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REVIEW

Expert review of CLABSI prevention in the NICU: supporting the transition of investigational drugs into clinical practice

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Abstract

Central venous catheters (CVCs) are essential for administering life-saving medications, parenteral nutrition, and fluids in extremely premature (EP; i.e., 28 weeks' gestational age) infants. Indeed, CVCs have enabled increased survival and improved outcomes in EP infants over the last several decades. However, CVCs remain a major risk factor for central line-associated bloodstream infection (CLABSI), which can lead to serious complications in this vulnerable population. While many neonatal intensive care units (NICUs) have adopted CVC bundles to reduce CLABSI risk, implementation remains inconsistent, contributing to significant variability across centers. A minimized and reproducible baseline rate of CLABSI is important not only to physicians caring for EP infants and their families but also to clinical investigators and regulatory authorities in the evaluation of experimental therapies aimed at combating the complications of prematurity, such as bronchopulmonary dysplasia, retinopathy of prematurity, and impaired neurological development. CLABSIs may confound clinical outcomes and thus impact the interpretation of trial results. We propose a standardized central line bundle, informed by current clinical practice and a critical appraisal of the literature, for mandatory use in clinical trials.

Conclusion: Consistent application of a standardized central line bundle would reduce variability in baseline CLABSI rates across study sites, enabling more accurate benefit-risk assessments of experimental therapies, particularly those requiring central venous access, in this population of infants with a high unmet medical need.

What is Known:

- *Central venous catheters (CVCs) are essential for administering life-saving treatments in extremely premature infants, significantly improving their survival and outcomes. CVCs, however, are known to increase the risk of central line-associated bloodstream infection (CLABSI).*
- *Central line bundles are routinely implemented in clinical practice with demonstrable benefit in reducing CLABSI. Still, their impact often wanes as the focus and stringency on bundle components and audit programs decrease.*

What is New:

- *We propose a standardized central line bundle for mandatory use in clinical trials. This will help reduce variability in baseline CLABSI rates across study centers, enabling a more accurate evaluation of the benefit-risk profile of experimental therapies—especially those requiring administration via central venous catheters.*

Keywords Neonatology · Central venous catheter · Sepsis · CLABSI · BPD

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Abbreviations

BAPM	British association of perinatal medicine
BPD	Bronchopulmonary dysplasia
CDC	Center for disease control and prevention
CI	Confidence interval
CICC	Centrally inserted central catheter
CLABSI	Central line-associated bloodstream infection
CRP	C-reactive protein
CVC	Central venous catheter
ECC	Epicutaneo-cava catheter
EP	Extremely premature
ELBW	Extremely low birth weight
EMA	European Medicines Agency
ESCNH	European standards of care for newborn health
FICC	Femorally inserted central catheter
GA	Gestational age
HeRO	Heart rate observation
HR	Hazard ratio
HRC	Heart rate characteristics
IDSA	Infectious disease society of america
IL	Interleukin
IV	Intravenous
LOS	Late-onset sepsis
NANN	National association of neonatal nurses
NHSN	National healthcare safety network
NICU	Neonatal intensive care unit
NNTB	Number needed to treat for an additional beneficial outcome
OPCA	Oropharyngeal colostrum application
PICC	Peripherally inserted central catheter
PMA	Postmenstrual age
rhIGF-1	Recombinant human insulin-like growth factor-1
rhIGF-BP3	Recombinant human insulin-like growth factor binding protein-3
RR	Risk ratio
RD	Risk difference
UVC	Umbilical venous catheter
VLBW	Very low birth weight

Introduction

Central venous catheters (CVCs) have become the mainstay for stable vascular access in the neonatal intensive care unit (NICU) [1, 2]. The routine use of CVCs for parenteral nutrition, intravenous fluids, and medications has advanced neonatal care and contributed to increased survival and improved outcomes for extremely premature (EP, < 28 weeks' gestational age [GA]) infants [3–5]. However, establishing intravenous (IV) access presents specific challenges in these infants due to the smaller diameter and thin blood vessel walls, fragile skin barrier, and increased susceptibility to infection [6]. Furthermore, catheter insertion and maintenance are associated with an increased risk for complications, including line extravasation, damage to organs and tissues, thrombosis, and infection [7–14].

Minimizing complications of CVCs has improved in recent decades due to the availability of standardized kits and better and smaller catheters, techniques to guide placement, and the introduction of central line bundles to reduce the risk of central line-associated bloodstream infections (CLABSI) [15–17]. While central line bundles are routinely implemented, what constitutes a bundle can vary considerably, which is a contributor to CLABSI rates being reported to vary up to seven-fold across NICUs [18]. Such variability in CLABSI rates not only impacts outcomes for physicians, infants, and families in routine practice but also represents an important confounder for clinical trials in EP infants. The development of drugs in EP infants is rare, but over the past decade, more IV therapies are being evaluated to address the unmet medical needs in this population, such as bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), impaired neurological development, and gastrointestinal problems [19, 20]. As central line bundles are already incorporated in standard neonatal care, what remains is their standardization for use in the clinical trial setting, defining acceptable rates and metrics to support regulatory decision-making.

The aim of this paper is, therefore, to review the literature on CLABSI in EP infants and propose a recommended central line bundle based on current evidence and clinical expertise for the safe use of CVCs in the clinical trials context.

Maximizing the potential benefit of future treatments delivered via a CVC

Improvements in maternal and neonatal care have resulted in increased rates of survival of EP infants, leading to a new set of management challenges, including neurodevelopmental disabilities, cardiovascular and metabolic disorders, and an emerging population of long-term survivors of BPD [21–23]. BPD is the most common respiratory complication of premature infants affecting an average 40–50% of those born at < 28 weeks GA, which can lead to increased mortality, longer hospitalization rates, and cost burden, as well as long-term respiratory morbidity with a lifelong impact on respiratory health [22, 24]. The incidence is likely underestimated, as some centers do not currently monitor and record BPD rates, and rates as high as approximately 75% have been reported in VLBW infants born between 22 and

29 weeks' gestation [25]. Currently, there are no approved medications for BPD.

Recent findings suggest that treatment with recombinant human insulin-like growth factor 1 (rhIGF-1) complexed with its main binding protein recombinant human IGF-1 binding protein-3 (BP-3), as a replacement for IGF-1 deficiency that develops in EP infants, could potentially prevent BPD in these infants by promoting lung maturation [26, 27]. The efficacy and safety of rhIGF-1/rhIGF-1BP3 (OHB-607) are currently being assessed in an ongoing multicenter, randomized, phase 2b study targeting 338 infants between 23^{+0} weeks and 27^{+6} weeks GA [28]. OHB-607 has the potential to be the first major therapeutic breakthrough for EP infants since the global approval of pulmonary surfactants over four decades ago and could pave the way for other treatments aimed at addressing the complications of prematurity [29].

Successful replacement of IGF-1 during the weeks after birth with OHB-607 requires continuous IV infusion optimally through a CVC to maintain steady-state levels until endogenous levels of IGF-1 rise at around 30 weeks postmenstrual age (PMA) [30]. CLABSI has been associated with systemic inflammation, increased oxygen requirements, disrupted nutrition, and prolonged hospitalization, which contribute to a broad range of conditions of prematurity including BPD [15, 16, 31]. Therefore, practices to minimize the risk of CLABSI, the most common CVC-related complication, for the 2–7 weeks (depending on GA at birth) until 30 weeks PMA are critical to the success of OHB-607 and are the focus of this review. Other strategies to enhance the safety of CVC use in EP infants, such as to mitigate the risk of non-elective catheter removal, mechanical complications, thrombosis, and extravasation, should also be considered.

Neonatal sepsis

Neonatal sepsis is widely recognized as a major contributor worldwide to increased morbidity, mortality, and healthcare costs among EP infants [19, 32–36]. While various definitions of neonatal sepsis exist, no internationally recognized standard exists [37]. Most definitions include a positive blood culture and clinical signs consistent with sepsis [36, 38]. For example, the European Medicines Agency (EMA) neonatal sepsis criteria include having at least two clinical signs and at least two laboratory signs confirming the presence of infection (Table 1) [39]. However, a multicenter prospective study evaluating the validity and reliability of the EMA criteria in predicting verifiable neonatal sepsis reported a sensitivity and specificity of only 44.1% and 64.4%, respectively [40]. Regarding Gram-positive sepsis, modified criteria used in the NeoVanc clinical trial required the presence of (a) at least three clinical or laboratory signs of sepsis or a positive culture with Gram-positive bacteria and (b) at least one additional clinical or laboratory indicator [41]. This modified criteria successfully identified infants with clinical sepsis attributable to Gram-positive bacteria, with > 40% positive baseline blood cultures [41]. In Japan, emphasis was placed on one or more clinical indicators plus a positive culture: fever, hypothermia, temperature instability, apnea, bradycardia, respiratory distress, increased oxygen requirements, feeding intolerance, lethargy or hypotonia, and one positive blood culture for a single organism [42, 43]. An editorial from China highlights that accurate diagnosis of neonatal sepsis can be challenging due to its atypical clinical presentation and the low rate of specific diagnostic indicators, such as a positive blood culture [44]. The Chinese guidelines include laboratory non-specific markers such as C-reactive protein (CRP) or complete blood cell count for screening and diagnosis [44, 45]. Australian guidelines are similar to the aforementioned but recommend two blood cultures, one from the central line and one from a peripheral line [46]. This is an area that remains controversial, as blood drawing from a CVC may increase the risk for creating biofilms and possible microbial exposure, and neonatal peripherally inserted central catheters (PICCs) are too small to safely withdraw blood without the risk of clotting off the catheter. While definitions of neonatal sepsis vary, the consistent identification of bloodstream infections and the appropriate course of therapy are the mainstays for reducing complications potentially related to or associated with CVCs.

CVC-associated infection

Bacteremia arising from CVC-associated infection is a significant nosocomial infection, particularly in the NICU, and one major cause of neonatal late-onset sepsis (LOS), i.e., sepsis occurring ≥ 72 h after birth [19, 47–50]. The infection can occur not only when the line is inserted or undergoing maintenance but also during line access for infusions and/or when the integrity of the catheter dressings is compromised [51]. It is caused by microorganisms colonizing the external or internal surface of the catheter or the fluid pathway when the catheter is inserted or during routine maintenance [52].

Central-line associated bloodstream infection (CLABSI)

CLABSI is defined by the U.S. Center for Disease Control and Prevention (CDC)/National Healthcare Safety Network (NHSN) for healthcare-associated infection surveillance [52–54] as a primary bloodstream infection, e.g., recovery of a pathogen from a blood culture (on two separate

Table 1 European Medicines Agency criteria for neonatal sepsis [39]

Clinical signs	Laboratory signs
Modified body temperature • Core temperature > 38.5 °C or < 36 °C **AND/OR** • Temperature instability	Whole blood cell count • $< 4000 \times 10^9$ cells/L **OR** • $> 20{,}000 \times 10^9$ cells/L
Cardiovascular instability • Bradycardia (mean heart rate less than the 10th percentile for age in the absence of external vagal stimulus, beta-blockers, or congenital heart disease **OR** otherwise unexplained persistent depression over a 0.5 h time) **OR** • Tachycardia (mean heart rate greater than 2 SD above normal for age in the absence of external stimulus, chronic drugs, and painful stimuli **OR** otherwise unexplained persistent elevation over a 0.5 h to 4 h time) **AND/OR** • Rhythm instability • Reduced urinary output (less than 1 mL/kg/h), • Hypotension (mean arterial pressure less than the 5th percentile for age), • Mottled skin, • Impaired peripheral perfusion	Immature to total neutrophil ratio • > 0.2 Platelet count • $< 100{,}000 \times 10^9$ cells/L C reactive protein > 15 mg/L OR procalcitonin ≥ 2 ng/mL[a] • Glucose intolerance confirmed at least 2 times • Hyperglycemia (blood glucose > 180 mg/dL or 10 mmol/L) **OR** • Hypoglycemia (glycemia < 45 mg/dL or 2.5 mmol/L) when receiving age-specific normal-range glucose amounts
Skin and subcutaneous lesions • Petechial rash • Sclerema	Metabolic acidosis • Base excess < − 10 mEq/L **OR** • Serum lactate > 2 mmol/L
Respiratory instability • Apnea episodes **OR** • Tachypnea episodes (mean respiratory rate over 2 SD above normal for age) **OR** • Increased oxygen requirements **OR** • Requirement for ventilation support	
Gastrointestinal • Feeding intolerance, • Poor sucking • Abdominal distention	
Non-specific • Irritability • Lethargy • Hypotonia	

[a]The cut-off for procalcitonin in neonatal sepsis has not been clearly defined, as the currently available published data are still controversial

occasions) in a patient of any age with a central line within 48 h before developing an infection that must not be related to an alternative cause [53, 54]. In infants ≤ 1 year of age, there is the additional requirement of having at least one of the following signs: fever (> 38 °C), hypothermia (< 36 °C), apnea, or bradycardia [19, 55]. This latter definition, however, may not be suitable for EP infants or neonates due to differences in infection symptomatology with increasing age and that they may have an endotracheal tube in place and be on the ventilator [56]. Currently, the CDC definition is the most commonly used, but worldwide, there is some variation regarding standardized definitions and protocols for diagnosing and reporting CLABSI in neonates in the NICU [19, 56].

The incidence of CLABSI is inversely correlated with GA at birth and can vary considerably across NICUs depending on several factors, including definitions and clinical practice protocols followed; staff turnover, education, training, and experience; patient-nurse ratio; equipment used (e.g., type of line, glue); and structural and logistic features, including but not limited to where the NICU is located (e.g., linked with maternity or surgical unit or not) [57–61]. A systematic review of 18 studies found significant variability in nosocomial infection rates, with CLABSI incidence ranging from 3.2/1000 to 21.8/1000 catheter days among centers that reported CLABSI [18]. A recent meta-analysis of CLABSI incidence in NICUs through September 2023 provided a pooled incidence of 6.52/1000 catheter days in neonates across 14 studies in multiple countries [61].

Table 2 Preventive strategies against neonatal nosocomial infections and their effectiveness

Effective (supported by evidence)	Not effective (not supported by evidence)	Uncertain efficacy (equivocal evidence)
• Fresh human milk • Colostrum • Skin-to-skin (via enhanced lactation) • Avoiding H2 blockers • Fluconazole • Prevention of hyperglycemia • Bundles for CVC positioning • Bundles for CLABSI prevention • Hand hygiene: alcohol, gloving[a] • RSV prevention with palivizumab (via decreased VAP) • US-CICC to reduce infectious complications upon catheter insertion, when longer-line maintenance is required • Staff training and education • Avoiding understaffing and overcrowding, guarantee nurse: patient ratio, e.g., 1:1 or 1:2 • Proactive extubation policy and use of non-invasive respiratory support techniques	• Banked donor milk • Immunoglobulins − IVIg − IV IgM • Anti-Staph monoclonals • Routine antibiotic prophylaxis for CVC	• Probiotics[b] • Human or bovine origin of the proteins used for fortifiers • Bovine lactoferrin • Active microbiological surveillance programs

CLABSI central line-associated bloodstream infection, *CVC* central venous catheter, *IgM* immunoglobulin M, *IV* intravenous, *IVIg* intravenous immunoglobulin, *LOS* late-onset sepsis, *NEC* necrotizing enterocolitis, *PCT* procalcitonin, *US-CICC* ultrasound-guided centrally inserted central catheter, *VAP* ventilator-associated pneumonia

[a]Importantly, gloves should be used for sterile procedures and should not be considered to reduce infection risk per se

[b]Although a direct association with the prevention of infections is still debated, an indirect protective effect may be seen via the prevention of NEC, which is often associated with LOS

Prevention strategies for CVC-associated infection (CLABSI) in the NICU

Management of CVC-associated infection in EP infants can be challenging due to their unique risk and vulnerability to infection requiring specifically adapted criteria for the identification and treatment as well as prevention of these infections [19, 62]. Multiple guidelines, recommendations, and expert consensuses have been developed for CLABSI prevention [51, 52, 63–65]. However, guidance specifically adapted for neonatal patient subsets is limited to catheter insertion, maintenance, and removal [2, 56, 62, 66]. It is important to note that CVC stewardship includes both bundles aimed at the prevention of CLABSIs specifically as well as the prevention of all other causes of LOS. Prevention of other causes will indirectly protect the CVC from colonization and infection while it is in place. Several evidence-based strategies have been reported in the literature, some effective, some with equivocal evidence, and others with no or limited supporting evidence for minimizing nosocomial infections and LOS in neonates (Table 2).

Early diagnosis of neonatal sepsis

Several studies have demonstrated comparable diagnostic accuracy of point-of-care biomarkers (e.g., CRP, procalcitonin, interleukin-6 [IL-6], neutrophil CD64, serum amyloid A, presepsin) to facilitate rapid diagnosis of neonatal sepsis [62, 67–72]. While a single biomarker may be insufficiently specific or sensitive, and there is no optimal combination of biomarkers for sepsis detection, biomarkers can provide rapid information in cases of suspected sepsis [36, 48]. If the decision has been made to obtain cultures and start antibiotics, in most cases, serial biomarkers do not add to management decisions and are associated with increased antibiotic days.

Thermal gradient alterations were shown to be independently associated with LOS (OR 23.60, 95% CI, 6.80–81.88), with a sensitivity of 83% and a negative predictive value of 94% in VLBW (< 1500 g) infants [39]. In 71% of cases, a thermal gradient alteration was the first clinical sign of sepsis, while CRP was < 1.5 mg/dL in 64% of cases and procalcitonin < 2 ng/mL in 36% [73].

The Impact of Heart Rate Characteristics Monitoring (HeRO) randomized trial showed a reduction in the mortality of VLBW infants from 10.2 to 8.1% (hazard ratio [HR] 0.78, 95% CI, 0.61–0.99, $p = 0.04$) in infants whose heart characteristic monitoring (HRC) was displayed to treating physicians [74]. For infants with culture-positive LOS, 30-day mortality was reduced from 16.1 to 10% [74]. The HeRO device is intended for use under the direct supervision of a healthcare practitioner in a hospital NICU and was designed to acquire, store, analyze, and report on electrocardiogram

data collected from infants [75]. HeRO monitoring has been adopted in multiple hospitals worldwide and has proven an effective early warning system, preventing one death related to sepsis for every 23 extremely low birth weight (ELBW, < 1000 g) and 48 VLBW infants [76, 77].

Fresh milk and colostrum

A recent systematic review and meta-analysis of 21 studies assessing the impact of oropharyngeal colostrum application (OPCA) on the incidence of culture-proven neonatal sepsis in preterm neonates demonstrated a significant reduction in mortality (relative risk 0.73, 95% CI, 0.59–0.90) and sepsis rates (relative risk 0.78, 95% CI, 0.65–0.94) [78]. In a prospective cohort study of 175 VLBW infants, a decrease of 19% in the odds of sepsis was reported for every human milk dose increase of 10 mL/kg/day [79]. A single-center, randomized clinical trial in infants ≤ 32 weeks' GA reported a 73% reduction (relative risk 0.27, 95% CI, 0.08–0.94) with OPCA compared with the control group [80]. To foster fresh milk and colostrum feeding, a recent open-label, randomized trial in healthy infants ≥ 35 weeks' GA showed that increasing the duration of early skin-to-skin contact had a dose–response benefit on exclusive breastfeeding rates and breastfeeding behavior [81].

Avoiding gastric acid inhibitors

Exposure to H2 blockers has been associated with increased rates of sepsis and should be avoided [82]. A secondary analysis of prospectively collected data from a multicenter, randomized clinical trial in 235 VLBW infants treated with gastric acid inhibitors for ≥ 1 day showed an additional 3.7% odds of developing LOS for each day of exposure to gastric acid inhibitors, albeit this effect was counteracted by co-administration of lactoferrin [82, 83].

Systemic antifungal prophylaxis

Use of prophylactic systemic antifungals, particularly fluconazole, has effectively reduced invasive fungal infection in VLBW infants [84]. A meta-analysis of 10 clinical trials comparing systemic antifungal prophylaxis versus placebo showed a statistically significant lower incidence of invasive fungal infection in the intervention group (risk ratio [RR] 0.43, 95% CI, 0.31–0.59; risk difference [RD] − 0.09, 95% CI, − 0.12 to − 0.06) [85]. Antifungal prophylaxis with fluconazole should be a key part of preventive policies against invasive fungal infections. In addition, targeted prophylaxis in EP infants at high risk of infection, particularly when they have two or more risk factors including the CVC, parenteral nutrition, or broad-spectrum antibiotics, is effective in preventing invasive infection while avoiding the development of resistance or adverse effects.

Prevention of hyperglycemia

Following coagulase-negative staphylococci, *Staphylococcus aureus* is the second most common microorganism implicated in neonatal CLABSI [58, 86, 87]. An in vitro study of dose–response of *Staphylococcus epidermidis* and *Staphylococcus aureus* biofilm formation to glucose concentration showed a significant increase in biofilm production beyond a glucose concentration threshold of 200–240 mg/dL [88]. Several studies have investigated the link between plasma glucose levels and mortality rate in neonatal sepsis, highlighting the importance of glycemic status [89, 90]. Hyperglycemia can also be one of the signs of LOS. In VLBW infants, early hyperglycemia was linked to the risk of LOS in the NICU [91, 92]. Therefore, preventing and treating hyperglycemia may improve the outcomes of EP infants.

Bundles for CVC CLABSI prevention

There is no single action that can effectively prevent CLABSI, but a bundle addresses placement, maintenance, and removal. The bundle, a joint network of actions implemented together, includes competency, regular training, education, adherence to infection prevention protocols, and organization within a NICU staff. Bundles for CLABSI prevention are crucial for optimal management [93], and recommended core bundle components are presented in Table 3 [94–97]. The introduction of proactive management of central lines in hospitalized neonates < 1000 g at birth reduced the incidence of CVC-related infections from 15.8/1000 to 5.1/1000 catheters per day [98].

Hand hygiene, wearing sterile gloves and gowns, and non-sterile masks and caps are key components of any bundle when undertaking sterile procedures, including CVC placement, and have been shown to reduce the risk of LOS in preterm infants. In general, maximal sterile barrier precautions (i.e., sterile gowns and gloves, caps, and masks) during CVC insertion are highly recommended by several scientific societies in various medical specialties [99] and included in the CDC guidelines and neonatal literature [66, 100].

Regarding line contact in components of CLABSI maintenance prevention, glove use after hand hygiene before patient and line contact was associated with fewer gram-positive bloodstream infections and possible CLABSIs in preterm infants [101]. The addition of gowning provides no additional benefit during non-sterile procedures and routine contact [62].

Care of the CVC entry site, dressing maintenance and changes, and hub care are key components of maintenance

Table 3 Bundles for CLABSI prevention focus areas

1	Insertion of lines with sterile precautions	• Organized process using maximal sterile barriers
2	Hand hygiene	• Hand sanitizer dispensers at each bedside or close within arm's reach or a few steps
3	Gloving with CVC contact	• Hand hygiene before donning and after doffing nonsterile gloves
		• When making or breaking a connection
		• Accessing an injection port
4	Hub care	• Scrub hub for 15 s and let dry
		• Alcohol or 2% chlorhexidine can be used
		• Use alcohol-impregnated hubs on ports without continuous infusions
		• Decrease the number of times the hub needs to be accessed
		• Use closed medication systems when feasible
5	IV fluids and medications	• Prepare and administer under sterile conditions
6	Dressing and skin entry site care	• Sterile clear occlusive dressings
		• Change dressing when loose, detached, bloody, or soiled
		• Chlorhexidine dressings are not needed for every patient in NICU. May be considered in specific patients at high risk of infection or if CLABSI rates are higher than expected for infants ≥ 28 weeks' GA and ≥ 7 days of age
7	Microbial control	• Environmental cleaning of bedside and common areas
		• Chlorhexidine bathing may be added for specific patients at high risk of infection or if CLABSI rates are higher than expected balancing systemic absorption and skin irritation for infants born < 37 weeks' GA
		• Treat bacterial bloodstream infections via CVC
		• Targeted antifungal prophylaxis of patients at high risk of infection with additional risk factors while CVC in place
8	Teamwork: two-person process for insertion and maintenance procedures	• Insertion
		• Dressing changes
		• Tubing, IV fluids, and hub changes
9	CVC stewardship	• Have enteral feeding guidelines to decrease CVC, lipid, and parenteral nutrition days
		• Discuss daily need for CVC and possible removal
		• Discuss daily changing any IV medication to an enteral form or substitute
		• Most enteral medications can be used once on 50% of total enteral feeding volume
		• Feedback, monitoring, auditing practices
		• Quality improvement

CLABSI central line-associated bloodstream infection, *CVC* central venous catheter, *EP* extremely premature, *GA* gestational age, *IV* intravenous, *NICU* neonatal intensive care unit. Adapted from https://www.cdc.gov/infection-control/media/pdfs/Guideline-NICU-CLABSI-508.pdf [66]

to prevent external and internal microbial exposure and colonization. Dressing changes should occur when soiled, damp, or loose, regardless of GA.

There is high-quality evidence that medication-impregnated dressings reduce the incidence of CLABSI relative to all other dressing types in adults (RR 0.60, 95% CI, 0.39–0.93), but the data is not significant for neonates [102]. One consensus group recommends that if other interventions have failed to reduce CLABSIs in specific patients or a NICU, or if there is an increase in the NICU's baseline CLABSI rates, chlorhexidine-impregnated dressings may be considered in infants ≥ 28 weeks' GA and ≥ 7 days of age [31].

Hub care is another critical element of CVC bundles. Each hub should be scrubbed for a minimum of 15 s prior to each access. If continuous fluids are not infused, impregnated alcohol caps clean the hub in 5 min.

What constitutes a CVC bundle can vary between centers [103]; for example, in Europe, most drugs are prepared at the bedside, and one person might perform procedures due to staffing limitations, while in the U.S., drugs are often prepared under laminar flow conditions in the pharmacy, and procedures are performed by two staff members. European NICUs are usually smaller than their equivalents in the U.S. The goal is to ensure that all IV administrations are sterile and prepared under aseptic conditions.

Additional microbial control includes environmental cleaning of the bedside and common areas each shift, antibiotic stewardship, antifungal prophylaxis in EP infants at high risk of infection, and treating bacterial culture-proven infections through the CVC. Similarly to

chlorhexidine-impregnated dressings, chlorhexidine bathing is not required for every patient or NICU. The same infectious disease consensus group that provided the chlorhexidine-impregnated dressings recommendation advises that if other interventions have failed to reduce CLABSIs in a specific patient or a NICU, chlorhexidine baths can be added for infants ≥ 37 weeks' GA or < 37 weeks' GA and > 4 weeks of age due to concern for systemic absorption and skin irritation [31]. Antimicrobial lock solutions have been studied to reduce CLABSIs in two randomized control trials. A single center study in 98 infants born < 30 weeks' GA reported a statistically significant reduction in catheter-related bloodstream infections with zeolite-impregnated umbilical venous catheters compared with non-impregnated catheters (2% vs 22%, respectively, $p = 0.005$) [104]. However, the PREVAIL randomized clinical trial in 861 infants, of whom 419 (49%) infants were born < 28 weeks' GA, did not find any significant difference in CLABSIs per 1000 days with antimicrobial-coated (rifampin and rifampicin-miconazole) PICC compared with non-impregnated PICC (1.84 vs 2.35, respectively, $p = 0.65$) [105]. Further studies are needed with analysis of specific products separately demonstrating their efficacy and safety.

CVC stewardship involves discussing daily if the line is still needed, weaning IV medications, changing any IV medications to enteral substitutes if possible, and having standard enteral feeding advances to facilitate weaning off parenteral nutrition. Teamwork is another key component that involves the two-person buddy system for placement, dressing changes, and hanging IV fluids [106]. Finally, tracking CLABSI rates is paramount. The NICU team should monitor CLABSI rates and regularly audit bundle components to assess the effectiveness of current practices, implement new measures, and continually improve prevention efforts.

What is critically important is that sufficient practices are employed to gain and maintain staff competency in applying the bundle and that this practice is regularly monitored and reported for continuous quality improvement, if required. In addition, the creation of a dedicated task force of skilled doctors and nurses to proactively manage CVC insertion, maintenance, and implementation of CVC bundles has been reported to decrease infection incidence in VLBW infants. The better the organizational model, the better the outcomes for preventing infections. The effectiveness of the CVC bundle at preventing CLABSI was correlated with the comprehensiveness of policies and the centers' and staff's compliance. Having two staff members placing a line, hanging new IV fluids and dressing changes (buddy system), adhering to written policies, and facilitating adherence to hand hygiene (e.g., by putting hand sanitizer dispensers at each bedside) could, in some contexts, assist in attaining improved outcomes [106].

Choice of catheter

Catheter choice is a case-by-case clinical decision that should be guided by the infant's clinical condition (e.g., stable vs unstable; severity of hemodynamic and respiratory impairment), expected duration of IV infusion (e.g., < 7 days; 7–14 days; > 14 days), and type of infusion [107]. Evidence-based guidelines are available to inform the optimal choice of catheter, including approaches for catheter placement, securement, and maintenance to minimize the risk of CLABSI [31, 102, 103, 107, 108]. The umbilical venous catheter (UVC) is widely used in NICUs due to its fast and easy insertion, which provides a stable central access. However, to reduce the risk of associated CLABSI and thrombotic complications, early removal of the UVC is recommended (i.e., often at 3–4 days and up to 7 days for a limited number of cases), and replacement with another central line if still required [107]. While there is a limited understanding of the impact of UVC dwell time on CLABSI in the current NICU setting, a study conducted before the implementation of catheter insertion and maintenance bundles reported an increased risk of CLABSI beyond 3–4 days of UVC dwell time, with a doubling risk every 2 days thereafter, if the UVC was followed by PICC insertion [66, 109]. Epicutaneo-cava catheters (ECCs) are preferred for stable preterm infants requiring parenteral nutrition or drug administration for 7–14 days [107, 108]. If ECCs cannot be placed in a suitable position, or for unstable infants who often require a prolonged central line, centrally inserted central catheters (CICCs) and femorally inserted central catheters (FICCs) are recommended [107, 108]. Both CICCs and FICCs provide stable central access for hemodynamic monitoring, high-flow infusions, and blood sampling in critically ill newborns. The use of polyurethane catheters is preferred, with 1-Fr catheters for infants below 2 kg to reduce thrombosis risk [107, 108]. Choosing the fewest number of lumens based on the infant's clinical needs is recommended [66]. However, double lumen catheters with larger bore size (3–4 Fr) can be accommodated for administering infusions of multiple non-compatible drugs, when an appropriate catheter-to-vein ratio is available [108].

Staff training and education

There is also a consideration for an attitudinal shift from accepting sepsis as an unavoidable consequence of prematurity to actively fostering a unit culture that prioritizes CLABSI prevention. Transparent surveillance and feedback systems reporting low infection rates with strict control measures, high compliance, and a positive attitude reinforce

the belief that such infections are indeed preventable [110]. CLABSIs are considered an adverse event and should be reported, but shifting from blame to root cause analysis is paramount and should be seen as a positive driver for change and improvement. Continually evaluating, reporting, and rigorously benchmarking performance is key. The continuous monitoring of microbial epidemiology in the NICU and periodic feedback to the staff is useful to achieve the best adherence to infection prevention and control measures (e.g., hand washing and sterile procedures). Responsible management of human resources, maintaining an optimal nurse-to-patient ratio, and avoiding overcrowding and understaffing are crucial to preventing organizational fatigue and limiting outbreaks occurrence in the NICU [111–115]. For infants in the NICU, a nurse:patient ratio of 1:1 has been recommended by the British Association of Perinatal Medicine (BAPM) due to the complex needs of both the infant and their family, and 1:2 for high dependency neonatal care [116]. This recommendation is further supported by the European Standards of Care for Newborn Health (ESCNH) [117]. The National Association of Neonatal Nurses (NANN) recommends that staffing in NICUs be based on the acuity of the population served, with lower ratios for higher-acuity infants such as those with central lines [118]. Based on acuity, the estimated nurse:infant staffing ratios in clinical practice in the U.S. range between 1:1 for complex critical care and 1:2 for intensive care [111].

Conclusion

The improved survival of EP infants highlights the importance of developing new therapeutics for this vulnerable population, as the impact of complications of prematurity has reached staggering proportions with a rising socioeconomic burden [119]. While the benefit-risk profile of CVCs remains to be established in EP infants receiving experimental therapies, advances in pediatric oncology, an equally fragile patient population at high risk of infections, have been made possible through the incorporation of CVCs for delivering life-saving medications following robust clinical trials [120–122]. Similar to other intensive care environments, CVCs have been utilized in NICUs for decades, supported by CVC bundles and imaging technologies to facilitate catheter placement (e.g., point-of-care ultrasound), which has significantly contributed to a reduction in line placement complications [46, 65, 66, 123–125]. Therefore, the routine application of CVCs in both neonatal care and clinical trial settings is well positioned to enable drug development for conditions of prematurity (e.g., BPD) and to drive necessary advancements in the field.

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Declarations

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