conducted by the SHEA Pediatric Leadership Council in April 2014 showed that one third (9 of 27) of participating NICUs used ethanol or alcohol caps in all hubs or ports of the intravenous administration set in all NICU patients (31).

Question 5: In which NICU patients are the benefits of CHG bathing likely to outweigh the risks?

Answer 5:

- Routine CHG bathing is not recommended for all NICU infants.
- In NICUs with high CLABSI rates (see **Question 10**), despite implementation of other evidence-based strategies, CHG bathing may be used in the NICU for infants with CVCs. The optimal frequency of CHG-bathing has not been established and depends on chronological age and gestational age:
    - CHG bathing in term infants (≥37 weeks): may be performed from birth.
    - CHG bathing in preterm infants <37 weeks gestation may be considered beginning at 4 weeks of chronological age, recognizing the potential for skin irritation and systemic absorption (the latter being of unknown clinical significance).
    - CHG bathing in preterm infants (<37 weeks gestation) and <4 weeks of age: not recommended due to potential adverse local and systemic effects. In these infants, an alternative approach of bathing with sterile water with or without mild soap may help decrease skin bacterial counts.
- When CHG bathing is utilized, NICUs should ensure careful surveillance for local and systemic adverse effects, including allergic reactions.

The use of CHG for skin antisepsis and the use of CHG for bathing are distinct interventions with unique sets of benefits and risks in NICU infants. Daily bathing of ICU patients ≥8 weeks (i.e., ≥2 months) is now considered to be standard infection prevention practice (23, 39)

including patients in the NICU. With the exception of children with cancer or those undergoing hematopoietic stem cell transplantation, daily CHG bathing of children in the PICU who were ≥2 months of age (8 weeks) resulted in decreased bacteremia and CLABSIs (40). Recommendations for bathing younger infants, especially preterm infants, is more nuanced. Bathing infants with cloths infused with CHG decreases skin bacterial colony counts transiently (41, 42). Non-randomized trials in NICU patients suggest a decrease in CLABSI rates in CHG-bathed neonates in the absence of observed adverse events (43, 44); however, safety concerns persist, especially in very preterm infants whose poor skin integrity may predispose them to contact dermatitis, chemical burn, and systemic absorption (45). An additional concern comes from studies in pediatric and adult patients that have noted higher prevalence of reduced CHG susceptibility in organisms that cause CLABSI in units that perform daily CHG bathing of patients (46). In adults, the potential development of cross-resistance to other cell envelope agents such as daptomycin and colistin has raised further concerns. These phenomena have not been evaluated in NICU patients.

For these reasons, CHG bathing has not been used routinely in extremely preterm (<28 weeks' gestation) infants with birth weight of ≤1,000 grams who are <4 weeks of age, and alternate bathing methods with sterile water and/or mild soap are advocated; however, based on decreases in CLABSI rates in CHG-bathed neonates as noted above, CHG bathing may be considered in more mature preterm and term infants between 4 and 8 weeks of age if CLABSI rates remain high despite implementation of other evidence-based interventions.

Question 6: What are practical strategies for minimizing central line entry in NICU patients?

Answer 6:

- NICUs should perform laboratory and diagnostic stewardship (i.e., consolidation of necessary tests and elimination of those not clinically relevant).
- HCP should avoid using the CVC to obtain routine blood tests.
- Although not a universal recommendation, NICUs may consider the use of closed blood sampling systems.
- The utility of obtaining blood cultures through an indwelling CVC remains an unresolved issue.

Infants in the NICU require frequent blood draws for clinical monitoring. CDC guidelines for CLABSI prevention in NICU patients recommend minimizing the number of times central line hubs are accessed and minimizing blood sampling through central lines, even though high quality data are lacking (9, 47). Only one study among infants in the NICU reported an increased risk of CLABSI from procedures involving catheter manipulation such as disinfection of the catheter hub following disconnection of the CVC (OR 1.2, 95% CI 1.1-1.3) and blood sampling other than for blood gases (OR 1.4, 95% CI 1.1-1.8) (48). The authors reported a cumulative dose-effect of the number of blood samples obtained from the CVC with an OR of 1.04 for 1 to 7 blood samples to 8.4 (95% CI; not statistically significant) for more than 14 blood samples. Obtaining blood samples by other methods may also create risk. In an observational case-control study, there was an increased risk of CLABSI among NICU infants who had at least 3 capillary blood draws by heel punctures within 48 hours before CLABSI onset (OR 5.36; 95% CI, 2.37–12.15) (49). This retrospective study could not confirm causality, but it is plausible that multiple skin breaks contributed to the development of bacteremia.

The first steps to decrease the number of central line system entries are not using CVCs for routine blood draws and performing laboratory and diagnostic stewardship to minimize tests that are not clinically relevant. Reducing laboratory testing is an achievable goal. After implementing a multi-faceted quality improvement project that included guideline development, dashboard creation and distribution, electronic medical record optimization, and expansion of noninvasive and point-of-care testing, one NICU achieved a 26.8% decrease in routine laboratory testing per 1000 patient days over a 24-month period (50).

The utility of obtaining blood cultures through an indwelling CVC remains controversial. In general, catheter drawn blood cultures have higher rates of contamination (i.e., false positives) (51) and some expert guidance recommends peripheral venipuncture as the preferred method for obtaining blood cultures (52). The Bright Star Collaborative is a multicenter quality improvement collaborative that includes children's hospitals in 17 states across the United States (53). The mission of the group is to reduce bacterial culture overuse in critically ill children by implementing diagnostic stewardship interventions. Consensus recommendations from the group for pediatric intensive care unit patients advise against obtaining blood cultures from every lumen of a CVC or from a peripheral intravenous catheter. The group did not reach consensus regarding the utility of a blood culture drawn from a CVC, since a positive culture cannot

differentiate between catheter colonization or BSI (54). NICU-specific recommendations do not exist but the issues are likely to be similar.

The clinician must weigh practical considerations when deciding how to obtain blood cultures in a NICU patient. The NHSN surveillance definitions for CLABSI require 2 positive blood cultures, taken at different sites or at different times, when potential commensal bacteria (e.g., coagulase-negative staphylococci) are detected in order to diagnose a true device-associated infection. It may be difficult to obtain two separate samples by peripheral venipuncture in NICU infants. A CVC sample may be paired with a peripherally obtained sample to help differentiate between catheter colonization and a true BSI, especially when a commensal organism is isolated. A CVC culture is considered to have higher sensitivity compared to peripheral specimens, at the cost of lower specificity (55). Finally, HCP also may opt to draw a blood culture from a CVC to minimize painful procedures. A recent study conducted at a level IV NICU compared concurrently drawn peripheral and catheter blood cultures and found that the majority of blood cultures were positive with the same organism from both sites, although a small but important minority of episodes (12%) grew virulent pathogens from either culture site alone (51). The authors concluded that while dual-site blood culture practices may be useful, the gain in sensitivity of bacteremia detection should be weighed against additive contamination risk. Even when HCP want to obtain a blood culture from a CVC, it may not be feasible. Catheters with very small lumens may collapse when suction is applied during the blood draw.

Adopting the Bright Star Consensus Recommendations for PICU patients may reduce the total number of blood cultures ordered, as well as the number of samples obtained through the catheter. Before ordering a blood culture, the HCP should review the patient's clinical data, including previous cultures, perform a physical examination, and discuss the patient's status with the bedside nurse. If a blood culture needs to be drawn from the CVC, then one may perform additional blood draws at the same time or schedule the blood culture with other required laboratory tests to decrease system entry (54). Since bacteremia occurs before the onset of fever, once the fever has occurred, the timing of the blood culture is not as critical except in situations when obtaining a blood culture before a change in antimicrobial therapy informs antimicrobial stewardship efforts.

Previous studies have shown that closed infusion systems are associated with a decrease in overall CLABSI rates when compared to open infusion systems. Other studies have proposed

that closed blood sampling systems, such as the venous arterial blood management and protection (VAMP™) and KidsKit™ systems, decrease system entry, blood waste, and microbial contamination (56-58). A pediatric study evaluated both systems and compared implementation of the KidsKit™ system to the conventional three-way stopcock methods used on umbilical arterial catheters in the PICU and NICU. The authors found a decrease in CLABSIs below the national benchmark (58). NICUs may consider use of a closed blood sampling system as one potential intervention when CLABSI rates remain elevated despite high rates of compliance with insertion and maintenance bundles.

Question 7: When and how should prophylactic antimicrobial lock therapy be implemented in NICU patients?

Answer 7:

- Prophylactic antimicrobial lock therapy as a universal prevention measure is not recommended.
- Antimicrobial locks may be considered as an additional intervention in NICU infants with recurrent CLABSIs.

Antimicrobial locks are solutions used for prophylactic or adjunctive treatment of CLABSI when the catheter cannot be removed in the setting of bacteremia. They contain a solution of highly concentrated antimicrobial agent in combination with an anticoagulant that is inserted into the lumen of a CVC and removed after a specified period of time (dwell time). Three randomized controlled trials in NICU infants demonstrated that use of prophylactic antimicrobial lock therapy decreased CLABSIs in NICUs with high baseline CLABSI rates (59-61). These studies, however, were conducted before routine implementation of insertion and maintenance bundles that have reduced NICU CLABSI rates substantially. We do not, therefore, recommend prophylactic antimicrobial lock therapy as a universal prevention measure although it may be considered in individual infants who experience recurrent CLABSIs. The authors recommend collaboration with a pediatric infectious diseases specialist and the NICU vascular access team (VAT) before implementation of lock therapy.

NICUs will need to consider practical implementation challenges, including that some catheters are not suitable for antimicrobial locks and that the optimal minimum dwell time for lock therapy is 4 hours (see **Table 4**).

There is no single preferred antimicrobial lock preparation. Several concentrations of antimicrobial agents and ethanol have been studied in combination with heparin and other anticoagulants (see **Table 5**). When used, antimicrobial locks should have activity against common CLABSI pathogens, the ability to penetrate biofilms, compatibility with anticoagulants such as heparin or an alternative ion chelator such as citrate, and prolonged stability (62). In addition, they should have low risk of toxicity and low potential for inducing antimicrobial resistance. Ampicillin and other beta lactam agents, with and without an extended spectrum, have been studied in combination with heparin and form stable locking solutions. Aminoglycosides and vancomycin have been studied with different additives such as heparin, citrate, and tissue plasminogen activator (TPA) (62). In the NICU population, there is insufficient evidence for the effectiveness and safety of citrate locking solutions, although some institutions use sodium citrate 4% as the anticoagulant in the antimicrobial locks in combination with antimicrobial agents such as cefepime, vancomycin, or gentamicin (63).

The safety and efficacy of ethanol locks have not been studied in NICU patients, but limited data exist on their use in infants with intestinal failure (64) as young as 0.3 years and who weigh at least 5kg (65-71). A recent systematic review and meta-analysis concluded that prophylactic ethanol locks in patients with intestinal failure reduced CLABSIs and catheter replacements but were associated with an increased need for catheter repair (72). The potential for alcohol-related toxicity was also assessed in a pilot study that enrolled 10 infants (mean age 3.5 months, mean weight 4.5 kg). Blood alcohol concentrations were assessed one hour after a 0.4 mL dose of ethanol was flushed through the CVC, equivalent to the volume that would be used during ethanol lock therapy (73). Eight patients had undetectable blood alcohol concentrations at 5 minutes, while 2 patients had alcoholaemia of 0.011%. Blood alcohol concentrations were undetectable in all infants at one hour and there was no evidence of hepatic injury. There are no data on the repeated use of ethanol locks in the neonatal population. The cost and general availability of ethanol lock solutions many limit their potential use.

When the decision is made to use antimicrobial lock therapy, practical guidance for implementation is presented in **Table 6**.

Question 8: Should prophylactic antimicrobials be administered to a NICU patient at the time of PICC removal to reduce the incidence of CLABSI or culture-positive sepsis?

Answer 8:

- Prophylactic antimicrobials are not recommended at the time of PICC removal.

The proposed rationale for prophylactic antimicrobials administered to NICU patients at the time of PICC removal is to mitigate the potential impact of dislodgement of intra- or extra-luminal bacterial biofilm and subsequent bacteremia that elevates the frequency of BSI or culture-positive sepsis in the days following catheter removal. The actual risk of BSI following catheter removal is not well described. One single center retrospective cohort study of 101 preterm infants did not identify an increased risk of catheter-related BSI in the 48 hours following removal of PICCs (74). A second retrospective cohort study that included 1,002 PICCs in 856 infants did not find a difference in the prevalence of BSIs or culture-negative sepsis when comparing the 72 hours before PICC removal to the 72 hours after removal (75); however, for infants with birth weight <1500g, the odds for culture-negative sepsis increased 6.3-fold following removal of PICC not used for antimicrobial delivery (95% CI 1.78-26.86; $p < 0.01$). A third retrospective cohort study conducted before the widespread implementation of CVC insertion and maintenance bundles reported a high rate of culture-positive sepsis within 5 days of PICC removal (24/345; 7%) (76). The incidence of sepsis was lower in infants who received antimicrobials at the time of catheter removal (2/132 [1.5%] vs. 22/213 [10.3]; p=0.002). Subsequent studies have not demonstrated a benefit to prophylactic antimicrobials before PICC removal. One retrospective study identified no difference in clinical or culture-positive sepsis in 137 infants who received a single dose of vancomycin before PICC removal and 64 infants who received no antimicrobial (77). In a second retrospective cohort study of 216 NICU patients with PICCs, the occurrence of microbiologically proven (n=6) or clinical sepsis (n=8) was uncommon within 5 days of catheter removal and no benefit was identified with antimicrobial use at the time of PICC removal (OR 0.6; 95% CI 0.1,2.7; p= 0.74) (78). A single randomized, unblinded trial enrolled 88 infants who received intravenous cefazolin administered one hour before or 12 hours after catheter removal (79). Although the authors reported a difference in culture-positive sepsis within 48 hours (0% of treated infants vs. 11% of controls, p=0.021), there were significant methodological issues and subsequent analyses suggest this difference was not statistically significant (RR 0.09, 95% CI 0.01 to 1.60) (80, 81). No studies have systematically evaluated

potential harms of antimicrobial prophylaxis at the time of catheter removal, such as impact on the neonatal microbiome. A 2018 Cochrane review concluded that there is insufficient evidence to assess the efficacy or safety of antimicrobials given at the time of catheter removal (80).

Question 9: What are practical considerations for the implementation of a neonatal vascular access team (VAT)?

Answer 9:

- NICUs should consider use of a VAT. Such teams have demonstrated effectiveness in reducing catheter-related complications and are cost-effective (21, 82-84).
- VAT proceduralists should receive education and clinical training, and upon completion, demonstrate knowledge and proficiency in PICC insertion, care, and removal, and a commitment to the team-based approach.
- VAT proceduralists should successfully insert a pre-defined number of PICCs as defined by the local facility's delineation of privileges.
- The team should monitor relevant quality measures (see **Table 7**).

This document refers to the VAT, defined as any organized group of HCP involved in the management of vascular access. Prevention of CLABSIs benefits from the establishment of a team dedicated to all aspects of intravenous therapy. A recommendation of the Consensus Conference on Prevention of Central Line-Associated Bloodstream Infections was the establishment of dedicated intravenous therapy teams, citing studies that showed reductions in infections and complications from central and peripheral intravenous catheters (85). In practice, the duties of VAT toward the catheters they care for vary by institution. The authors suggest that the VAT's responsibilities include catheter insertion, daily inspection, and maintenance, as well as development and education related to policies and procedures. A dedicated team with expertise in PICC assessment, placement, and care can serve as an invaluable resource for the NICU. The VAT also can provide information to infection preventionists in the form of data collection and identification of trends to inform quality improvement efforts. Including the team members in infection prevention meetings will assist in guiding the focus of prevention during insertion of the PICC. Duties may also include investigation of positive blood cultures, in conjunction with the healthcare epidemiology and infection prevention teams (86). This places the focus of the team on prevention rather than just job duties. In one medical center, including a

VAT as part of a "better bundle" strategy was associated with a significant decrease in CLABSIs (86). Published guidelines state that specialized "IV teams," such as VAT, have shown unequivocal effectiveness in reducing the incidence of catheter-related BSI (CR-BSI), associated complications, and costs (82).

Proper sterile technique during the placement of CVCs remains paramount for reduction of CLABSIs. Standardization of procedures for long-term maintenance of CVCs helps to reduce the incidence of CLABSIs in intensive care patients (87). An identified VAT allows organizations to centralize the responsibility for PICC-related activities with a select group of proceduralists, thus enhancing accountability and ultimately, clinical outcomes (84). The upfront investment in a VAT results in cost savings from a reduction in the number of CLABSIs and other CVC-related complications. In one NICU, the initiation of a dedicated PICC insertion and maintenance team resulted in a nearly 50% decrease in the risk of CLABSI in patients who required long-term (>30 days) central venous access (88).

Additionally, by developing a VAT, a facility may reduce the resources spent training and retraining proceduralists and ancillary support staff in central line insertion and maintenance (21). Regardless, standards for the training of proceduralists vary. A recent national survey showed that a majority of proceduralists attend informal training sessions with less stringent training requirements for physicians than registered nurses or nurse practitioners (89). Many of proceduralists have less than 5 successful placements before being allowed to insert PICC independently. **Table 7** provides a list of recommended education, training, and competencies for members of a neonatal VAT.

Question 10: What threshold should prompt a NICU to consider implementing additional preventive measures?

Answer 10:

- Zero CLABSIs is the aspirational and potentially achievable goal. While there is no nationally endorsed threshold above which additional CLABSI prevention measures should be implemented, a variety of quantitative or qualitative metrics may be utilized to identify CLABSI prevention success over time and determine when additional intervention is necessary.
- A decision to identify a threshold for action in an individual NICU should assess a variety of factors including:

    - Local interest in setting a specific lower target with input from Infection Prevention and Control (infection preventionists, healthcare epidemiologist)
    - Patient mix and clinical acuity, which may predict general likelihood of CLABSI
    - Resource and personnel capacity for initiation and/or maintenance of specific interventions and practice processes.
- Any quantitative or qualitative metric that is defined should be developed and accepted by all stakeholders.

CLABSI prevention should be a continuous goal and integrated into usual NICU practices and processes. Successful CLABSI prevention requires attention to the importance of practices related to central line insertion and maintenance over time and collaboration among a variety of stakeholders, including infection preventionists, nurses, physicians, advanced practice HCP, and educators, among others. The decision to increase infection prevention efforts requires the involvement of NICU leadership or a local champion to ensure that new processes and education are prioritized within existing workflows. Individual units have achieved very low rates of CLABSIs–even zero CLABSIs–over sustained time periods (6, 21).

A variety of quantitative metrics can be used to reveal a lapse in CLABSI prevention success. Quantitative metrics may include total NICU-wide CLABSI incidence over a pre-defined period of time, compared to a similar time period that allows for adjustment for time-varying confounders (e.g., season, census, staff shortages and turnover). Alternatively, an absolute number of CLABSIs may be deemed "acceptable" in a particular NICU per time period or per a given patient census. Either of the above metrics also may be considered for a subset of high-risk infants as a marker for general CLABSI prevention effectiveness (e.g., post-operative patients, premature infants, others). Lastly, a NICU may consider a pre-defined target standard infection ratio (SIR), a risk-adjusted metric generated by CDC using NICU-specific surveillance data reported to NHSN (90) (e.g., SIR < 1.0).

NICUs may also choose to increase CLABSI prevention efforts based upon rigorously evaluated or even anecdotal qualitative observations in the unit. Qualitative observations can be performed actively on an ad hoc basis or via routine mechanisms such as team huddles with checklists or overt comprehensive audits of any or all practices. Real-time perceptions among staff of waning vigilance toward CVC maintenance practices or repeated breaches in protocol for specific practices related to line insertion or maintenance must be taken seriously and properly

investigated. Ultimately, any developed target metric that may trigger more intensive CLABSI prevention efforts should be acceptable to all *a priori*, particularly those involved with CVC use and CLABSI prevention at the bedside.

Before a decision is made to introduce new processes for CLABSI prevention, it is important to assess the adherence to existing prevention practices in the NICU in a systematic fashion, for example, through a quality improvement (QI) program. Such assessments should include direct input from infection preventionists, nurses, advance practice HCP, and physicians. If additional CLABSI measures are deemed necessary, it is helpful to distinguish between those shown to be effective and those that are not proven robustly, but may have impact nonetheless. Known effective evidence-based interventions have been identified by CDC (see **Table 3**) (8, 16).

If an effort to enhance CLABSI prevention activities is deemed necessary, it must be recognized that staff at various levels of responsibility may have different attitudes or willingness to add tasks to the workflow (91). Simply having a written policy is insufficient to effect practice change(s) that will lead to fewer CLABSIs. In 2011, a national survey noted that 84-93% of NICUs had written policies for insertion checklist and for bundle practices, but ≥75% adherence for individual components was achieved only 68-73% of the time for at least one component and only 28% for all monitored processes (92). Allowance for adaptations–dependent on local workflows and priorities–is important, and quantitative metrics should be used as a guide to effectiveness (93).

Question 11: What preventive bundle elements, above and beyond those recommended by CDC, could be considered by a NICU experiencing ongoing CLABSI?

Answer 11:

- Additional practices that lack robust evidence may be effective. There are many different products, technologies, and processes that NICUs may consider, examples of which are described below.
- Implementation of an expanded NICU central line care bundle should take into account the risks and benefits of additional measures, as well as the needs, resources, and local expertise at individual institutions.

If implemented, the impact of these practices should be evaluated by a multidisciplinary team.

Evidence-based care bundles effectively reduce CLABSIs in the NICU. A meta-analysis performed by Payne et al reported a 60% decrease in CLABSI rates after the introduction of a

care bundle in neonatal units (4). Additionally, care bundles contribute to a reduction in total central line use and duration. CDC has recommended basic insertion and maintenance bundles for all patients with CVCs, including NICU patients (**Table 3**). Nevertheless, published reports suggest substantial variability in bundles utilized in NICUs and little consensus about what constitutes the optimal bundle. A variety of CLABSI prevention bundles with different individual components have been shown to minimize CLABSIs in NICU settings, although most include hand hygiene, maximal sterile barrier precautions, and effective skin antisepsis (94). Few studies have compared the effectiveness of different bundles in a way that permits assessment of individual bundle components.

Throughout this document, we have reviewed practices and products that *could* be added to basic prevention bundles, including CHG bathing, CHG-containing sponges at central line insertion sites, ethanol disinfectant caps, and prophylactic antimicrobial locks. Additional practices may be effective and have been implemented by some NICUs but lack robust evidence and therefore have not been reviewed in detail in these recommendations. Such practices include but are not limited to regular sharing of CLABSI incidence data with NICU staff, the use of non-sterile gloves for all central line care (95), and a standard process for assessing when to discontinue a central line, such as when the infant is tolerating full enteral feeds and medications can be provided enterally (21, 96). For the assessment of continued need or discontinuation of a CVC, a short checklist in the nurse or physician daily note with discussion on multidisciplinary patient rounds may be a useful tool.

Most studies of bundle effectiveness have been conducted in larger, higher level-of-care NICUs. Similar effectiveness is anticipated in community NICUs that care for infants with CVCs.

Acknowledgements

The authors wish to thank NICU Advisory Panel Chairs, Drs. Alexis Elward and Deborah Yokoe. The authors thank Valerie Deloney, MBA and John Heys for their organizational expertise in the development of this manuscript.

NICU Advisory Panel

Kenneth M. Zangwill, MD, American Academy of Pediatrics Section on Infectious Diseases (AAP/SOID)

Nancy Foster, American Hospital Association (AHA)

Jessica R. Rindels, MBA, BSN, RN, CIC, Association for Professionals in Infection Control and Epidemiology (APIC)

Jill Jones MS, APRN, NNP-BC, National Association of Neonatal Nurses (NANN)

Pablo J. Sánchez, MD, Infectious Diseases Society of America (IDSA)

Aaron M. Milstone, MD, Pediatric Infectious Diseases Society (PIDS)

Margaret VanAmringe, MHS, The Joint Commission

Judith Guzman-Cottrill, DO, The Vermont Oxford Network (VON)

Conflict of Interest Disclosure

The following disclosures are a reflection of what has been reported to SHEA. In order to provide thorough transparency, SHEA requires full disclosure of all relationships, regardless of relevancy to the guideline topic. Evaluation of such relationships as potential conflicts of interest is determined by a review process. The assessment of disclosed relationships for possible COI will be based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The reader of this guidance should be mindful of this when the list of disclosures is reviewed.

MM, CE, JAJ, CQ, JRR, DLS, and KMZ report nothing to disclose. KAB reports being a Principal investigator on multicenter clinical trials funded by Pfizer, Gilead, and Enanta (payments made to institution) and serving as Immediate Past President of the Pediatric Infectious Diseases Society. PJS reports a grant for institution support from Merck (completed prior to publication) and current participation on the CDC Advisory Committee on Immunization Practices (ACIP).

Appendices

Table 1. Abbreviations

AAP	American Academy of Pediatrics
AAP/SOID	American Academy of Pediatrics Section on Infectious Diseases
AHA	American Hospital Association
APIC	Association for Professionals in Infection Control and Epidemiology
CDC	US Centers for Disease Control and Prevention
CHG	Chlorhexidine gluconate
CLABSI	Central line-associated bloodstream infection
CVC	Central venous catheter
FDA	US Food and Drug Administration
HCP	Healthcare personnel
IDSA	Infectious Diseases Society of America
kg	Kilogram
mg	Milligram
mL	Milliliter
NANN	National Association of Neonatal Nurses
NICU	Neonatal intensive care unit
NS	Normal saline
PICC	Peripherally inserted central catheter
PIDS	Pediatric Infectious Diseases Society
SHEA	Society for Healthcare Epidemiology of America
TPN	Total parenteral nutrition
VAT	Vascular access team
VON	Vermont Oxford Network

Table 2. Questions and Recommendations

#	Question	Answer
1	Which NICU patients are likely to benefit from use of chlorhexidine (CHG) skin antisepsis for CVC insertion and maintenance?	• Skin antisepsis should occur for all infants in the NICU, and optimally should be performed with a CHG-containing product. • For infants ≥8 weeks of age or older, 2% CHG in 70% alcohol should be used. • For infants <8 weeks of age, the authors' clinical experience shows that a CHG-containing product may be used safely. Additionally, FDA has stated that CHG may be "[used] with care in premature infants or infants under 2 months of age" (13). • For infants born at <28 weeks' gestation, especially when ≤7 days of age, NICUs may consider use of aqueous 2% CHG for skin antisepsis.
2	How often should CVC dressings be changed in NICU infants?	• To reduce skin barrier breakdown and the risk for dislodgement of the CVC, CVC dressings should be changed only if soiled, damp, or loose, regardless of gestational age (and not according to a specific interval of time, e.g., every 7 days). • The integrity of the CVC dressing should be inspected by designated HCP at least daily.
3	In which NICU patients should CHG-impregnated sponges or other CHG-impregnated dressings be used?	• CHG-impregnated dressings are associated with an increased risk of contact dermatitis in NICU infants. Benefits have not been demonstrated in NICU infants and these products are not recommended by the authors (25). • If other interventions have failed to reduce CLABSI in an infant in the NICU, or if there is an increase in the NICU's baseline CLABSI rates, CHG-impregnated dressings may be considered in infants ≥28 weeks' gestation and ≥7 days of age.
4	Should alcohol disinfectant caps be used in the NICU?	NICUs may consider use of disinfectant caps as an additional intervention to reduce CLABSI rates when other interventions have

		failed.

5	In which NICU patients are the benefits of CHG bathing likely to outweigh the risks?	• Routine CHG bathing is not recommended for all NICU infants.
		• In NICUs with high CLABSI rates, despite implementation of other evidence-based strategies, CHG bathing may be used in the NICU for infants with CVCs. The optimal frequency of CHG-bathing has not been established and depends on chronological age and gestational age:
		  ○ CHG bathing in term infants (≥37 weeks): may be performed from birth.
		  ○ CHG bathing in preterm infants <37 weeks gestation may be considered beginning at 4 weeks of chronological age, recognizing the potential for skin irritation and systemic absorption (the latter being of unknown clinical significance).
		  ○ CHG bathing in preterm infants (<37 weeks gestation) and <4 weeks of age: not recommended due to potential adverse local and systemic effects. In these infants, an alternative approach of bathing with sterile water with or without mild soap may help decrease skin bacterial counts.
		• When CHG bathing is utilized, NICUs should ensure careful surveillance for local and systemic adverse effects, including allergic reactions.

6	What are practical strategies for minimizing central line entry in NICU patients?	• NICUs should perform laboratory and diagnostic stewardship (i.e., consolidation of necessary tests and elimination of those not clinically relevant). • HCP should avoid using the CVC to obtain routine blood tests. • Although not a universal recommendation, NICUs may consider the use of closed blood sampling systems.

		• The utility of obtaining blood cultures through an indwelling CVC remains an unresolved issue.
7	When and how should prophylactic antimicrobial lock therapy be implemented in NICU patients?	• Prophylactic antimicrobial lock therapy as a universal prevention measure is not recommended. • Antimicrobial locks may be considered as an additional intervention in NICU infants with recurrent CLABSIs.
8	Should prophylactic antimicrobials be administered to a NICU patient at the time of PICC removal to reduce the incidence of CLABSI or culture-positive sepsis?	Prophylactic antimicrobials are not recommended at the time of PICC removal.
9	What are practical considerations for the implementation of a neonatal vascular access team (VAT)?	• NICUs should consider use of a VAT. Such teams have demonstrated effectiveness in reducing catheter-related complications and are cost-effective (21, 82-84). • VAT proceduralists should receive education and clinical training, and upon completion, demonstrate knowledge and proficiency in PICC insertion, care, and removal, and a commitment to the team-based approach. • VAT proceduralists should successfully insert a pre-defined number of PICCs as defined by the local facility's delineation of privileges. • The team should monitor relevant quality measures (see **Table 7**).
10	What threshold should prompt a NICU to consider implementing additional preventive measures?	• Zero CLABSIs is the aspirational and potentially achievable goal. While there is no nationally endorsed threshold above which additional CLABSI prevention measures should be implemented, a variety of quantitative or qualitative metrics may be utilized to identify CLABSI prevention success over time and determine when additional intervention is necessary. • A decision to identify a threshold for action in an individual NICU should assess a variety of factors including: ○ Local interest in setting a specific lower target with input from Infection Prevention and Control

		(infection preventionists, healthcare epidemiologist) ○ Patient mix and clinical acuity, which may predict general likelihood of CLABSI ○ Resource and personnel capacity for initiation and/or maintenance of specific interventions and practice processes. • Any quantitative or qualitative metric that is defined should be developed and accepted by all stakeholders.
11	What preventive bundle elements, above and beyond those recommended by CDC, could be considered by a NICU experiencing ongoing CLABSI?	• Additional practices that lack robust evidence may be effective. There are many different products, technologies, and processes that NICUs may consider, examples of which are described below. • Implementation of an expanded NICU central line care bundle should take into account the risks and benefits of additional measures, as well as the needs, resources, and local expertise at individual institutions.

Table 3. Adapted CDC Checklist for Prevention of CLABSI*

Insertion	Maintenance
□ Perform hand hygiene before insertion.	□ Perform hand hygiene.
□ Adhere to aseptic technique.	□ Bathe ICU patients who are □2 months of age with CHG daily.
□ Use maximal sterile barrier precautions (i.e., mask, cap, gown, sterile gloves, and sterile full body drape).	□ Use only sterile devices to access catheters.
□ Choose the best insertion site to minimize infections and noninfectious complications based on individual patient characteristics. □ Prepare the insertion site with >0.5% CHG with alcohol* (see **Question/Answer 1**).	□ Scrub the access port or hub with friction immediately prior to each use with an appropriate antiseptic (CHG, povidone iodine, an iodophor, or 70% alcohol).
□ Place a sterile gauze dressing or a sterile, transparent, semipermeable dressing over the insertion. □ For patients □18 years of age, use a CHG-impregnated dressing with an FDA cleared label that specifies a clinical indication for reducing CLABSI for short-term non-tunneled catheters unless the facility is demonstrating success at preventing CLABSI with baseline prevention practices*.	□ Immediately replace dressings that are wet, soiled, or dislodged. □ Perform routine dressing changes using aseptic technique with clean or sterile gloves: □ Change gauze dressings at least every 2 days. □ Change semipermeable dressings at least every 7 days. □ For patients ≥18 years of age, use a chlorhexidine impregnated dressing with an FDA cleared label that specifies a clinical indication for reducing CLABSI for short-term non-tunneled catheters unless the facility is demonstrating success at preventing CLABSI*.

	□ Change administrations sets for continuous infusions no more frequently than every 4 days, but at least every 7 days. □ If blood or blood products or fat emulsions are administered, change tubing every 24 hours. □ If propofol is administered, change tubing every 6-12 hours or when the vial is changed.
	□ Perform daily audits to assess if central line is still needed

(8, 23)

*This is the complete CDC checklist. Some recommendations are different from those in this paper or are not pertinent because they are specific to older patients. The recommendations in this paper reflect the nuances of care in the NICU.

Table 4. Considerations for Use of Lock Therapies in NICU Patients

Prophylactic Antimicrobial Lock Therapy	
Optimal Procedures:	• Pharmacy-dispensed volume-specific syringes for each lumen • Minimum dwell time of 4 hours, without disruption, while all lumens are locked • Changing all line lock solutions inserted into ports every 24 hours • Routine administration of a thrombolytic drug other than saline or heparin to maintain catheter patency (e.g., alteplase). Each lumen of the catheter should be easy to flush and aspirate. • VAT evaluation and intervention if unable to withdraw antimicrobial lock from any lumen
Do not use for:	• Infants with allergy to any component of antimicrobial lock therapy • 2 French or smaller PICCs, umbilical arterial and venous catheters, arterial lines, midline catheters, and peripheral intravenous catheters • Infants who are receiving continuous infusions that require a dedicated lumen line (e.g., amiodarone, heparin, narcotics, pressors, and TPN) • Obtaining antimicrobial levels
Do not use if:	• Lock is incompatible with catheter being used • Patency of line cannot be assessed • Logistical challenges of rotating lumens when multiple lumens and/or catheters require antimicrobial lock therapy make use ineffective
Considerations for Ethanol Lock Therapy	
Ethanol lock therapy has very limited use in the NICU (66, 68, 71).	
Do not use in:	• A non-silicone central catheter • A peripherally inserted central catheter
Do not use if:	• The catheter has more than 1 lumen • The infant is less than 6 months of age • The infant weighs less than 5 kg • The infant is receiving continuous infusions. Ethanol may precipitate if in contact with TPN and cause catheter occlusion. • Inability to maintain the lock for a minimum of 4 hours (optimal dwell time).
Do not mix with heparin.	

(97)

Table 5. Examples of Antimicrobial Locks

Antimicrobial Lock Therapy	Vial Concentration	Vol. 1mL	Vol. 2mL	Vol. 3mL	Vol. 5mL	Final Concentration	Stability
Vancomycin	Vancomycin 50 mg/mL vial	0.2	0.4	0.6	1.0	10 mg/mL	7 days refrigerated
	0.9% normal saline (NS)	0.8	1.6	2.4	4.4		
	Vancomycin 5 mg/mL solution (dilute with NS)	0.5	1.0	1.5	2.5	2.5 mg/mL	
	Heparin 100 units/mL	0.5	1.0	1.5	2.5	50 units/mL	
Gentamicin	Gentamicin 10 mg/mL vial	0.5	1.0	1.5	2.5	5 mg/mL	7 days refrigerated
	0.9% NS	0.5	1.0	1.5	2.5		
Ceftazidime	Ceftazidime 100mg/mL vial	0.1	0.2	0.3	0.5	10 mg/mL	7 days refrigerated
	Heparin 100 units/mL	0.5	1.0	1.5	2.5	50 units/mL	
	0.9% NS	0.4	0.8	1.2	2.0	-	
Amphotericin B*	Amphotericin B 5mg/mL vial	0.5	1.0	1.5	2.5	2.5 mg/mL	7 days refrigerated
	Heparin 100 units/mL	0.5	1.0	1.5	2.5	50 units/mL	

(97) *Rarely used since removal of catheter is recommended in the setting of fungemia.

Table 6. Antimicrobial Lock Implementation

Instilling an Antimicrobial Lock
1. Order the antimicrobial lock therapy through the electronic medical record system, if used in the facility, to avoid errors 2. Obtain pharmacy-dispensed volume-specific syringes for each lumen 3. Prepare for: a. 4 hours of dwell time (optimal) b. Changing all line locks solutions inserted into ports every 24 hours 4. Flush each lumen with 0.9% sodium chloride before instilling the antimicrobial lock 5. At the end of the dwell time, withdraw the instilled antimicrobial lock priming volume and discard. Some institutions will withdraw an additional 0.1 mL, or an additional percentage of the total volume 6. After removing and discarding the lock, flush the lumen(s) with 0.9% sodium chloride before infusion of other medications or fluids through the line 7. If patient is being transferred to a procedure area (line may be accessed), withdraw all lock solutions prior to patient leaving the unit 8. Obtain VAT evaluation and intervention if unable to withdraw antimicrobial lock from any lumen
Assessing Fill or Priming Volume of Existing CVCs
1. Perform hand hygiene 2. Disinfect cap/lumen connection with hospital-approved antiseptic 3. Clamp the lumen and remove existing needleless access device from the CVC hub of the lumen 4. Attach empty 3 mL luer-lock syringe directly to the hub of the lumen 5. Aspirate plunger slowly and gently until blood reaches the end of the hub 6. Clamp the line 7. Remove the syringe: the volume of fluid in the 3 mL syringe is the volume to be used for the lock volume 8. Attach a prime needleless access and flush the line

Table 7. Neonatal Vascular Access Team (VAT) Training, Evaluation, and Responsibilities

After receiving training, **who** may be a proceduralist on a Neonatal VAT?	Neonatal nurse practitioners, registered nurses (in accordance with State Board of Nursing scope of practice), neonatal fellows with appropriate supervision, neonatologists
What should **clinical training and education** for proceduralists include?	• Indications and contraindications of PICC placement • Increased awareness of pain management • Knowledge of the anatomy of venous and arterial systems • Maintenance of the sterile insertion bundle
What **knowledge and clinical competencies** should a proceduralist be able to demonstrate after training?	• Knowledge of published guidelines and standards of infusion therapy • Appropriate catheter care and maintenance • Ability to recognize and manage complications • Successful placement of at least 5 PICC lines
How many procedures should a proceduralist perform to maintain competency?	Proceduralists should consistently perform a requisite number of procedures, as defined by the local facility's delineation of privileges. At a minimum, a proceduralist should perform 5 successful PICC insertions per year.
What are examples of **quality measures** that a VAT should monitor?	• Success rate of individual proceduralists • Rates of complications (CLABSI, thrombus, pericardial and pleural effusions, etc.)

	• Confirmation of final line location via radiographic imaging or point-of-care ultrasound
What **additional responsibilities** might a VAT handle?	• Troubleshooting and managing complications • Providing formal and informal staff education related to care and maintenance of central lines • Performing catheter site surveillance and dressing changes • Discussing removal of PICC line when patient reaches 120 ml/kg/day of enteral intake (98).

(15, 99-101)

Figure 1. Representative Use of Antiseptics in the NICU at CHU Sainte-Justine (QC, Canada)*

	All Antiseptics		
Minimum contact time	>30 seconds		
Drying time	Let all dry completely		
	All Infants		
Vial cap	Alcohol 70% swab 		
Injections IM, SC, ID, etc.	Alcohol 70% swab 		
Injection site, needleless connectors, "scrub the hub"	Alcohol 70% swab 		
Blood procurement	Alcohol 70% swab 		
Age and weight / **Location**	• **<28 weeks' gestation *OR*** • **<1000g** ***AND*** • **<4 weeks of life**	**Everyone else** not included in columns to left or right	• **Term infant** ***AND*** • **≥4 weeks of life**
Blood cultures	CHG 2% aqueou 	CHG 0.5% + alcohol 70% swab 	CHG 2% + alcohol 70% swab 
Arterial draws	CHG 2% aqueou 	CHG 0.5% + alcohol 70% swab 	CHG 2% + alcohol 70% swab 
Peripheral IV insertion	CHG 2% aqueou 	CHG 0.5% + alcohol 70% swab 	CHG 2% + alcohol 70% swab 

CVC insertion (includes UVA/UVL, PICC)	CHG 2% aqueous swabstick 	CHG 0.5% + alcohol 70% swabstick 
CVC insertion site	CHG 2% aqueous swabstick 	CHG 0.5% + alcohol 70% swabstick 

*The recommendations in this table are presented as an example of how one hospital implemented CHG use in a NICU and are more detailed than the recommendations presented in the text.

References

1. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA. 2004;292:2357-65.

2. Bright HR, Babata K, Allred EN, Erdei C, Kuban KCK, Joseph RM, et al. Neurocognitive Outcomes at 10 Years of Age in Extremely Preterm Newborns with Late-Onset Bacteremia. J Pediatr. 2017;187:43-9 e1.

3. Bakhuizen SE, de Haan TR, Teune MJ, van Wassenaer-Leemhuis AG, van der Heyden JL, van der Ham DP, et al. Meta-analysis shows that infants who have suffered neonatal sepsis face an increased risk of mortality and severe complications. Acta Paediatr. 2014;103:1211-8..

4. Payne NR, Barry J, Berg W, Brasel DE, Hagen EA, Matthews D, et al. Sustained reduction in neonatal nosocomial infections through quality improvement efforts. Pediatrics. 2012;129:e165-73.

5. Schulman J, Stricof R, Stevens TP, Horgan M, Gase K, Holzman IR, et al. Statewide NICU central-line-associated bloodstream infection rates decline after bundles and checklists. Pediatrics. 2011;127:436-44.

6. Shepherd EG, Kelly TJ, Vinsel JA, Cunningham DJ, Keels E, Beauseau W, et al. Significant Reduction of Central-Line Associated Bloodstream Infections in a Network of Diverse Neonatal Nurseries. J Pediatr. 2015;167:41-6.e1.

7. Hsu HE, Mathew R, Wang R, Broadwell C, Horan K, Jin R, et al. Health Care-Associated Infections Among Critically Ill Children in the US, 2013-2018. JAMA Pediatr. 2020;174:1176-83.

8. Centers for Disease Control and Prevention. Checklist for Prevention of Central Line Associated Blood Stream Infections. Available from: https://www.cdc.gov/hai/pdfs/bsi/checklist-for-clabsi.pdf.

9. Recommendations for Prevention and Control of Infections in Neonatal Intensive Care Unit Patients: Central Line-Associated Bloodstream Infections. 2022.

10. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924-6.

11. Sandora TJ, Bryant KK, Cantey JB, Elward AM, Yokoe DS, Bartlett AH. SHEA neonatal intensive care unit (NICU) white paper series: Practical approaches to Clostridioides difficile prevention. Infect Control Hosp Epidemiol. 2018;39:1149-53.
12. Akinboyo IC, Zangwill KM, Berg WM, Cantey JB, Huizinga B, Milstone AM. SHEA neonatal intensive care unit (NICU) white paper series: Practical approaches to Staphylococcus aureus disease prevention. Infect Control Hosp Epidemiol. 2020;41:1251-7.
13. US Department of Health and Human Services. Supplemental New Drug Application. NDA 020832 ChloraPrep® [chlorhexidine gluconate (2% w/v) and isopropyl alcohol (70% v/v)] solution; NDA 021555 ChloraPrep® [chlorhexidine gluconate (2% w/v) and isopropyl alcohol (70% v/v)] solution 2012 [August 27, 2021]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/020832Origs030,021555Orig1s017ltr.pdf.
14. Sharma A, Kulkarni S, Thukral A, Sankar MJ, Agarwal R, Deorari AK, et al. Aqueous chlorhexidine 1% versus 2% for neonatal skin antisepsis: a randomised non-inferiority trial. Arch Dis Child Fetal Neonatal Ed. 2021;106:643-8.
15. Garland JS, Alex CP, Uhing MR, Peterside IE, Rentz A, Harris MC. Pilot trial to compare tolerance of chlorhexidine gluconate to povidone-iodine antisepsis for central venous catheter placement in neonates. J Perinatol. 2009;29:808-13.
16. Marschall J, Mermel LA, Fakih M, Hadaway L, Kallen A, O'Grady NP, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014;35:753-71.
17. Kieran EA, O'Sullivan A, Miletin J, Twomey AR, Knowles SJ, O'Donnell CPF. 2% chlorhexidine-70% isopropyl alcohol versus 10% povidone-iodine for insertion site cleaning before central line insertion in preterm infants: a randomised trial. Arch Dis Child Fetal Neonatal Ed. 2018;103:F101-F6.
18. Neri I, Ravaioli GM, Faldella G, Capretti MG, Arcuri S, Patrizi A. Chlorhexidine-Induced Chemical Burns in Very Low Birth Weight Infants. J Pediatr. 2017;191:262-5.e2.
19. Paternoster M, Niola M, Graziano V. Avoiding Chlorhexidine Burns in Preterm Infants. J Obstet Gynecol Neonatal Nurs. 2017;46:267-71.

20. The Joint Commision. Preventing Central Line-Associated Bloodstream Infections: Useful Tools, An International Perspective JointCommission.org: The Joint Commission; 2013 [cited 2021 August 29]. Available from: www.jointcommission.org/CLABSI/Toolkit.
21. Mobley RE, Bizzarro MJ. Central line-associated bloodstream infections in the NICU: Successes and controversies in the quest for zero. Semin Perinatol. 2017;41:166-74.
22. Bizzarro MJ, Sabo B, Noonan M, Bonfiglio MP, Northrup V, Diefenbach K, et al. A quality improvement initiative to reduce central line-associated bloodstream infections in a neonatal intensive care unit. Infect Control Hosp Epidemiol. 2010;31:241-8.
23. Compendium of Strategies to Prevent Central Line-Associated Bloodstream Infections in Acute Care Hospitals: 2022 Update. 2022.
24. D'Andrea V, Pezza L, Barone G, Prontera G, Pittiruti M, Vento G. Use of cyanoacrylate glue for the sutureless securement of epicutaneo-caval catheters in neonates. J Vasc Access. 2021:11297298211008103.
25. Bryant KA, Guzman-Cottrill JA, editors. Handbook of Pediatric Infection Prevention and Control. Oxford, UK: Oxford University Press; 2019.
26. NICE. Biopatch for venous or arterial catheter sites: Medtech innovation briefing (MIB117): National Institute for Health and Care Excellence (NICE); 2017 [updated August 9, 2017; cited 2021 December]. Available from: www.nice.org.uk/guidance/mib117.
27. Miller MR, Niedner MF, Huskins WC, Colantuoni E, Yenokyan G, Moss M, et al. Reducing PICU central line-associated bloodstream infections: 3-year results. Pediatrics. 2011;128:e1077-83.
28. NHS. Broviac Lines for Central Venous Access: A Guide for Neonatal Staff. In: Southern West MIdlands Newborn Network: Hereford W, Birmingham, Sandwell & Solihull, editor. Ed2014.
29. Lai NM, Taylor JE, Tan K, Choo YM, Ahmad Kamar A, Muhamad NA. Antimicrobial dressings for the prevention of catheter-related infections in newborn infants with central venous catheters. Cochrane Database Syst Rev. 2016;3:CD011082.
30. Johnson J, Bracken R, Tamma PD, Aucott SW, Bearer C, Milstone AM. Trends in Chlorhexidine Use in US Neonatal Intensive Care Units: Results From a Follow-Up National Survey. Infect Control Hosp Epidemiol. 2016;37:1116-8.

31. SHEA. Neonatal Intensive Care Unit (NICU) Survey on Infection Prevention Practices. [Survey]. Unpublished 2014.
32. Wright MO, Tropp J, Schora DM, Dillon-Grant M, Peterson K, Boehm S, et al. Continuous passive disinfection of catheter hubs prevents contamination and bloodstream infection. Am J Infect Control. 2013;41:33-8.
33. Sauron C, Jouvet P, Pinard G, Goudreault D, Martin B, Rival B, et al. Using isopropyl alcohol impregnated disinfection caps in the neonatal intensive care unit can cause isopropyl alcohol toxicity. Acta Paediatr. 2015;104:e489-93.
34. Hjalmarsson LB, Hagberg J, Schollin J, Ohlin A. Leakage of isopropanol from port protectors used in neonatal care-Results from an in vitro study. PLoS One. 2020;15:e0235593.
35. O'Connell S, Dale M, Morgan H, Carter K, Carolan-Rees G. Curos Disinfection Caps for the Prevention of Infection When Using Needleless Connectors: A NICE Medical Technologies Guidance. Applied health economics and health policy. 2021;19:145-53.
36. Voor In 't Holt AF, Helder OK, Vos MC, Schafthuizen L, Sulz S, van den Hoogen A, et al. Antiseptic barrier cap effective in reducing central line-associated bloodstream infections: A systematic review and meta-analysis. Int J Nurs Stud. 2017;69:34-40.
37. Helder OK, van Rosmalen J, van Dalen A, Schafthuizen L, Vos MC, Flint RB, et al. Effect of the use of an antiseptic barrier cap on the rates of central line-associated bloodstream infections in neonatal and pediatric intensive care. Am J Infect Control. 2020;48:1171-8.
38. Milstone AM, Rosenberg C, Yenokyan G, Koontz DW, Miller MR, Group CA. Alcohol-impregnated caps and ambulatory central-line-associated bloodstream infections (CLABSIs): A randomized clinical trial. Infect Control Hosp Epidemiol. 2021;42:431-9.
39. Marschall J, Mermel LA, Classen D, Arias KM, Podgorny K, Anderson DJ, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals. Infect Control Hosp Epidemiol. 2008;29 Suppl 1:S22-30.
40. Milstone AM, Elward A, Song X, Zerr DM, Orscheln R, Speck K, et al. Daily chlorhexidine bathing to reduce bacteraemia in critically ill children: a multicentre, cluster-randomised, crossover trial. Lancet. 2013;381:1099-106.
41. Johnson J, Suwantarat N, Colantuoni E, Ross TL, Aucott SW, Carroll KC, et al. The impact of chlorhexidine gluconate bathing on skin bacterial burden of neonates admitted to the Neonatal Intensive Care Unit. J Perinatol. 2019;39:63-71.

42. Sankar MJ, Paul VK, Kapil A, Kalaivani M, Agarwal R, Darmstadt GL, et al. Does skin cleansing with chlorhexidine affect skin condition, temperature and colonization in hospitalized preterm low birth weight infants?: a randomized clinical trial. J Perinatol. 2009;29:795-801.
43. Quach C, Milstone AM, Perpete C, Bonenfant M, Moore DL, Perreault T. Chlorhexidine bathing in a tertiary care neonatal intensive care unit: impact on central line-associated bloodstream infections. Infect Control Hosp Epidemiol. 2014;35:158-63.
44. Cleves D, Pino J, Patino JA, Rosso F, Velez JD, Perez P. Effect of chlorhexidine baths on central-line-associated bloodstream infections in a neonatal intensive care unit in a developing country. J Hosp Infect. 2018;100:e196-e9.
45. Milstone AM, Bamford P, Aucott SW, Tang N, White KR, Bearer CF. Chlorhexidine inhibits L1 cell adhesion molecule-mediated neurite outgrowth in vitro. Pediatric research. 2014;75:8-13.
46. Suwantarat N, Carroll KC, Tekle T, Ross T, Maragakis LL, Cosgrove SE, et al. High prevalence of reduced chlorhexidine susceptibility in organisms causing central line-associated bloodstream infections. Infect Control Hosp Epidemiol. 2014;35:1183-6.
47. Maki DG, Rosenthal VD, Salomao R, Franzetti F, Rangel-Frausto MS. Impact of switching from an open to a closed infusion system on rates of central line-associated bloodstream infection: a meta-analysis of time-sequence cohort studies in 4 countries. Infect Control Hosp Epidemiol. 2011;32:50-8.
48. Mahieu LM, De Dooy JJ, Lenaerts AE, Ieven MM, De Muynck AO. Catheter manipulations and the risk of catheter-associated bloodstream infection in neonatal intensive care unit patients. J Hosp Infect. 2001;48:20-6.
49. Dahan M, O'Donnell S, Hebert J, Gonzales M, Lee B, Chandran AU, et al. CLABSI Risk Factors in the NICU: Potential for Prevention: A PICNIC Study. Infect Control Hosp Epidemiol. 2016;37:1446-52.
50. Klunk CJ, Barrett RE, Peterec SM, Blythe E, Brockett R, Kenney M, et al. An Initiative to Decrease Laboratory Testing in a NICU. Pediatrics. 2021;148.
51. Coggins SA, Harris MC, Srinivasan L. Dual-site blood culture yield and time to positivity in neonatal late-onset sepsis. Arch Dis Child Fetal Neonatal Ed. 2021.
52. Miller JM, Binnicker MJ, Campbell S, Carroll KC, Chapin KC, Gilligan PH, et al. A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2018

Update by the Infectious Diseases Society of America and the American Society for Microbiology. Clin Infect Dis. 2018;67:813-6.
53. Woods-Hill CZ. Diagnostic Stewardship for Blood Cultures in Critically Ill Children: Results of the Bright STAR Collaborative. JAMA Pediatr. 2022.
54. Woods-Hill CZ, Koontz DW, Voskertchian A, Xie A, Shea J, Miller MR, et al. Consensus Recommendations for Blood Culture Use in Critically Ill Children Using a Modified Delphi Approach. Pediatr Crit Care Med. 2021;22:774-84.
55. Falagas ME, Kazantzi MS, Bliziotis IA. Comparison of utility of blood cultures from intravascular catheters and peripheral veins: a systematic review and decision analysis. J Med Microbiol. 2008;57:1-8.
56. Tang M, Feng M, Chen L, Zhang J, Ji P, Luo S. Closed blood conservation device for reducing catheter-related infections in children after cardiac surgery. Crit Care Nurse. 2014;34:53-60; quiz 1.
57. Oto J, Nakataki E, Hata M, Tsunano Y, Okuda N, Imanaka H, et al. Comparison of bacterial contamination of blood conservation system and stopcock system arterial sampling lines used in critically ill patients. Am J Infect Control. 2012;40:530-4.
58. Benedict A, Mayer A, Craven H. Closed arterial lab sampling devices: a study of compliance and best practice. Br J Nurs. 2017;26:S24-S9.
59. Filippi L, Pezzati M, Di Amario S, Poggi C, Pecile P. Fusidic acid and heparin lock solution for the prevention of catheter-related bloodstream infections in critically ill neonates: a retrospective study and a prospective, randomized trial. Pediatr Crit Care Med. 2007;8:556-62.
60. Garland JS, Alex CP, Henrickson KJ, McAuliffe TL, Maki DG. A vancomycin-heparin lock solution for prevention of nosocomial bloodstream infection in critically ill neonates with peripherally inserted central venous catheters: a prospective, randomized trial. Pediatrics. 2005;116:e198-205.
61. Seliem WA-H, Hesham; El-Nady, Ghada. Amikacin-heparin lock for prevention of catheter-related bloodstream infection in neonates with extended umbilical venous catheters use: A randomized controlled trial. Journal of neonatal-perinatal medicine. 2010;3:33-41.
62. Justo JA, Bookstaver PB. Antibiotic lock therapy: review of technique and logistical challenges. Infect Drug Resist. 2014;7:343-63.

63. CCHMC. Na citrate. Cincinnati Children's CCHMC Pharmacy & Therapeutics Policy2021.
64. Abu-El-Haija M, Schultz J, Rahhal RM. Effects of 70% ethanol locks on rates of central line infection, thrombosis, breakage, and replacement in pediatric intestinal failure. J Pediatr Gastroenterol Nutr. 2014;58:703-8.
65. Jones BA, Hull MA, Richardson DS, Zurakowski D, Gura K, Fitzgibbons SC, et al. Efficacy of ethanol locks in reducing central venous catheter infections in pediatric patients with intestinal failure. J Pediatr Surg. 2010;45:1287-93.
66. Ardura MI, Lewis J, Tansmore JL, Harp PL, Dienhart MC, Balint JP. Central catheter-associated bloodstream infection reduction with ethanol lock prophylaxis in pediatric intestinal failure: broadening quality improvement initiatives from hospital to home. JAMA Pediatr. 2015;169:324-31.
67. Mouw E, Chessman K, Lesher A, Tagge E. Use of an ethanol lock to prevent catheter-related infections in children with short bowel syndrome. J Pediatr Surg. 2008;43:1025-9.
68. Cober MP, Kovacevich DS, Teitelbaum DH. Ethanol-lock therapy for the prevention of central venous access device infections in pediatric patients with intestinal failure. JPEN J Parenter Enteral Nutr. 2011;35:67-73.
69. Pieroni KP, Nespor C, Ng M, Garcia M, Hurwitz M, Berquist WE, et al. Evaluation of ethanol lock therapy in pediatric patients on long-term parenteral nutrition. Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition. 2013;28:226-31.
70. Wales PW, Kosar C, Carricato M, de Silva N, Lang K, Avitzur Y. Ethanol lock therapy to reduce the incidence of catheter-related bloodstream infections in home parenteral nutrition patients with intestinal failure: preliminary experience. J Pediatr Surg. 2011;46:951-6.
71. Mezoff EA, Fei L, Troutt M, Klotz K, Kocoshis SA, Cole CR. Ethanol Lock Efficacy and Associated Complications in Children With Intestinal Failure. JPEN J Parenter Enteral Nutr. 2016;40:815-9.
72. Rahhal R, Abu-El-Haija MA, Fei L, Ebach D, Orkin S, Kiscaden E, et al. Systematic Review and Meta-Analysis of the Utilization of Ethanol Locks in Pediatric Patients With Intestinal Failure. JPEN J Parenter Enteral Nutr. 2018;42:690-701.

73. Chhim RF, Crill CM, Collier HK, Arnold SR, Pourcyrous M, Meibohm B, et al. Ethanol lock therapy: a pilot infusion study in infants. Ann Pharmacother. 2015;49:431-6.
74. Brooker RW, Keenan WJ. Catheter related bloodstream infection following PICC removal in preterm infants. J Perinatol. 2007;27:171-4.
75. Casner M, Hoesli SJ, Slaughter JC, Hill M, Weitkamp JH. Incidence of catheter-related bloodstream infections in neonates following removal of peripherally inserted central venous catheters. Pediatr Crit Care Med. 2014;15:42-8.
76. van den Hoogen A, Brouwer MJ, Gerards LJ, Fleer A, Krediet TG. Removal of percutaneously inserted central venous catheters in neonates is associated with the occurrence of sepsis. Acta Paediatr. 2008;97:1250-2.
77. Bhargava V, George L, Malloy M, Fonseca R. The Role of a Single Dose of Vancomycin in Reducing Clinical Sepsis in Premature Infants Prior to Removal of Peripherally Inserted Central Catheter: A Retrospective Study. Am J Perinatol. 2018;35:990-3.
78. Hoffman MA, Snowden JN, Simonsen KA, Nenninger TM, Lyden ER, Anderson-Berry AL. Neonatal late-onset sepsis following peripherally inserted central catheter removal: association with antibiotic use and adverse line events. J Infus Nurs. 2015;38:129-34.
79. Hemels MA, van den Hoogen A, Verboon-Maciolek MA, Fleer A, Krediet TG. Prevention of neonatal late-onset sepsis associated with the removal of percutaneously inserted central venous catheters in preterm infants. Pediatr Crit Care Med. 2011;12:445-8.
80. McMullan RL, Gordon A. Antibiotics at the time of removal of central venous catheter to reduce morbidity and mortality in newborn infants. Cochrane Database Syst Rev. 2018;3:CD012181.
81. Degraeuwe PL, Kessels AG. The removal-associated sepsis prevention trial in preterm newborns was ended in an untimely manner. Pediatr Crit Care Med. 2012;13:248-9.
82. Wyckoff MM, Sharpe EL. Peripherally Inserted Central Catheters: Guideline for Practice 3rd ed. Chicago, IL: National Association of Neonatal Nurses; 2015.
83. Krein SL, Kuhn L, Ratz D, Chopra V. Use of Designated Nurse PICC Teams and CLABSI Prevention Practices Among U.S. Hospitals: A Survey-Based Study. J Patient Saf. 2019;15:293-5.
84. Stevens TP, Schulman J. Evidence-based approach to preventing central line-associated bloodstream infection in the NICU. Acta Paediatr. 2012;101:11-6.

85. Segreti J, Garcia-Houchins S, Gorski L, Moureau N, Shomo J, Zack J, et al. Consensus conference on prevention of central line-associated bloodstream infections: 2009. J Infus Nurs. 2011;34:126-33.
86. Royer T. Implementing a better bundle to achieve and sustain a zero central line-associated bloodstream infection rate. J Infus Nurs. 2010;33:398-406.
87. Savage TJ, Lynch AD, Oddera SE. Implementation of a Vascular Access Team to Reduce Central Line Usage and Prevent Central Line-Associated Bloodstream Infections. J Infus Nurs. 2019;42:193-6.
88. Taylor T, Massaro A, Williams L, Doering J, McCarter R, He J, et al. Effect of a dedicated percutaneously inserted central catheter team on neonatal catheter-related bloodstream infection. Adv Neonatal Care. 2011;11:122-8.
89. Sharpe E, Pettit J, Ellsbury DL. A national survey of neonatal peripherally inserted central catheter (PICC) practices. Adv Neonatal Care. 2013;13:55-74.
90. National Healthcare Safety Network (NHSN). Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central Line Associated Bloodstream Infection) 2021. Available from: https://www.cdc.gov/nhsn/pdfs/pscmanual/4psc_clabscurrent.pdf.
91. Goldman J, Rotteau L, Shojania KG, Baker GR, Rowland P, Christianson MK, et al. Implementation of a central-line bundle: a qualitative study of three clinical units. Implement Sci Commun. 2021;2:105.
92. Zachariah P, Furuya EY, Edwards J, Dick A, Liu H, Herzig CT, et al. Compliance with prevention practices and their association with central line-associated bloodstream infections in neonatal intensive care units. Am J Infect Control. 2014;42:847-51.
93. Mathew R, Simms A, Wood M, Taylor K, Ferrari S, Rhein M, et al. Reduction of Central Line-associated Bloodstream Infection Through Focus on the Mesosystem: Standardization, Data, and Accountability. Pediatr Qual Saf. 2020;5:e272.
94. Paplawski S. Prevention of central line-associated bloodstream infections in the neonatal intensive care unit: A literature review. Journal of Neonatal Nursing. 2020;26(3):142-8.
95. Kaufman DA, Blackman A, Conaway MR, Sinkin RA. Nonsterile glove use in addition to hand hygiene to prevent late-onset infection in preterm infants: randomized clinical trial. JAMA Pediatr. 2014;168:909-16.

96. Payne V, Hall M, Prieto J, Johnson M. Care bundles to reduce central line-associated bloodstream infections in the neonatal unit: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2018;103:F422-F9.
97. Hospital SLCs. Antimicrobial Lock Therapy (ALT) Organizational Policies/Guidelines [Dec. 2021]. Available from: https://www.stlouischildrens.org/healthcare-professionals/resources/clinical-resources/antimicrobial-stewardship-program-asp.
98. Fisher D, Cochran KM, Provost LP, Patterson J, Bristol T, Metzguer K, et al. Reducing central line-associated bloodstream infections in North Carolina NICUs. Pediatrics. 2013;132:e1664-71.
99. Chapman AK, Aucott SW, Milstone AM. Safety of chlorhexidine gluconate used for skin antisepsis in the preterm infant. J Perinatol. 2012;32:4-9.
100. Mahieu LM, De Dooy JJ, De Muynck AO, Van Melckebeke G, Ieven MM, Van Reempts PJ. Microbiology and risk factors for catheter exit-site and -hub colonization in neonatal intensive care unit patients. Infect Control Hosp Epidemiol. 2001;22:357-62.
101. Mahieu LM, De Muynck AO, Ieven MM, De Dooy JJ, Goossens HJ, Van Reempts PJ. Risk factors for central vascular catheter-associated bloodstream infections among patients in a neonatal intensive care unit. J Hosp Infect. 2001;48:108-16.