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Recommendations for Prevention and Control of Infections in Neonatal Intensive Care Unit Patients: Central Line-associated Blood Stream Infections

Centers for Disease Control and Prevention
National Center for Emerging and Zoonotic Infectious Diseases
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A. Executive Summary

Recommendations for the Prevention and Control of Central Line-associated Blood Stream Infections in Neonatal Intensive Care Unit Patients provide new, evidence-based recommendations specific to the prevention and control of Central Line-associated Blood Stream Infections (CLABSI) in neonatal intensive care unit (NICU) patients. This document is one section of the full *Guideline for Infection Prevention and Control in Neonatal Intensive Care Unit Patients*. This guideline will be published in a segmental manner as sections are completed. This section does not provide a comprehensive set of infection control recommendations for the prevention of CLABSI in NICU patients. Core infection prevention and control recommendations for the prevention of CLABSI that apply across all healthcare settings are summarized in the Healthcare Infection Control Practices Advisory Committee (HICPAC) Core Practices document,[1] and the original recommendations can be found in the respective Centers for Disease Control and Prevention (CDC) and HICPAC Guidelines.[2]

This document is intended for use by infection prevention staff, healthcare epidemiologists, healthcare administrators, nurses, neonatologists, other healthcare personnel, and persons responsible for developing, implementing, and evaluating infection prevention and control programs for NICUs. The guideline can also be used as a resource for societies or organizations that wish to develop more detailed implementation guidance for the prevention of infection in NICU patients.

The recommendations were based on a systematic review of the best available evidence in the literature from the beginning date of each database through February 2017. Subject matter experts supplemented the literature search results by recommending relevant references published since February 2017. In order to provide explicit links between the evidence and recommendations, a GRADE approach was used to evaluate the strength and direction of the evidence and formulate recommendations. The Methods section of this guideline provides additional detail on the development of this document. Where evidence was insufficient to formulate evidence-based recommendations in this effort, interim guidance is available to inform the delivery of healthcare in NICUs. [SHEA neonatal intensive care unit (NICU) white paper series: Practical approaches for the prevention of central line-associated bloodstream infections].

The evidence review was guided by the following questions:

1. Does the use of non-sterile gloves after hand hygiene, compared with hand hygiene alone, prevent CLABSI in NICU Patients?
2. Does the use of one central line catheter type, compared with another, prevent CLABSI in NICU patients?
3. Does the use of one central line catheter insertion site, compared with another, prevent CLABSI in NICU patients?
4. Does the use of single-lumen, compared with double-lumen, umbilical venous catheters prevent CLABSI in NICU patients?
5. In NICU patients requiring skin antisepsis for catheter insertion and maintenance, does alcoholic chlorhexidine, compared with alcoholic povidone-iodine, prevent CLABSI?
6. Does chlorhexidine bathing, compared with no bathing or bathing with placebo, prevent CLABSI in NICU patients?
7. In NICU patients with central line catheters, does minimizing the number of times central line hubs are accessed prevent CLABSI?
8. In NICU patients with central line catheters, does the use of central line antimicrobial locks, compared with standard of care, prevent CLABSI?

9. What is the optimal duration of umbilical artery and umbilical venous catheters to prevent CLABSI in NICU patients?
10. What is the optimal duration for peripherally inserted central catheters to prevent CLABSI in NICU patients?
11. Does the use of a dedicated PICC care team, compared with standard of care, prevent CLABSI in NICU patients?
12. Does the use of "bundled" interventions for central line insertion and maintenance, compared with standard of care, prevent CLABSI in NICU patients?
13. What is the efficacy of prophylactic antimicrobials, compared with standard of care, to prevent CLABSI in NICU patients?
14. What is the efficacy of prophylactic anticoagulant infusions, compared with standard of care, to prevent CLABSI in NICU patients?

Readers wishing to examine the primary evidence underlying the recommendations are referred to the Evidence Review in the body of this document and to the Tables in the Appendix (Appendix, Section C). The Appendix contains clearly delineated search strategies, Evidence Tables containing study-level data, and GRADE Tables which aggregate the overall strength and direction of the evidence organized by outcome.

B. Summary of Recommendations

Key Question 1: Does the use of non-sterile gloves after hand hygiene, compared with hand hygiene alone, prevent CLABSI in NICU Patients?

Recommendation 1. The use of non-sterile gloves after hand hygiene, but before all patient contact, compared with hand hygiene alone, to reduce central line-associated bloodstream infection (CLABSI) in neonatal intensive care unit (NICU) patients, remains an unresolved issue. **No Recommendation**

- **Supporting Evidence:** One randomized, non-blinded, controlled trial.[3]
- **Level of Confidence in the Evidence:** The level of confidence in this evidence is moderate due to imprecision.
- **Benefits:** The evidence suggested a benefit to using non-sterile gloves after hand hygiene and prior to all patient contact to decrease possible CLABSI and gram-positive bloodstream infections (BSIs) in a subset of preterm infants (for infants <1000 g or <29 weeks gestational age and <8 days old) admitted into a single facility. Definitive CLABSI diagnosed using the 2008 National Healthcare Safety Network (NHSN) definition were not reduced.[4]
- **Risks and Harms:** Harms were not assessed in this study.
- **Resource use:** Implementing glove use after hand hygiene could likely result in an increase in material cost, but it is anticipated that this cost could be offset by the decrease in costs associated with CLABSI.
- **Benefit-Harm Assessment:** Even though harms were not assessed, the evidence suggested a potential benefit to implementing glove use after hand hygiene practices as a part of infection prevention and control practices with the potential to decrease possible CLABSI and gram-positive BSI in preterm infants.
- **Value Judgments:** Value judgments considered in the formulation of this recommendation include the age of the study compared to the current standard of care, and patient safety.
- **Intentional Vagueness:** The standard of care for hand hygiene in a given NICU may be different from the control in this study (alcohol hand rub or use of an antimicrobial soap, e.g., 2% chlorhexidine gluconate). Hand hygiene compliance reported in this study was 79%. It is unknown if similar outcomes would have been reported with higher compliance.
- **Exceptions:** There are no exceptions to this recommendation.

Key Question 2: Does the use of one central line catheter type, compared with another, prevent CLABSI in NICU patients?

Recommendation 2.A. Choose the central line type (e.g., umbilical venous catheter (UVC), peripherally inserted central catheter (PICC), tunneled catheter, etc.) based on the clinical needs of the neonatal intensive care unit (NICU) patient. **Recommendation**

Recommendation 2.B. The choice of central line type to insert in a neonatal intensive care unit (NICU) patient should not be based solely on central line-associated blood stream infection (CLABSI) prevention. **Recommendation**

- **Supporting Evidence:** Eleven observational studies.[5-15]
- **Level of Confidence in the Evidence:** The level of confidence in this evidence is very low due to imprecision: each study compared different interventions and reported heterogeneous outcome measures for infection. Three studies compared UVCs to PICCs. Six studies compared various catheter

types that included umbilical arterial catheters (UACs), UVCs, percutaneous arterial catheters, percutaneous venous catheters, peripherally inserted central catheters, phlebotomy catheters, extended dwell peripheral intravenous catheters (EPIV), and tunneled catheters. Four of these studies were conducted after the widespread implementation of central line insertion and maintenance bundles in 2010.

- **Benefits:** This evidence did not suggest clear benefit of one catheter type over another; however, the studies evaluated different patient populations with varying clinical indications for central venous access, which was likely reflected in the evidence. The variations in dwell time according to catheter type confounded interpretation of the results.
- **Risks and Harms:** One study suggested that the risk of infiltration was higher with PICCs than with other catheter types, and another suggested that the risk of infiltration was higher in EPIVs.
- **Resource Use:** One study reported that use of EPIVs is more cost effective than PICCs, however this study did not incorporate line success or the cost of hyaluronidase to treat EPIV infiltration into their assessment. Other than this study, the literature search did not retrieve data on the comparative material costs of different catheter types. It is likely that material and human resource costs for insertion and maintenance of each catheter type will vary from facility to facility. Insertion of some catheter types (i.e., tunneled catheters) requires technical expertise that may not be available in all facilities.
- **Benefit-Harm Assessment:** The balance of benefits and harms was unclear in this evidence. Factors that influence catheter type selection include, but are not limited to, the chronologic and gestational age of the patient, patient size, the presence or absence of congenital abnormalities, prior device utilization, and the projected duration of central venous catheterization. CLABSI prevention is not the primary consideration when choosing which catheter type to insert in a NICU patient.
- **Value Judgments:** Value judgments considered in the formulation of these recommendations include patient safety and economic and human resource costs.
- **Intentional Vagueness:** There is no intentional vagueness in these recommendations.
- **Exceptions:** There are no exceptions to these recommendations.

Key Question 3: Does the use of one central line catheter insertion site, compared with another, prevent - central line associated blood stream infection (CLABSI) in neonatal intensive care unit (NICU) patients?

Recommendation 3.A. Choose the insertion site appropriate to the central line type to be inserted in a neonatal intensive care unit (NICU) patient (e.g., UVC, PICC, etc.) based on the clinical needs of the patient. **Recommendation**

Recommendation 3.B. The choice of insertion site in a neonatal intensive care unit (NICU) patient should not be based solely on central line associated blood stream infection (CLABSI) prevention. **Recommendation**

- **Supporting Evidence:** Ten observational studies.[16-25]
- **Level of Confidence in the Evidence:** The level of confidence in this evidence was low due to inconsistent results or no difference. The studies reported heterogeneous outcome measures for infection. The two studies evaluating femoral lines vs. non-femoral lines were conducted in the same NICU with overlapping study periods.[19, 20] All studies were conducted prior to the widespread implementation of central line insertion and maintenance bundles in 2010.
- **Benefits:** The evidence was limited regarding the benefit of one insertion site versus another for percutaneous and tunneled catheters. No benefit of one site versus another was suggested for PICCs.

- **Risks and Harms:** Associations between adverse events and insertion sites were limited and inconsistent, but data suggested that adverse events were associated with upper extremities and non-femoral sites.
- **Resource Use:** The literature search did not retrieve studies comparing resource utilization associated with different insertion sites for tunneled catheters or PICCs. No difference in human or materials costs to place a catheter in one site or another are anticipated, but in two studies, the femoral insertion site was chosen only if insertion in other sites failed. If placement in the first insertion site chosen is technically more challenging and results in multiple attempts, both human and material costs could increase.
- **Benefit-Harm Assessment:** The benefit associated with different insertion sites was unclear. Limited data suggest an increase in adverse events associated with inserting PICCs in upper extremity sites and non-femoral sites. The choice of catheter insertion site is often limited by the availability of venous access sites in NICU patients.
- **Value Judgments:** Value judgments considered in the formulation of this recommendation include patient safety and economic and human resource costs, as well as practical considerations. There may be logistical challenges associated with maintaining femoral catheters in diapered children.
- **Intentional Vagueness:** There is no intentional vagueness in this recommendation.
- **Exceptions:** There are no exceptions to this recommendation.

Key Question 4: Does the use of single-lumen, compared with double-lumen, umbilical venous catheters prevent central line-associated blood stream infection (CLABSI) in neonatal intensive care unit (NICU) patients?

Recommendation 4. – Consider choosing the fewest number of lumens based on the clinical needs of the neonatal intensive care unit patient. **Conditional recommendation**

- **Supporting Evidence:** One randomized controlled trial[26], and two observational studies[24, 27]
- **Level of Confidence in the Evidence:** The level of confidence in this evidence is low due to imprecision.
- **Benefits:** Two observational studies[24, 27] reported an increase in the adjusted risk or odds of CLABSI with the use of double lumen catheters, compared with single lumen catheters, however there is concern for confounding by indication in these studies. The RCT[26] was small and reported no infections ; however, a reduction was found in the number of additional intravenous catheters required with the use of double-lumen catheters.[27]
- **Risks and Harms:** One observational study reported a non-significant increase in complications with double lumens compared with single lumens, however limited conclusions can be drawn from this because this increase also included CLABSI.[27] The RCT[26] reported no difference in adverse events. Notably, increasing number of lumens in other types of catheters has been associated with an increased risk of infection in adults.[28]
- **Resource Use:** No difference in human or material costs associated with the insertion and maintenance of single- versus double-lumen catheters was reported.
- **Benefit-Harm Assessment:** The balance of benefits or harms was inconsistent across studies; however, the confidence in this evidence is low because patients requiring more care will likely have more CVC inserted or more lumens in their CVCs. Thus, it is likely these studies are subject to confounding by indication. Future publications may change the strength and direction of this evidence. Increasing the number of lumens has been associated with increased risk of thrombotic and other infectious complications in adult populations.
- **Value Judgments:** Value judgments considered in the formulation of this recommendation include patient safety and economic and human resource costs.

- **Intentional Vagueness:** There is no intentional vagueness in this recommendation.
- **Exceptions:** There are no exceptions to this recommendation.

Key Question 5: In neonatal intensive care unit (NICU) patients requiring skin antisepsis for catheter insertion and maintenance, does the use of alcoholic chlorhexidine, compared with alcoholic povidone-iodine, prevent central line-associated blood stream infection (CLABSI)?

Recommendation 5. 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. Gestational age, chronologic age, and skin maturity should be considered when assessing risks and benefits of chlorhexidine-containing agents in determining eligible patients. **Conditional Recommendation.**

- **Supporting Evidence:** One randomized controlled trial.[29]
- **Level of Confidence in the Evidence:** The level of confidence in this evidence is very low due to indirectness and imprecision.
- **Benefits:** Alcoholic chlorhexidine gluconate (CHG) for skin preparation for central line insertion and maintenance for CLABSI prevention has demonstrated efficacy in other populations, compared to povidone iodine (PI). In NICU patients, a single study (Garland) reported no reduction in infections when using either alcoholic CHG or PI with an unspecified base for catheter insertion or maintenance.
- **Risks and Harms:** One study reported an increased incidence of CHG absorption after single use for skin preparation; no significant systemic side effects were observed. The clinical impact of this level of systemic CHG absorption on neonatal health and microbiome is unknown. Garland reported no increased risk of contact dermatitis, although the trial enrolled a select group of NICU patients (those weighing >1500 gm and >7 days of age). Harms were not assessed in smaller or younger infants.
- **Resource use:** There is no additional resource use as skin preparation for central line insertion and maintenance is standard of care. Minimal differences in human, education, and material costs between alcoholic CHG and alcoholic PI are anticipated.
- **Benefit-Harm Assessment:** The use of CHG for skin preparation is associated with both potential benefits and potential harms. The balance of benefits and harms may vary based on individual patient characteristics (e.g., gestational age, chronologic age, skin maturity).
- **Value Judgments:** Value judgments considered in the formulation of this recommendation include the age of the studies and the applicability of the evidence base, the current standard of care, and patient safety.
- **Intentional Vagueness:** The NICU populations for whom CHG skin antisepsis is most appropriate are not clearly defined.
- **Exceptions:** Alcoholic chlorhexidine will not be appropriate for all NICU patients.

Key Question 6: Does chlorhexidine bathing, compared with no bathing or bathing with placebo, prevent central line-associated blood stream infection (CLABSI) in neonatal intensive care unit (NICU) patients?

Recommendation 6.A. Consider use of chlorhexidine bathing 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. **Conditional Recommendation**.

Recommendation 6.B. The identification of neonatal intensive care unit (NICU) patients who might benefit from chlorhexidine bathing remains an unresolved issue. **No recommendation**.

Recommendation 6.C. If undertaken, the frequency of chlorhexidine bathing for neonatal intensive care unit (NICU) patients remains an unresolved issue. **No recommendation**.

- **Supporting Evidence:** One randomized controlled trial[30] and 3 observational studies.[31-33]
- **Level of Confidence in the Evidence:** The level of confidence in this evidence is low due to imprecision. One of the studies was published prior to the widespread implementation of central line insertion and maintenance bundles in 2010.
- **Benefits:** The efficacy of CHG bathing to prevent CLABSI has been demonstrated in other populations. This evidence suggested a benefit to routine CHG bathing for NICU patients in facilities with high baseline rates despite implementation of, and adherence to, insertion and maintenance bundles and infection prevention and control practices. The evidence suggested no benefit to a single CHG bath.
- **Risks and Harms:** Hypothermia was not observed when using CHG washcloths for a single bath.[30] All three studies reported no skin reaction associated with CHG bathing with washcloths or solutions. CHG resistance was not assessed in any of the studies, nor was systemic absorption or effects on the microbiome.
- **Resource use:** Implementing CHG bathing could result in an increase in human, education, and material cost, but it is anticipated that this cost could be offset by the decrease in costs associated with CLABSI.
- **Benefit-Harm Assessment:** The evidence suggested a benefit to routine CHG bathing in facilities with high baseline CLABSI rates despite implementation of, and adherence to, insertion and maintenance bundles and infection prevention and control practices. Other adverse events were not reported in association with CHG bathing. The long-term impact of CHG bathing on the development of resistance and cross-resistance was not adequately assessed in the evidence.
- **Value Judgments:** Value judgments considered in the formulation of these recommendations include the age of the studies compared to the current standard of care, and patient safety.
- **Intentional Vagueness:** The delivery method for CHG bathing (impregnated bath wipes vs traditional bath), the frequency of bathing, and the target population are left intentionally vague in these recommendations.
- **Exceptions:** CHG bathing will not be appropriate for all NICU patients.

Key Question 7: In neonatal intensive care unit (NICU) patients with central line catheters, does minimizing the number of times central line hubs are accessed prevent central line-associated blood stream infection (CLABSI)?

Recommendation 7. Minimize the number of times central line hubs are accessed and minimize blood sampling through central lines to decrease the risk for central line-associated blood stream infection (CLABSI) in neonatal intensive care unit (NICU) patients. **Recommendation**

- **Supporting Evidence:** One observational study.[34]
- **Level of Confidence in the Evidence:** The level of confidence in this evidence is very low due to imprecision.
- **Benefits:** The evidence suggested an association between increased catheter manipulations and an increase in catheter-associated bloodstream infections.
- **Risks and Harms:** Potential harms associated with reduced catheter manipulations were not reported.
- **Resource Use:** Reducing the number of times catheters are physically accessed could reduce human and material costs because supplies are needed every time the line is accessed; however, thoughtful planning and coordination of multiple access needs is required to achieve this reduction.
- **Benefit-Harm Assessment:** The evidence suggests benefit to reducing catheter hub manipulations. Reducing the number of times central line hubs are accessed is considered standard of care, and it is unlikely that future research will be conducted in this area.
- **Value Judgments:** Value judgments considered in the formulation of this recommendation include patient safety and economic and human resource costs.

- **Intentional Vagueness:** "Central line hub access" is left intentionally vague to capture the range of possible manipulations to the hub (e.g., disinfection, access). Strategies to decrease catheter hub manipulation were not assessed.
- **Exceptions:** There are no exceptions to this recommendation.

Key Question 8: In neonatal intensive care unit (NICU) patients with central line catheters, does the use of central line antimicrobial locks, compared with standard of care, prevent central line-associated blood stream infection (CLABSI)?

Recommendation 8. Consider central line antimicrobial locks for neonatal intensive care unit (NICU) patients in addition to core infection prevention and control strategies when a unit is experiencing ongoing central line-associated blood stream infection (CLABSIs). **Conditional Recommendation.**

- **Supporting Evidence:** Three randomized controlled trials.[35-37]
- **Level of confidence in evidence:** The level of confidence in this evidence is high because randomized controlled trials are considered at low risk of bias; however, the level of confidence could decrease due to indirectness, as the studies were not conducted in the current standard of care.
- **Benefits:** A reduction in definite catheter-related blood stream infection (CRBSI) was seen in all three studies. No benefit was seen in the outcomes of suspected or probable CRBSI, or BSI without a source.
- **Risks and Harms:** Harms that could result from this recommendation include hypoglycemia, adverse product-related events, and the development of antimicrobial resistance to the agent used. The presence of a lock results in the interruption of fluid to the neonate: asymptomatic hypoglycemia occurred in greater than 10% of infants during use of the locks, whether the lock contained antibiotics-heparin or saline-heparin. In one study, antibiotic levels were not detected in the majority of NICU infants' blood, and when antibiotics were detected, they were at very low levels.
- **Benefit-Harm Assessment:** The benefits of CRBSI reduction are balanced with the potential harms of hypoglycemia and the development of antimicrobial resistance. However, all three studies reported high baseline CRBSI rates, which may confound the benefit, as the implementation of evidence-based insertion and maintenance practices has resulted in baseline CRBSI rates that are much lower than the baseline rates at the time of the studies. In the context of high baseline rates, these benefits may outweigh the harms.
- **Resource use:** The use of antimicrobial lock prophylaxis will result in increased human and material cost; however, in the context of high baseline rates, it is anticipated that this cost could be offset by the decrease in costs associated with reduced infections.
- **Value judgments:** Value judgments considered in the formulation of this recommendation include patient safety, facility infection rates, economic and human resource use, and the development of antimicrobial resistance.
- **Intentional vagueness:** The antimicrobial agent is not specified in this recommendation. Facilities with ongoing CLABSIs can review their antibiograms and the causal bacteria when determining the optimal antibiotic agent. Not all catheters may be compatible with all antimicrobial agents.
- **Exceptions:** Some NICU patients require continuous infusions that cannot be interrupted.

Key Question 9: What is the optimal duration of umbilical artery and umbilical venous catheters to prevent central line-associated blood stream infection (CLABSI) in neonatal intensive care unit (NICU) patients?

Recommendation 9.A. Remove umbilical venous and umbilical arterial catheters in neonatal intensive care unit (NICU) patients as soon as possible and when no longer needed due to the concern for increasing risk of

central line-associated blood stream infection (CLABSI) associated with each day of increasing dwell time.
Recommendation

- **Supporting Evidence:** One randomized controlled trial[38] and five observational studies.[6, 11, 39, 40 27]
- **Level of Confidence in the Evidence:** The level of confidence in this evidence is very low due to imprecision. Two studies were conducted in the current standard of care.[27, 40]
- **Benefits:** Increasing risk of infection was reported with increasing UVC dwell time, suggesting a benefit to removing UVCs at the earliest opportunity. Three studies suggested the risk of CLABSI was notably different at either 4 days[11] or 7 days;[39] however, two studies used data collected after the widespread implementation of central line insertion and maintenance bundles in 2010 . One of the two studies to be conducted in this era[27, 40] suggested a slight increase in risk at 7 days of dwell time, but the more substantial increases in risk occurred at 14 days of use. The other study noted no difference in CLABSI when UVC duration was extended from 5 to 7 days as a part of a quality improvement (QI) initiative.
- **Risks and Harms:** The evidence suggested that increasing dwell time for UVCs resulted in an increase in the risk of infections, with no difference in other adverse events.
- **Resource Use:** The impacts of reducing UVC dwell time on material and human resource costs is unknown.
- **Benefit-Harm Assessment:** While the evidence did not indicate an optimal day by which to remove a UVC to prevent CLABSI, the benefits of removing UVCs at the earliest opportunity outweigh the harms. It is important to note that UVC dwell time and the risk of CLABSI is only one consideration to balance in the clinical needs of a patient.
- **Value Judgments:** Value judgments considered in the formulation of this recommendation include patient safety and economic and human resource costs.
- **Intentional Vagueness:** Facilities can determine the need for longer-term access based on patient characteristics.
- **Exceptions:** There are no exceptions to this recommendation.

Recommendation 9.B. Consider removal of umbilical artery catheters at or before 7 days of dwell time in neonatal intensive care unit (NICU) patients. **Conditional Recommendation**

- **Supporting Evidence:** Two observational studies.[6, 27]
- **Level of Confidence in the Evidence:** The level of confidence in this evidence is low because observational studies start at low quality evidence in the GRADE methodology. One study[6] was not conducted in the current standard of care.
- **Benefits:** Increasing risk of infection was reported with increasing UAC dwell time in one study[6], suggesting a benefit to removing UACs at the earliest opportunity. The study suggested the risk of sepsis was higher in UACs in situ for ≥8 days when compared with those in situ for ≤7 days. The other study[27] reported two CLABSI, and limited conclusions can be drawn on the impact of UAC dwell time on the risk of CLABSI in this population.
- **Risks and Harms:** The evidence suggested that increasing dwell time for UACs was associated with a higher proportion of infections including occlusion and thrombosis.
- **Resource use:** The impact of reducing UAC dwell time on material and human resource costs is unknown.
- **Benefit-Harm Assessment:** While the evidence suggested the optimal duration for UACs may be up to 7 days, the data did not provide certainty regarding the optimal day for UAC removal to prevent CLABSI. It

is important to note that UAC dwell time and the risk of CLABSI is only one consideration to balance in the clinical needs of a patient.

- **Value Judgments:** Value judgments considered in the formulation of this recommendation include patient safety and economic and human resource costs.
- **Intentional Vagueness:** Facilities can determine the need for longer-term access based on patient characteristics.
- **Exceptions:** There are no exceptions to this recommendation.

Recommendation 9.C. Consider removal of umbilical venous catheters at or before 7 days of dwell time in neonatal intensive care unit (NICU) patients. **Conditional Recommendation**

- **Supporting Evidence:** Four observational studies.[6, 11, 27, 40]
- **Level of Confidence in the Evidence:** The level of confidence in this evidence is very low due to imprecision and inconsistency across studies. Only one study was conducted in the current standard of care.[40]
- **Benefits:** Increasing risk of infection was reported in association with increasing UVC dwell time, suggesting a benefit to removing UVCs at the earliest opportunity. One study suggested the risk of CLABSI was significantly different at 4 days;[11] however, this study used data collected before the widespread implementation of central line insertion and maintenance bundles in 2010. Two studies were conducted in this era[27, 40] and noted no difference in CLABSI when UVC duration was extended from 5 to 7 days as a part of a quality improvement (QI) initiative. The other reported an increase in risk at 7 days followed by a three-fold increase in risk at 14 days.
- **Risks and Harms:** The evidence suggested that increasing dwell time for UVCs resulted in an increase in the risk of infections, and one of the two studies[27, 40] suggested adverse events such as occlusion were associated with increasing dwell time.
- **Resource Use:** The impact of reducing UVC dwell time on material and human resource costs is unknown.
- **Benefit-Harm Assessment:** While the evidence did not suggest an optimal day by which to remove a UVC to prevent CLABSI, the benefits of removal of UVCs at the earliest opportunity outweigh the harms. The data also did not support extending UVC dwell time past 7 days. It is important to note that UVC dwell time and the risk of CLABSI is only one consideration to balance in the clinical needs of a patient.
- **Value Judgments:** Value judgments considered in the formulation of this recommendation include patient safety and economic and human resource costs.
- **Intentional Vagueness:** Facilities can determine the need for longer-term access based on patient characteristics.
- **Exceptions:** There are no exceptions to this recommendation.

Recommendation 9.D. Consider removal of umbilical venous catheters and inserting a peripherally inserted central catheter (PICC) or other long-term central venous catheter at or before 7 days of umbilical venous catheter dwell time for neonatal intensive care unit (NICU) patients requiring long-term central venous access. **Conditional Recommendation**

- **Supporting Evidence:** One randomized controlled trial[38] and three observational studies.[11, 39, 40]
- **Level of Confidence in the Evidence:** The level of confidence in this evidence is low due to imprecision. Only one study was conducted in the current standard of care.[40]
- **Benefits:** Increasing risk of infection was reported with increasing UVC dwell time, suggesting a benefit to removing UVCs at the earliest opportunity. Two studies suggested the risk of CLABSI was significantly

different at either 4 days[11] or 7 days;[39] however, neither study used data collected after the widespread implementation of central line insertion and maintenance bundles in 2010. The only study to be conducted in this era[40] noted no difference in CLABSI when UVC duration was extended from 5 to 7 days as a part of a quality improvement (QI) initiative.

- **Risks and Harms:** The evidence suggested that increasing dwell time for UVCs resulted in an increase in infection risk, with no difference in other adverse events.
- **Resource Use:** The impact of reducing UVC dwell time on material and human resource costs is unknown.
- **Benefit-Harm Assessment:** While the evidence did not suggest an optimal day by which to replace a UVC with a longer-term catheter to prevent CLABSI, the benefits of replacement with a longer-term catheter at the earliest opportunity outweigh the harms. The data also did not support extending UVC dwell time past 7 days. It is important to note that UVC dwell time and the risk of CLABSI is only one consideration to balance in the clinical needs of a patient.
- **Value Judgments:** Value judgments considered in the formulation of this recommendation include patient safety and economic and human resource costs.
- **Intentional Vagueness:** Facilities can determine the need for longer term access based on patient characteristics.
- **Exceptions:** There are no exceptions to this recommendation.

Key Question 10: What is the optimal duration for peripherally inserted central catheters to prevent central line-associated blood stream infection (CLABSI) in neonatal intensive care unit (NICU) patients?

Recommendation 10.A. For neonatal intensive care unit (NICU) patients, remove peripherally inserted central catheters (PICCs) as soon as possible and when no longer needed due to the concern for increasing risk of central line-associated blood stream infection (CLABSI) associated with increasing dwell time. **Recommendation**

Recommendation 10.B. For neonates with ongoing need for central venous access, whether to remove and replace a peripherally inserted central catheter (PICC) that has been in place for a prolonged period of time to reduce central line-associated blood stream infection (CLABSIs) in neonatal intensive care unit (NICU) patients remains an unresolved issue. **No Recommendation**

- **Supporting Evidence:** Eight observational studies.[10, 11, 41-46]
- **Level of Confidence in the Evidence:** The level of confidence in this evidence is very low due to imprecision from heterogeneous outcome definitions and methodologies across studies.
- **Benefits:** The evidence suggested a decreased risk of infection with decreasing PICC dwell time. In some patients, risk is higher in the first two weeks than in the last two weeks; however, there is not clear per-day increase in risk that represents an "inflection point."
- **Risks and Harms:** An increasing risk of infection with an increasing PICC dwell time was reported, but no specific inflection point was determined to suggest that infection risk increases at a specific time. Other PICC-related harms were not reported in relation to dwell time.
- **Resource use:** The impact of reducing PICC dwell time on material and human resource costs is unknown.
- **Benefit-Harm Assessment:** The evidence suggested a decreased risk of infection with decreasing dwell time, and no harms were reported in association with decreased dwell time. Each study assessed different durations of risk for infection, and none of the studies was able to control for how

infection risk may vary over time, precluding confidence in an optimal catheter day for PICC removal to prevent CLABSI.

- **Value Judgments:** Value judgments considered in the formulation of this recommendation include patient safety and economic and human resource costs.
- **Intentional Vagueness:** There is no intentional vagueness in this recommendation.
- **Exceptions:** There are no exceptions to this recommendation.

Key Question 11: Does the use of dedicated catheter care teams compared with standard of care, prevent central line-associated blood stream infection (CLABSI) in neonatal intensive care unit (NICU) patients?

Recommendation 11. Consider implementing a dedicated catheter care team to prevent central line-associated blood stream infection (CLABSI) in neonatal intensive care unit (NICU) patients. **Conditional recommendation**

- **Supporting Evidence:** Two observational studies. [47, 48]
- **Level of Confidence in the Evidence:** The level of confidence in this evidence is very low due to imprecision.
- **Benefits:** The evidence consisted of two studies, one reported the clinical outcome of CRBSI and the other reported the surveillance outcome of CLABSI, and both suggested a decrease in risk of infection with the use of a catheter care team in NICU patients. One study suggested CRBSI reductions when patients were stratified by duration of catheter use: patients with an indwelling central line ≥30 days had a 50% lower risk of CRBSIs, while there was no difference in risk of CRBSI for patients with an indwelling catheter <30 days. Another study reported a decrease in CLABSI rate, regardless of birthweight when a catheter care team was implemented.
- **Risks and Harms:** Harms attributable to the catheter care team were not reported.
- **Resource use:** Implementing a catheter care team could result in an increase in human resource cost, but it is anticipated that this cost could be offset by the decrease in costs associated with CLABSI.
- **Benefit-Harm Assessment:** The benefits outweighed the harms.
- **Value Judgments:** Value judgments considered in the formulation of this recommendation include the age of the studies compared to the current standard of care, and patient safety.
- **Intentional Vagueness:** The composition of the catheter care team and assigned duties are not specified.
- **Exceptions:** Exceptions do not apply to an unresolved issue.

Key Question 12: What are the optimal elements of central line insertion and maintenance bundles to prevent central line-associated blood stream infection (CLABSI) in neonatal intensive care unit (NICU) patients?

Recommendation 12. Use “bundled” interventions for central line insertion and maintenance as part of a single or multiple intervention quality improvement effort to reduce rates of central line-associated blood stream infection (CLABSI) in neonatal intensive care unit (NICU) patients. Elements of insertion and maintenance bundles for all patients have been recommended by the Centers for Disease Control and Prevention.[49] **Recommendation**

- **Supporting Evidence:** Three observational studies.[50-52]
- **Level of Confidence in the Evidence:** The level of confidence in this evidence is low.
- **Benefits:** The evidence suggested a benefit to using insertion and maintenance bundles to decrease CLABSI. The evidence did not suggest a benefit to one bundle element or a specific combination of bundle elements over another.

- **Risks and Harms:** Harms of neither specific, nor bundled, interventions were assessed in the studies.
- **Resource use:** Implementing insertion and maintenance checklists or bundles could result in an increase in material and human resource cost, but it is anticipated that this cost could be offset by the decrease in costs associated with CLABSI.
- **Benefit-Harm Assessment:** Even though harms were not assessed, the evidence suggested a benefit to implementing insertion and maintenance bundles as part of infection prevention and control practices with the potential to decrease CLABSI.
- **Value Judgments:** Value judgments considered in the formulation of this recommendation include the age of the studies compared to the current standard of care, and patient safety. Use of insertion and maintenance bundles has become the standard of care in patients with central lines, including NICU patients.
- **Intentional Vagueness:** The components of insertion and maintenance bundles studied in NICU patients vary, and no study has compared the effectiveness of one bundle versus another in this population. The optimal components of NICU-specific bundles, above and beyond the standard measures recommended by CDC, cannot be determined from the available evidence.
- **Exceptions:** There are no exceptions to this recommendation.

Key Question 13: What is the efficacy of prophylactic antimicrobials, compared with standard of care, to prevent central line-associated blood stream infection (CLABSI) in neonatal intensive care unit (NICU) patients?

Recommendation 13. Do not use prophylactic antimicrobial infusions routinely to decrease the risk of bacterial central line-associated blood stream infection (CLABSI) in neonatal intensive care unit (NICU) patients. **Recommendation.**

- **Supporting Evidence:** One randomized controlled trial[53] and 3 observational studies.[54-56]
- **Level of Confidence in the Evidence:** The level of confidence in this evidence is very low due to imprecision resulting from different definitions of outcome measures across studies. One study was considered at high risk of bias. All of the studies were published prior to the widespread implementation of central line insertion and maintenance bundles in 2010.
- **Benefits:** Prophylactic amoxicillin did not result in a reduction of infections. The use of vancomycin prophylaxis did result in a reduction in coagulase-negative staphylococci (CoNS)-related bloodstream infections.
- **Risks and Harms:** An increase in the incidence of thrombotic events was associated with the administration of prophylactic amoxicillin. The long-term impacts of prophylaxis on the development of antimicrobial resistance and the neonatal microbiome were not adequately assessed in these studies.
- **Resource use:** One study reported that prophylactic vancomycin resulted in a reduction in overall administration of vancomycin when compared to treatment only with vancomycin; however, this study was small, and its results may not be applicable in every environment.
- **Benefit-Harm Assessment:** The benefits do not clearly outweigh the harms given concerns for the development of antimicrobial resistance. All of the studies were published prior to 2004, and the impact of the use of prophylactic antimicrobials in the current standard of care is unknown.
- **Value Judgments:** Value judgments considered in the formulation of this recommendation include the time since publication of the studies, patient safety, resource use, and the development of antimicrobial resistance.
- **Intentional Vagueness:** There is no intentional vagueness in this recommendation.
- **Exceptions:** There are no exceptions to this recommendation.

Key Question 14: What is the efficacy of prophylactic anticoagulant infusions, compared with standard of care, to prevent central line-associated blood stream infection (CLABSI) in neonatal intensive care unit (NICU) patients?

Recommendation 14. Do not use prophylactic anticoagulant infusions for the purposes of preventing central line-associated blood stream infection (CLABSI) in neonatal intensive care unit (NICU) patients.
Recommendation

- **Supporting Evidence:** Four randomized controlled trials.[57-60]
- **Level of Confidence in the Evidence:** The level of confidence in this evidence is moderate due to inconsistent results across studies, heterogeneous outcome measures, and heterogeneous heparin preparations used across studies. All of the studies were published before the widespread implementation of central line insertion and maintenance bundles in 2010.
- **Benefits:** No reduction in catheter-related sepsis associated with the use of prophylactic anticoagulants was reported. Reduction in occlusion was inconsistent across studies.
- **Risks and Harms:** Administering anticoagulant comes with the risk of harm; however, the evidence reported no increase in intravascular hemorrhaging associated with the use of prophylactic anticoagulants.
- **Resource Use:** While resource use data were not retrieved by this literature search, theoretically the implementation of prophylactic heparin could likely increase human and material costs.
- **Benefit-Harm Assessment:** No benefits were reported, and there is concern that harms are under-reported. There are reasons other than the prevention of CLABSI to administer prophylactic anticoagulants.
- **Value Judgments:** Value judgments considered in the formulation of this recommendation include patient safety and economic and human resource costs.
- **Intentional Vagueness:** There may be clinical reasons other than the prevention of CLABSI to use prophylactic heparin. The specific anticoagulant agent is left intentionally vague in this recommendation.
- **Exceptions:** There are no exceptions to this recommendation.

C. Introduction

Central line-associated bloodstream infection (CLABSI) cause significant patient harm across patient populations, especially NICU patients. In this vulnerable population, CLABSIs increase adverse neurodevelopmental outcomes, adjusted hospital costs, lengths of stay and mortality.[34, 61, 62] Factors that increase the risk for CLABSI include intrinsic factors, such as immunologic immaturity and poor skin integrity, and extrinsic factors, such as frequent and prolonged catheter use and frequent catheter manipulation associated with the need for medication and total parenteral nutrition.

A robust body of evidence supports effective strategies to prevent CLABSIs in adults, and to a large extent, older children. Data in NICU patients are more limited. Efforts to develop evidence-based recommendations for CLABSI-prevention in NICUs are complicated by the heterogeneity in settings and the populations they serve. The risks for infection as well as the feasibility of specific infection prevention strategies differ for a 500-gram infant born at 24 weeks gestation and a term infant who needs surgery to correct a congenital malformation. Clinical decisions that have the potential to increase or decrease the risk for CLABSI (e.g., the choice of central line type or insertion site, the timing of catheter removal or replacement) are primarily determined by considerations other than infection prevention, alone. Factors such as gestational and chronologic age, skin

maturity, and the presence of co-morbidities will affect decisions regarding central line use, and these decisions are made on a patient-by-patient basis, weighing relative risks and benefits for each individual. At the unit level, factors such as patient acuity, patient mix, central venous catheter utilization, and length of stay, impact CLABSI rates and may shape prevention efforts. The needs and resources of Level II NICU in a community hospital may be different than Level IV NICU that serves as a regional referral center for infants with the most complex problems.

Nevertheless, single centers and multi-center collaboratives have demonstrated that reductions in CLABSI are possible with implementation of bundled interventions focused on central line insertion and maintenance.[50, 63] The components of these bundles vary, raising questions about which interventions are essential to prevention efforts.

This Guideline was developed to provide targeted, evidence-based recommendations for the prevention of CLABSI in NICU patients. When considering how and when to implement these recommendations, healthcare facilities should consider the characteristics of the population they serve, individual patient needs, and baseline CLABSI rates. Healthcare facilities should use their own data to determine when to add interventions and where to target prevention efforts when infections are occurring. As a part of a comprehensive infection prevention and control strategy, healthcare providers can employ a quality improvement framework to maximize efficiency in reducing infections in their facility. Tools such as CDC's Targeted Assessment for Prevention (TAP) Strategy Toolkit enable hospitals to target locations within facilities, assess gaps, and implement interventions to prevent CLABSI.[64] For important topics where evidence was insufficient to formulate evidence-based recommendations, companion guidance is available to inform the delivery of healthcare in NICUs [link to SHEA Companion Document]. Additionally, guidance is available elsewhere regarding the management of CLABSIs in healthcare settings.[2]

D. Methods

This guideline is based on a targeted, systematic review of the best available evidence on the prevention and control of infections in NICUs.

D.1. Development of Key Questions

In order to inform the development of the Central Line-associated Blood Stream Infections (CLABSI) Key Questions, electronic searches were conducted to retrieve existing relevant guidelines and to identify gaps and areas where new evidence may have been published. The strategies used for the guideline searches and results can be found in the *Appendix.* (Appendix Section A) The results of this initial review informed the development of a preliminary list of Key Questions. Key Questions were finalized after vetting them with HICPAC.

D.2. Literature Search

A list of search terms was developed to identify the literature most relevant to the Key Questions. The terms were incorporated into search strategies, and these searches were performed in MEDLINE, EMBASE, CINAHL, and the Cochrane Library. Subject matter experts supplemented the literature search results by recommending relevant references published after the final search in May 2021.

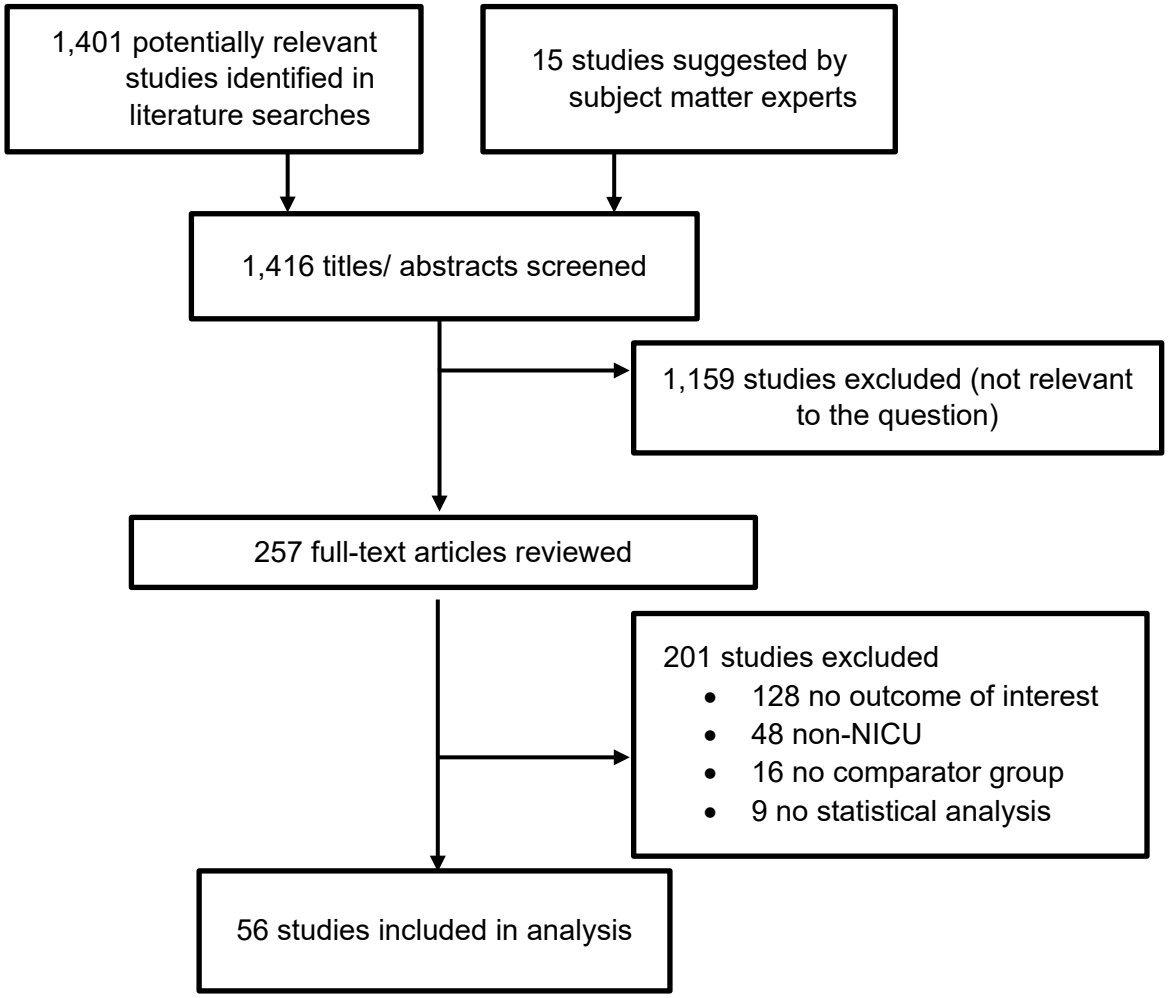
D.3. Study Selection

Titles and abstracts from references were screened by dual review (A.E., C.H., J.H., M.I., A.D.O., K.T.R., S.S., or E.C.S.). Full-text articles were retrieved if they were:

1. Relevant to one or more Key Question(s);
2. Primary research, systematic reviews, or meta-analyses; and
3. Written in English.

The *Appendix* presents the full list of exclusion criteria. (Appendix Section B) The full texts of selected articles were then screened by two independent reviewers, and disagreements were resolved by discussion (K.B., A.E., L.F., J.H., W.C.H., M.I., A.M., A.D.O., K.T.R., S.S., N.S., or E.C.S.). After the full-text screening was complete, a bibliography of the articles selected for inclusion was vetted with subject matter experts. Additional studies suggested by the subject matter experts were screened for inclusion as described above. The results of the study selection process are depicted in *Figure 1.*

Figure 1. Results of the Study Selection Process



D.4. Data Extraction and Synthesis

Methodologic data and results of clinically relevant outcomes from the studies meeting inclusion criteria were extracted into standardized evidence tables. Data and analyses were extracted as presented in the studies. For the purposes of this review, statistical significance was defined as $p \leq 0.05$.

D.5. Grading of the Evidence

The risk of bias associated with each study was assessed using scales developed by the University of Pennsylvania Center for Evidence-based Practice, and scores were recorded in the evidence tables. (Appendix Section D) The *Appendix* includes the questions used to assess the quality of each study design. The quality of the evidence base was then assessed using methods from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group, which considers randomized controlled trials (RCTs) the gold standard. (Appendix Section D) The GRADE approach[65, 66] was applied to provide explicit links between the available evidence and the resulting recommendations.

D.6. Formulating Recommendations

The criteria used to formulate the strength of each recommendation are described in the *HICPAC Update to the Recommendation Categorization Scheme*[67], and in the Appendix. (Appendix Section E.) The recommendation justification tables for each recommendation outline the factors weighed when determining the recommendation's strength.

D.7. Reviewing and Finalizing the Guideline

Recommendations, including narrative evidence reviews, recommendation justification tables, GRADE tables, and evidence tables, were presented to HICPAC for review and input at public meetings in November 2017; May and November 2018; and May, August, and November 2019. Following further revisions, the Guideline was announced in the *Federal Register* and published on Regulations.gov for a public comment period of 60 days. After this period, the public comments received were reviewed at a HICPAC meeting. The Recommendations were revised accordingly and finalized.

D.8. Updating the Guideline

Future revisions to this Guideline will be guided by new research and technological advancements for preventing and managing infections and infectious disease outbreaks in the NICU setting.

E. Evidence Summaries

E.1. Non-sterile Gloves

Key Question 1: Does the use of non-sterile gloves after hand hygiene, compared with hand hygiene alone, prevent CLABSI in NICU Patients?

One RCT[3] examined the efficacy of non-sterile glove use after hand hygiene, compared with hand hygiene alone in NICU patients. This study reported the outcomes of CLABSI, possible CLABSI, bloodstream infection (BSI), gram-positive BSI, and gram-negative BSI in NICU patients. This study reported no difference in the outcomes of CLABSI, BSI, and gram-negative BSI, but found a reduction in possible CLABSI and gram-positive BSI. Possible CLABSI was defined as "the detection ≥1 blood culture of any organism, and the presence of central line within 72 hours in the absence of another source of infection." Hand hygiene compliance was measured monthly and an overall 79% compliance was reported. This compliance was not reported according to study group. Product-

related adverse events were not reported. This study may have been underpowered to detect a difference in CLABSI. The confidence in this evidence is moderate.

E.2. Central Line Type

Key Question 2: Does the use of one central line catheter type, compared with another, prevent CLABSI in NICU patients?

Eleven studies[6-15, 68] evaluated the impact of use of different catheter types on the risk of BSI in NICU patients using the outcomes of CLABSI,[9-11, 13-15, 68] catheter-associated BSI,[8, 12] nosocomial BSI,[7] nosocomial sepsis,[6] and late onset sepsis.[12] One study[13] evaluated the impact of different catheter types on infiltration.

Four studies[9, 10, 13, 15] evaluated the risk of BSIs among neonates with umbilical venous catheters (UVCs) or percutaneously inserted central venous catheters. Very low-quality evidence suggested no difference in infectious risk when comparing UVCs with percutaneously inserted central catheters. Two studies[15, 68] evaluating the incidence of CLABSI reported no difference in the incidence of CLABSI for UVCs compared with peripherally-inserted central catheters (PICCs). In one of these studies, patients with PICCs were of younger gestational age and lower birthweight at time of insertion and had longer catheter dwell times; in the smaller study the groups were well balanced in terms of these confounding factors.[15] Another study[11] found similar CLABSI rates in those with PICCs and UVCs, but reported a two-fold increase in the risk of CLABSI for UVCs compared with PICCs when adjusting for gestational age, birthweight, and catheter dwell time. The third study[12] reported no difference in adjusted catheter-associated BSI (CA-BSI) and late onset sepsis rates between UVCs and percutaneously inserted central catheters. Only one study[68] reported adverse events associated with UVCs and PICCs and reported no difference. UVCs are usually intended for short-term use and are removed or replaced by peripheral venous lines or percutaneously inserted central venous catheters if longer-term access is needed. Of note, two of these studies[12, 68] evaluated data that were collected before the United States focused on evidence-based CVC insertion and maintenance practices that have been shown to reduce CLABSIs. In the setting of current standard of care, the impact of prioritizing different catheter types is unknown.

Six studies[6-10, 13] evaluated the risk of BSIs among neonates with different central line types. Each study compared a different series of catheter types including umbilical arterial catheters, umbilical venous catheters, percutaneous arterial catheters, percutaneous venous catheters, peripherally inserted central catheters, intracath, phlebotomy catheters, and tunneled catheters. Very low-quality evidence did not allow for a clear determination about the BSI risk among neonates with different central line types. One study[9] compared UVCs, central venous catheters (CVCs), and PICCs, and found the lowest CLABSI incidence for UVCs. One large, multicenter study[10] reported a tunneled catheter CLABSI incidence that was 2.4 times as high as the CLABSI incidence for PICCs. Neither study reported an analysis for the confounding factor of dwell time on CLABSI incidence. The third study[13] compared the risk of CLABSI among umbilical arterial catheters (UACs), UVCs, short duration venous catheters (SDVCs), PICCs, and tunneled catheters, and found no difference. One study[8] reported the outcome of catheter-associated BSI and found a higher rate for PICCs than for other catheters, including UVC, intracaths, and phlebotomy catheters. One study[7] reported the outcome of nosocomial-BSIs and found higher infection rates associated with percutaneous venous and tunneled catheters compared with UVCs. One study[6] compared the incidence of sepsis for tunneled catheters, percutaneous catheters (used primarily in pediatric patients), PICCs, and UVCs, and found the lowest incidence associated with umbilical catheters. This study did not adjust for the confounding factor of dwell time and reported a longer dwell time was associated with umbilical and tunneled catheters. Finally, one study[14] compared outcomes for extended dwell peripheral intravenous catheters (EVIP) also known as midline catheters, compared with PICCs in NICU patients, and found no difference in CLABSI rates between catheter types.

Three studies[13-15] reported adverse events. One study[15] reported no difference in obstruction or thrombosis, however events and sample sizes were small. The other study[13] reported the incidence of infiltration for UACs, UVCs, SDVCs, PICCs and tunneled catheters, and found PICCs were associated with a higher incidence of infiltration. Finally, one cohort study[14] reported a higher rate of obstruction, peritonitis, and premature ventricular contractions in infants with PICCs compared with EPIVs which are not typically used in this population, however infants with EPIVs received a higher incidence of hyaluronidase treated IV fluid extravasation.

Each study compared different catheter types and different outcome measures, and three of the studies[6-8] reported results from data collected prior to the implementation of bundles, which impeded the ability to draw conclusions as to the efficacy of one catheter type over another. In the setting of current standard of care, the impact of prioritizing different catheter types is unknown.

E.3. Central Line Insertion Site

Key Question 3: Does the use of one central line catheter insertion site, compared with another, prevent CLABSI in NICU patients?

Two studies[19, 20] compared the risk for catheter-related sepsis (CRS) between percutaneous catheters placed in femoral versus non-femoral sites. However, these studies examined the same NICU population during overlapping study periods. Very low-quality evidence suggested an increase in CRS in neonates with a percutaneous central catheter placed directly into the femoral vein compared to those placed in non-femoral sites. This was based on two studies which found that a significantly higher proportion of neonates with a percutaneous catheter placed at a femoral site developed CRS[20] or that neonates with a percutaneous catheter placed at a femoral site had an increase in the adjusted odds ratio for CRS.[19] The findings in both of these studies may have been biased by choosing non-femoral sites first. In these studies, femoral sites were used only if attempts to place a percutaneous catheter via a non-femoral site were unsuccessful. Additionally, duration of percutaneous catheter placement was also found to be a significant risk factor for infectious outcomes in both studies, which may have also confounded the results.

Non-infectious complications were assessed in both studies. One study[20] reported that the adjusted odds of a noninfectious complication in a neonate with a femoral central line placement did not differ significantly from neonates with a non-femoral site placement. In the study analyzing VLBW infants,[19] the proportion of patients that developed phlebitis, catheter site inflammation, or that required early percutaneous central catheter line removal was significantly higher for non-femoral central lines. This study did not assess adverse events. Of note, both studies were conducted at a time before the United States focused on evidence-based CVC insertion and maintenance practices that have been shown to reduce CLABSIs. In the setting of current standard of care, the impact of prioritizing femoral or non-femoral insertion sites is unknown. As a practical consideration related to care, there can be greater difficulty keeping central line dressings clean and dry when placed in the groin area; however, the studies did not report on cleanliness and ease of line management.

Three studies evaluated the risk of CLABSI,[24, 25] catheter-related sepsis[21] and catheter-associated infections[17] for surgically implanted central lines in neonates placed in the subclavian, jugular, or femoral sites. Low quality evidence from one case control study[24] suggested an increase in the odds of internal jugular placement among patients with CLABSI, and no difference in the proportion of subclavian, saphenous, external jugular, or brachial placement among NICU patients with CLABSI. A cohort[25] study examined tunneled CVCs and reported no difference in the incidence of CLABSI when comparing lines placed femoral sites with those in subclavian sites. Very low-quality evidence from one study[17] suggested an increased risk for catheter-associated infections

among patients with central lines implanted in the internal jugular vein compared to those implanted in the subclavian vein. This difference remained significant after adjusting for confounding factors such as weight and age. Catheter removal due to obstruction of the CVC by kinking was significantly higher in infants with internal jugular catheters; however, there was no difference in clinical thrombosis and catheter dislocation between sites. Very low-quality evidence from one study[21] suggested a lower rate of catheter-related sepsis and accidental catheter removal in neonates with central lines placed at a femoral site when compared with central lines implanted in the neck, defined as either at the subclavian or the internal jugular site. This study did not define the criteria used to determine the outcomes of either catheter infection or catheter-related sepsis. In both studies, significant differences in weight may have impacted the site of successful catheterization. In both studies, the groups with lower weight had higher rates in infection. Of note, both studies were conducted before the widespread implementation of central line insertion and maintenance bundles in 2010. The impact of prioritizing different insertion sites is unknown in the context of the current standard of care.

Five studies evaluated the risk of a CLABSI,[16, 24] CRBSI,[18] sepsis,[23] and presumed sepsis[22] for CVCs in the upper extremity and lower extremity. Very low-quality evidence suggested the incidence of CLABSI, CRBSI, and presumed sepsis did not significantly differ between NICU infants in whom the PICC was placed in an upper extremity vein compared to those in whom the catheter was placed in a lower extremity vein. All four studies[16, 18, 22 23] were conducted to assess PICC-related complications associated with PICC removal. The incidence of infiltration was significantly higher in neonates with PICCs placed in the upper extremity in one study.[16] Limited data[18] suggested an increase in the risk of phlebitis and significantly longer dwell time[16] for PICCs placed in the lower extremity. Finally, one case control study suggested an increase in the proportion of upper limb insertions among patients with CLABSI compared to those without CLABSI. Additionally, for PICCs placed in upper extremities, limited data suggested an increase in the proportion of patients developing cholestasis and dislodgement,[16, 23] and the time to first complication was shorter.[18] In one of these studies[23], the gestational age for patients with upper extremity placement was two weeks younger than patients with lower extremity placement, which may have been a source of bias in the adverse event data, however more studies are needed to determine if gestational age biases these results. In many of these studies, the choice of site was guided by healthcare personnel preference, which may or may not have been dictated by the needs of the patient as much as the preference of the inserting healthcare personnel and could also confound the results. Of note, all three of the five studies (14, 15, 20) evaluated data that were collected before the United States focused on evidence-based CVC insertion and maintenance practices that have been shown to reduce CLABSIs. In the setting of current standard of care, the impact of prioritizing different catheter insertion sites is unknown.

E.4. Number of Catheter Lumens

Key Question 4: Does the use of single-lumen, compared with double-lumen, umbilical venous catheters prevent CLABSI in NICU patients?

One randomized trial[26] and two observational studies reported on CLABSI,[24, 27] and catheter-related sepsis[21] between single- and double-lumen umbilical venous catheters. Low-quality evidence from two observational studies suggests an increase in the risk of CLABSI is associated with the use of double-lumen catheters. One cohort[27] reported a significant increase in the adjusted incidence rate ratio of CLABSI for patients with double-lumen UVCs compared with single lumen UVCs. The case control study also reported an increase in the odds of CLABSI for patients with double-lumen catheters compared with single lumen catheters. The RCT [21]reported no difference in the proportion of neonates with single- or double-lumen umbilical venous catheters that developed catheter-related sepsis. Of note, there were no infections reported in this study, and neonates in this study had catheters in place only for about 3 days.

The two observational studies noted an increase in complications was associated with double-lumen catheters; however, the patients in these studies were not matched by severity of illness and there are concerns for confounding by indication. The RCT reported no difference in mechanical complications between the two catheter types. Use of double-lumen catheters was associated with a significant reduction in the number of additional intravenous catheters required, however this RCT was not conducted in the current era of widespread implementation of catheter care bundles.

E.5. Skin Antisepsis for Catheter Insertion and Maintenance

Key Question 5: In NICU patients requiring skin antisepsis for catheter insertion and maintenance, does the use of alcoholic chlorhexidine, compared with alcoholic povidone-iodine, prevent CLABSI?

The literature search did not retrieve any articles comparing the use of any concentration of alcoholic chlorhexidine (CHX) with alcoholic povidone iodine (PI). One RCT[29] compared the use of 2% alcoholic chlorhexidine gluconate (CHG) with povidone iodine (PI) in an unspecified base to prepare skin for catheter insertion and maintenance. This study suggested no difference in CRBSI, CABSI, presumed BSI, or septicemia between study groups. This study was terminated early due to slow enrollment.

Cutaneous absorption of chlorhexidine was found in half of the infants who were monitored for this outcome; however, no significant systemic side effects were noted. This study also reported no dermatitis at CHG application sites. The confidence in this evidence is very low. This study was published prior to the widespread implementation of insertion and maintenance bundles in 2010. The impact of this intervention in the current standard of care is unknown.

E.6. Chlorhexidine Bathing

Key Question 6: Does chlorhexidine bathing, compared with no bathing or bathing with placebo, prevent CLABSI in NICU patients?

One RCT[30] and three observational studies)[31-33] examined the use of chlorhexidine bathing for neonatal patients. The RCT[30] compared a single bath using 0.25% chlorhexidine-impregnated washcloths with a single bath using saline impregnated cloths or no baths in NICU patients. The two observational studies[31, 33] compared specific bathing regimens based on birthweight, gestational age and chronologic age, using 2% CHG impregnated washcloths compared with using soap[33] or no baths.[31] One of the observational studies compared a bath with 2% CHG in water with no bath.[32] Three of the four studies reported the outcomes of product-related adverse events, including hypothermia[30] and skin reactions.[30, 31, 33]

One RCT[30] examining the safety and efficacy of a single bath using 0.25% chlorhexidine-impregnated washcloths compared with saline impregnated washcloths or no bath, reported the outcomes of culture positive sepsis and clinical sepsis. This study suggested no difference in the incidence of culture-positive sepsis or the incidence of clinical sepsis at one week between groups. The confidence in this evidence is low.

Two observational studies examining the safety and efficacy of using 2% CHG washcloths compared with using soap[33] or no baths[31] reported the outcomes of CLABSI. These studies suggested a clinically meaningful[33] or significant[31] decrease in the rate of CLABSI in NICU patients. Both studies were conducted in facilities with high baseline CLABSI rates. While both studies reported adding chlorhexidine bathing to existing standard of care, and both were conducted in the era of widespread implementation of insertion and maintenance bundles in the United States, it is unclear if the study conducted in an international setting[31] implemented insertion and maintenance bundles for the prevention of CLABSI. The confidence in this evidence is low.

Finally, one cohort[32] study suggested a reduction in laboratory-confirmed sepsis and culture-negative for patients who received at least one bath in the first three days of life. These reductions reached statistical significance during the intervention period for laboratory-confirmed sepsis. This evidence as rated as very quality.

The RCT[30] reported on the effects of 0.25% chlorhexidine-impregnated washcloths on axillary temperature and skin reactions. This study reported no instances of moderate hypothermia (<36°C) and no difference in the incidence of cold stress (36.0° - 36.4 1°C) between groups of NICU patients. This study reported no adverse product-related skin reactions for a single chlorhexidine-impregnated washcloth bath, including skin erythema, fissuring, or crusting in NICU patients or adverse effects on skin condition in neonates. The confidence in this evidence is low.

Two observational studies[31] reported on the effects of 2% CHG impregnated washcloths on skin reactions. Both studies reported no adverse product-related events associated with using 2% CHG impregnated washcloths, including local or systemic adverse events[31] and dermatitis or other adverse events.[33] The confidence in this evidence is very low.

One of the studies[30] included in this section was published prior to the widespread implementation of insertion and maintenance bundles in 2010.

E.7. Catheter Hub Manipulation

Key Question 7: In NICU patients with central line catheters does minimizing the number of times central line hubs are accessed prevent CLABSI?

One study evaluated the effect of catheter hub manipulations and blood draws through the catheter on catheter-associated BSIs.[34] Very low-quality evidence suggested that more frequent central line hub manipulations requiring disinfection (e.g., disconnection of the infusion set from a central line) or drawing blood through a central line increases the risk of catheter-associated BSIs. These findings were based on an increase in the odds of catheter-associated BSI in a multivariate model. Of note, drawing arterial blood through an arterial catheter for a blood gas was not associated with an increase in the odds of BSI.

E.8. Central Line Antimicrobial Locks

Key Question 8: In NICU patients with central line catheters, does the use of central line antimicrobial locks, compared with standard of care, prevent CLABSI?

Three studies of neonates evaluated the effect of central line antimicrobial locks on catheter-related BSIs.[35-37] There was high-quality evidence that the use of catheter locks prevented catheter-related BSIs. This was based on studies of three different antimicrobial locks (vancomycin,[36] amikacin,[37] or fusidic acid,[35] in combination with heparin) that were used at least once per day that demonstrated a decrease in definite CRBSIs. No evidence was retrieved regarding the use of ethanol locks. None of the three studies reported a significant decrease in suspected or probable CRBSIs. The definition of CRBSI differed slightly across the studies.

The presence of a lock results in the disconnection of glucose infusion to a neonate and can result in the development of hypoglycemia. Hypoglycemia was evaluated in all three studies and was not found to be higher in the antimicrobial lock group as compared with the control saline-heparin-only locks. The rate of hypoglycemia was more than 10% in these studies, presumably because of the disconnection of the glucose infusion as a result of the lock. The development of antimicrobial resistance over the short term was evaluated in two of the studies,[36, 37] and no instances of resistance to the agent used in the antimicrobial lock were detected. The

incidence of bleeding complications was not evaluated in any of the studies. Of note, all three studies were conducted before the widespread implementation of central line insertion and maintenance bundles that have been shown to reduce CLABSIs, which may be why the rates of catheter-related BSIs were very high in the non-intervention groups. In the setting of current standard of care, the impact of central line antimicrobial locks is unknown.

E.9. Optimal Umbilical Arterial and Venous Catheter Dwell Time

Key Question 9: What is the optimal duration of umbilical artery and umbilical venous catheters to prevent CLABSI in NICU patients?

Six studies evaluated the risk of a BSI outcome for patients with umbilical catheters (6 venous, 1 arterial).[6, 11, 27, 38-40] Low-quality evidence suggested that the longer an umbilical arterial or venous catheter was in place, the higher the odds or risk of a BSI-related outcome. While the catheter dwell time break points varied among studies, three studies suggested an optimal UVC duration of up to 7 days.[3-5] One cohort suggested low risk in the first week of central line use, followed by a three-fold increase in risk at day 14 of use.[27] Two studies[11, 39] found that longer use of an umbilical venous catheter was associated with an increase in the risk of CLABSI. One study reported an increase in risk of CLABSI for UVCs in situ for >7 days,[39] and the other study[11] reported the risk of CLABSI increased beyond 3-4 days of dwell time for UVCs, and that risk doubled every 2 days thereafter if the UVC was followed by PICC insertion. One study[6] reported an increase in the incidence of sepsis in UVCs in situ for 4-6 days when compared with those in situ for 1-3 days, but this difference was not noted as significant. This study also found the incidence of sepsis was higher in umbilical artery catheters in situ for ≥8 days when compared with those in situ for ≤7 days. One study,[40] conducted after the widespread implementation of central line insertion and maintenance bundles in 2010, implemented a quality improvement initiative in uncomplicated NICU patients without congenital anomalies, with a gestational age of ≥27 weeks or weighing >1000g at birth. This study found no increase in CLABSI in infants with UVCs that were replaced by PICCs at 7 days compared with infants with UVCs replaced at 5 days. This study may have been underpowered. In an 11-year observational cohort study (2008-2018), CLABSIs occurred at a mean of 9.8 days (range 5 to 18). The risk began to rise in the second week, from <1% at day 7 to 3.6% at day 14.

One RCT evaluated the effect of routinely removing umbilical venous catheters and replacing them with a percutaneous central catheter after seven to ten days compared with replacement at up to 28 days.[38] There were no significant differences in the two study arms for time to catheter-related infection and the duration of catheter use before infection. However, while the overall incidence of catheter sepsis was not significantly different between groups, the study reported more than twice the incidence of infections in the long-term UVC group compared with the group in which UVCs were replaced by percutaneous central catheters. This study also reported no significant difference between the two groups in measured complications, including development of a thrombus.

Of note, 4 of the 6 studies included in this analysis were conducted using data collected prior to the implementation of catheter insertion and maintenance bundles.[6, 11, 38, 39] In the setting of current standard of care, there is limited understanding of the impact of umbilical catheter dwell time on CLABSI, CRBSI, and CA-BSI.

E.10. Optimal Peripherally Inserted Central Catheter Dwell Time

Key Question 10: What is the optimal duration for peripherally inserted central catheters to prevent CLABSI in NICU patients?

Eight studies[10, 11, 41-46] evaluated the risk of BSI over time for PICCs. Very low-quality evidence suggested that the longer a percutaneous central catheter was in place, the odds or risk of developing a CLABSI, CRBSIs, or catheter-related sepsis increased, although the time periods analyzed varied across studies. Three studies[11, 42, 46] reported increases in CLABSIs with increasing dwell time; however, none was able to pinpoint a clear inflection point for removal or replacement of PICC to reduce CLABSI risk. One study[10] reported an increased risk of CLABSI in the first week of dwell time and found that no other duration of catheter stay was associated with increased risk of CLABSI. Three studies[41, 44, 45] reported the outcome of CRBSI. Two studies[41, 44] found an increase in CRBSI with increasing dwell time; however, this increase did not reach significance in one study.[44] Almost all PICCS in this study were removed within two weeks of insertion. One study[45] found no difference in PICC dwell time between patients with CRBSI and those that did not develop CRBSI. One study[43] found significant increases in catheter-related sepsis in patients with peripherally-inserted central catheters in place for >9 days compared to those in place for ≤9 days. No product-related adverse events were reported in relation to PICC dwell time.

Of note, 6 studies[11, 41-44, 46] were conducted using data collected prior to the widespread implementation of central line insertion and maintenance bundles in 2010. One of these studies[42] conducted data analyses to account for this change in infection prevention and control practices; however, the others did not. In the setting of current standard of care, the impact of PICC dwell time on CLABSI, CRBSI, and CA-BSI is unknown.

E.11. Dedicated Catheter Care Team

Key Question 11: Does the use of dedicated catheter care teams compared with standard of care, prevent CLABSI in NICU patients?

Two observational studies reported the effect of a dedicated catheter care team on CLABSI[48] and CRBSI[69] One observational study[48] reported on the effect of a dedicated central line maintenance team on CLABSI in a NICU. This study reported a reduction in CLABSI that remained significant after adjustment for the NHSN CLABSI definition change. The other observational study[47] evaluated the effect of a dedicated PICC team on CRBSIs in extremely low birth weight NICU patients. Implementation of the PICC team was compared to previous standard of care and reported no difference in the risk of CRBSI. A duration stratification analysis showed a reduction in CRBSIs for NICU patients with indwelling central lines ≥30 days was associated with implementing catheter care teams. However, no difference was reported for patients with indwelling central lines <30 days. Adverse events attributable to catheter care teams were not reported. While the evidence suggests a benefit to implementation of catheter care teams when baseline rates are high, catheter care teams are a prevention measure, and not solely a reactive measure. Use of a catheter care team can prevent high CLABSI rates in addition to reducing them. The confidence in this evidence is very low due to imprecision.

E.12. Central Line Insertion and Maintenance Bundles

Key Question 12: What are the optimal elements of central line insertion and maintenance bundles to prevent CLABSI in NICU patients?

Three observational studies[50] implemented a central venous catheter insertion and maintenance bundle and measured concurrent compliance as part of a NICU-specific[50] or hospital-wide[51, 52] quality improvement initiative. Possible adverse events attributable to the implementation of an insertion only bundle or insertion and maintenance bundle were not assessed.

All three studies[50-52] reported reductions in CLABSI. All three studies also measured healthcare personnel bundle compliance and reported an increase in insertion and maintenance compliance from the baseline throughout

the intervention period. Compliance reporting was required for all bundle elements in order for the data to be included in the analysis. Although CLABSI decreased, none of the studies examined the possible association between bundle compliance and the reduction in CLABSI.

No studies were retrieved that directly compared the efficacy of different bundles.

E.13. Prophylactic Antimicrobial Administration

Key Question 13: What is the efficacy of prophylactic antimicrobials, compared with standard of care, to prevent CLABSI in NICU patients?

Four studies evaluated the effect of systemic prophylactic antibiotics on BSIs among patients with central lines.[53-56] Moderate-quality evidence did not suggest a clear net benefit to systemic prophylactic antibiotics to reduce total BSIs, although prophylactic vancomycin did appear to result in a decrease in BSIs due to coagulase-negative staphylococci (CoNS). This was based on three studies[54-56] that evaluated the use of prophylactic vancomycin and one that evaluated prophylactic amoxicillin.[53] The first,[56] a randomized trial, found a decrease in coagulase-negative staphylococcal BSIs among infants that had vancomycin added to doses of TPN. It was not clear in this study if this approach resulted in a significant change in overall catheter-related sepsis. A second pre-post study[55] evaluated the administration of prophylactic low-dose vancomycin (25 mcg/ml) through neonates' catheters and found an overall significant decrease in gram-positive infections, but no change in the percent of neonates with gram-negative or fungal infections. The third study[54] (pre-post) compared a period in which prophylactic vancomycin was provided with parenteral nutrition infusions to the period that followed, during which vancomycin was used only for treatment. This study found an overall significant decrease in positive blood cultures in the vancomycin group that was primarily due to a significant decrease in positive blood cultures for CoNS. The number of patients exposed to vancomycin decreased between the first and second periods, although the total amount of vancomycin use increased. The fourth study[53] (randomized trial) evaluated prophylactic amoxicillin daily and did not find statistically significant differences in proven septicemia or suspected septicemia in neonates receiving prophylactic amoxicillin. There did not appear to be large differences in mechanical and thrombotic complications between the two groups.

Three studies reported on antibiotic resistance. Two studies[55, 56] reported on vancomycin resistance, and one on amoxicillin resistance.[53] One study[56] reported no incidences of vancomycin resistance, and CoNS susceptibility patterns did not change; further, vancomycin-resistant strains of CoNS were not detected. One study[55] reported that no incidences of vancomycin resistance were observed during the study period; however, in the two years following the study, four cases of CoNS resistance to vancomycin appeared. The study evaluating prophylactic amoxicillin[53] reported one incidence of amoxicillin-resistant *Staphylococcus epidermidis* in the control group. The long-term development of antimicrobial resistance was not adequately evaluated in any of these studies, nor was impact on the infant microbiome. None of the studies included in this analysis were conducted using data collected after the widespread implementation of central line insertion and maintenance bundles. In the setting of current standard of care, the impact of prophylactic antimicrobials on CLABSI, CRBSI, and CA-BSI is unknown. In contrast, prolonged antibiotic exposure in uninfected neonates has been associated with adverse outcomes, including NEC and death.[70] In VLBW infants, each increased day of antibiotic exposures has been associated with an increased risk of bronchopulmonary dysplasia.[71] The current standard of care in NICUs is to limit unnecessary antimicrobial exposure.

E.14. Prophylactic Anticoagulant Administration

Key Question 14: What is the efficacy of prophylactic anticoagulant infusions, compared with standard of care, to prevent CLABSI in NICU patients?

Four studies[57-60] evaluated the effect of heparin infusions on BSI-related outcomes. Moderate-quality evidence suggested that neither continuous infusions of heparin, nor heparin added to or infused with TPN, resulted in significant reductions in catheter-related sepsis. This conclusion was based on four studies[57-60] that showed no decrease in catheter-related sepsis or definite catheter-related sepsis among neonates with PICCs receiving infusions of heparin. One study[57] suggested no difference in the incidence of probable or possible catheter-related sepsis, and another study[60] reported no difference in the incidence of septicemia.

Adverse events were evaluated in all four studies. Two studies[59, 60] demonstrated a significant reduction in catheter occlusion; the other two[57, 58] did not find a significant difference in this outcome. Three studies[57, 58, 60] reported no difference in the incidence of intraventricular hemorrhage between the two groups; however, a small number of infants was assessed for this outcome, limiting the confidence in these results. Of note, sepsis outcome definitions and heparin preparations were heterogeneous across studies. All of the studies were conducted using data collected prior to the widespread implementation of central line insertion and maintenance bundles in 2010. The effect of prophylactic anticoagulant on central line infections with the current standard of care is unknown.

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H. Acronyms and Abbreviations

Acronym	Expansion
BSI	Bloodstream Infection
CDC	Centers for Disease Control and Prevention
CRBSI	Catheter-Related Bloodstream Infection
CLABSI	Central Line-Associated Bloodstream Infection
CHG	Chlorhexidine Gluconate
CoNS	Coagulase-Negative Staphylococci
DES	Descriptive Study
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HHS	(United States Department of) Health and Human Services
HICPAC	Healthcare Infection Control Practices Advisory Committee
IV	Intravenous
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin-Sensitive *Staphylococcus aureus*
NICU	Neonatal Intensive Care Unit
OBS	Observational Study
PICC	Peripherally Inserted Central Catheter
PCR	Polymerase Chain Reaction
PI	Povidone Iodine
QI	Quality Improvement
RCT	Randomized Controlled Trial
S. aureus	*Staphylococcus aureus*
TAP	Targeted Assessment for Prevention
UAC	Umbilical Arterial Catheter
UVC	Umbilical Venous Catheter
VLBW	Very Low Birthweight