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Catheter-related bloodstream infections in neonatal intensive care units

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Central venous catheters (CVCs) are regularly used in intensive care units, and catheter-related bloodstream infection (CRBSI) remains a leading cause of healthcare-associated infections, particularly in preterm infants. Increased survival rate of extremely-low-birth-weight infants can be partly attributed to routine practice of CVC placement. The most common types of CVCs used in neonatal intensive care units (NICUs) include umbilical venous catheters, peripherally inserted central catheters, and tunneled catheters. CRBSI is defined as a laboratory-confirmed bloodstream infection (BSI) with either a positive catheter tip culture or a positive blood culture drawn from the CVC. BSIs most frequently result from pathogens such as gram-positive cocci, coagulase-negative *staphylococci*, and sometimes gram-negative organisms. CRBSIs are usually associated with several risk factors, including prolonged catheter placement, femoral access, low birth weight, and young gestational age. Most NICUs have a strategy for catheter insertion and maintenance designed to decrease CRBSIs. Specific interventions slightly differ between NICUs, particularly with regard to the types of disinfectants used for hand hygiene and appropriate skin care for the infant. In conclusion, infection rates can be reduced by the application of strict protocols for the placement and maintenance of CVCs and the education of NICU physicians and nurses.

Key words: Catheter, Bacteremia, Intensive care units, Newborn

Introduction

Central venous catheters (CVCs) are widely used in neonatal intensive care units (NICUs). They provide an intravenous route for the safe administration of hyperosmolar fluids and medications. The most common types of CVCs used in NICUs are umbilical venous catheters (UVC), peripherally inserted central catheters (PICC), and tunneled CVC (e.g., Hickman and Broviac)[1]. UVCs, which are CVCs inserted through the umbilical vein, have been frequently used in NICUs for many years[1]. Complications of UVC use are thrombosis, hemorrhage, arrhythmias, effusions, and portal hypertension. Due to heavy bacterial growth around the umbilicus and the risk of infection, UVC is considered as a short-term venous route.

PICCs are used in very-low-birth-weight infants (VLBW) when an intolerance for adequate oral feeding beyond 7 days of life is expected or when total parenteral nutrition is required for more than 1 week[2]. The peripheral veins used for cannulation include the greater and lesser saphenous veins of the lower extremities and the basilic or cephalic veins of the upper extremities, which are preferred over femoral sites. PICCs may lead to obstruction, rupture, vessel perforation, extravasation, thrombosis, and infection. To decrease the risk of these complications, correct positioning of the catheter tip is essential during placement. PICC tip placement in non-central sites in children, including the subclavian or brachiocephalic vein, has been shown to significantly increase the rate of complications[3]. Tip placement in the right atrium increases the risk of arrhythmia and pericardial tamponade[1,4]. The most appropriate location for the tip of PICCs is the lower one-third of the superior vena cava if the PICC is placed in an upper extremity and the inferior vena cava if the PICC is placed in a lower extremity[4]. Subcutaneous tunneled catheters are used as an alternative when PICC insertion is not possible. They are usually considered when the CVC is needed for more than 6 weeks[5].

VLBW infants are vulnerable to infections because of their immature immune systems, frequent contact with hospital personnel, and invasive procedures. The rates of catheter-related bloodstream infection (CRBSI) range from 6.4 to 8.3 episodes per 1,000 patient-days in the NICU[6], with the smallest and most immature infants being at the greatest risk. CRBSIs contribute to increased morbidity and mortality, prolonged hospitalization, and the need for additional therapies. Therefore, NICU staffs have attempted to reduce infection rates by using insertion and maintenance protocols to prevent CRBSI.

This review will define catheter-related infections and discuss their pathophysiology, risk factors, and microbiology as well as strategies to minimize CRBSI.

Definitions

The range of healthcare associated infections with CVC includes not only laboratory-confirmed bloodstream infection (BSI), but also clinical sepsis[7-9]. The definitions of laboratory-confirmed BSI is isolation of recognized pathogens from blood culture that were not related to infection at another site, with clini cal characteristics of sepsis.

The definition of catheter colonization is absence of infection signs and significant growth of micro-organisms from the catheter tip, subcutaneous segment of the catheter, or catheter hub. To identify the infection or colonization, distal portion of catheter is rolled four times over the surface of a sheep-blood agar plate and the number of micro-organisms (>15 colony-forming units) is determined after 48 hours of incubation. Like this, semiquantitative culture technique identifies only microorganisms from the external surface of the catheter, while quantitative cultures allow the identification of micro-organisms from both the internal and the external surfaces of the catheters.

CRBSI is defined as a laboratory-confirmed BSI with either a positive catheter tip culture or a positive blood culture drawn from the CVC. However, central line-associated bloodstream infection (CLABSI) is that bacteremia occurs with a central line in place or within 48 hours of a central line removal with clinical symptoms of sepsis and no other apparent source of infection, with or without positive culture through the catheter.

The definition of clinical sepsis requires the following conditions: clinical symptoms or signs for sepsis, blood culture not done or no organism or antigen detected in blood, and no apparent infection at another site.

Pathophysiology

Pathogenesis of CRBSI requires bacterial adherence and host defence mechanisms. CVCs are prone to bacterial infections, particularly *Staphylococcus aureus* and coagulase-negative *staphylococci.* It is known that fibrinogen and fibronectin are dominant plasma mediators in staphylococcal adherence and deposited on inserted catheters[10]. Also, *staphylococci* are colonized to the CVC surface by the formation of a multilayered biofilm (slime), conferring some protection against antibiotics[11].

Healthcare associated infections with CVC occur by four distinct pathways in infection process, including external and internal catheter surface colonization pathways, intrinsic contamination, and hematogenous seeding. External surface pathway infection may start with the colonization of the skin insertion site by micro-organisms of the skin flora that may move by capillary action through the transcutaneous part of the dermal tunnel surrounding the catheter. Internal surface pathway infection occurs by colonization of the hub and intraluminal surface of the catheter[12]. Contamination of the fluids or drugs intravenously administered (so-called "intrinsic contamination") constitutes another process responsible for CRBSIs, sometimes resulting in outbreaks. Uncommon micro-organisms such as *Enterobacter* spp., *Serratia marcescens, Malasezia furfur,* or *Candida parapsilosis* are identified in some circumstances[13]. Finally, hematogenous seeding of the catheter during BSI of any origin represents a third pathway of CRBSIs[14].

Risk factors

Major risk factor for development these infections is the indwelling time of CVCs. Zingg et al.[9] presented that the median time to a infection for PICCs and umbilical catheters was 7 (interquartile range, 5 to 10) and 7 (interquartile range, 5 to 8) days, respectively. Hoang et al.[15] reported a median time of 9 days for PICCs of the upper extremities, although the median time was longer (15 days) for PICCs of the lower extremities. The National Institute of Child Health and Human Development Neonatal Research Network showed that the risk of late-onset sepsis increased as the duration of CVC and parenteral nutrition increased, and infants who developed sepsis had higher mean indwelling times than infants without sepsis. The risk of late-onset sepsis increased significantly for catheters in place for 22 or more days[16].

Some authors reported that low birth weight is the most important factor for the occurrence of CLABSI/CRBSI. de Brito et al.[17] showed that neonates weighing less than 750 g revealed the highest CRBSI incidence rate (3.3/1,000 days CVC). In the National Healthcare Safety Network survey[18], the rate of CRBSIs was 4.4 to 6.4 per 1,000 catheter days among neonates weighing less than 1,000 g.

Anticoagulants are used widely to prevent catheter thrombosis. Because thrombi and fibrin deposits on catheters might serve as a nidus for microbial colonization of CVC, the use of anticoagulants might have a role in the prevention of CRBSI. It is known that surface heparinization appears to have a great impact on bacterial colonization and can be a significant approach to the prevention of catheter-associated bacteremia or fungemia[19].

Venous access can be difficult in VLBW infants, and a femoral vein can be the alternative site available for cannulation after failure to insert CVCs in all other peripheral veins. Although the Hospital Infection Control Practices Advisory Committee, Center for Disease Control and Prevention in United States recommends that femoral catheters should be avoided when possible, because they are associated with a higher risk for deep vein thrombosis and more likely to become infected[20], there were reports that there were no differences among sites of catheter placement[15,21].

Microbiology

Most microorganisms implicated in CRBSIs are gram-positive cocci, which are responsible for at least two-thirds of infections[2]. De Brito et al.[17] reported that coagulase-negative *Staphylococci* (CoNS) were the most common microorganism implicated in laboratory-confirmed BSI (39.7%) and CLABSI/CRBSI (42.9% and 60.0%, respectively), and *S. aureus* was the second leading cause of BSI. Gram-negative bacilli (*Klebsiella* spp., *Enterobacter* spp., *Acinetobacter baumannii, Escherichia coli, Pseudomonas aeruginosa*) are responsible for a higher proportion of CRBSIs in ICU patients than in non-ICU patients. These infections result from colonization of invasive pressure monitoring systems, complicated remote infections, or high levels of orotracheal colonization[22]. *Candida spp.* have emerged as important pathogens in CRBSIs and account for a high proportion of the dramatic increase in the rate of candidemia over recent decades. They represented more than 30% of pathogens reported from 1992 to 1998 in 204 mixed ICUs participating in the U.S. National Nosocomial Infection Surveillance System[23], confirming that intravascular devices constitute the leading cause of nosocomial candidemia. However, the incidence of each pathogen isolated from catheters differed among NICUs[2,9,15].

Management

Bacteremic infants have fewer infection-related complications when the CVC is removed promptly[24]. A single blood culture positive for *S. aureus* or a gram-negative rod warrants central line removal in a neonate. For neonates with 1 positive culture for CoNS, clinicians may attempt medical management without central catheter removal, but documentation of subsequent negative blood cultures is crucial. Once a neonate has had 3 positive blood cultures for CoNS, the central catheter should be removed.

There is evidence that fluconazole provides antifungal prophylaxis for infants <1,000 g and/or <27 weeks' gestation[25]. To have the greatest effect and target the highest risk period, antifungal prophylaxis should be started within the first 2 days of life and continue until central or peripheral IV access is no longer needed. Candidemia warrants prompt central line removal.

Prevention

Strategies to reduce CRBSI include: 1) precaution during line insertion; 2) management of CVC and CVC-connection; 3) reduction of the duration of time that the CVC is used; 4) vancomycin prophylaxis for CVCs; 5) removal of the CVC when there is a positive culture.

Good hand hygiene combined with appropriate technique during catheter insertion confers protection against CRBSI. Maximal universial precautions (e.g., caps, masks, sterile gowns, and sterile gloves) during catheter acquire reduction of CRBSI incidence, compared with standard precautions. Taylor et al.[26] reported that CRBSI in VLBW infants requiring long term central venous access was reduced by nearly half after the institution of a dedicated PICC

team in the NICU.

Schulman et al.[27] reported that statewide application of standardized, evidence-based central-line insertion and maintenance bundles substantially reduced NICU CLABSIs. Bundles are defined as a limited number of specific practices essential for effective and safe patient care that, when implemented together, result in additional improvements in patient outcomes. Insertion bundles include establishment of a CVC insertion kit, hand hygiene with appropriate antiseptic agents before the procedure, maximal universal precautions, and patient disinfection with appropriate antiseptics (e.g., 2% chlorhexidine, 70% alcohol). Proper maintenance bundles of the CVC should include hand hygiene with antiseptics before dressing catheter site, the establishment of a sterile field, limiting frequency of blood collection through the catheter, rubbing the hub vigorously with disinfectants (e.g., 2% chlorhexidine, 70% alcohol) at the time of hub entry or disconnection, daily change of administration sets (e.g., intravenous tubing set)[28], avoiding the use of multilumen catheters, integrity of the dressing, evaluation of catheter site for signs of infection, and re-evaluation of catheter necessity and prompt removal of catheter that you no longer need.

A 10% povidone-iodine solution is usually used as a disinfectant for whole-skin surfaces of all nursery patients. However, it can damage thyroid function, especially in premature infants. The use of CHG for the insertion and maintenance of CVCs is recommended for adult and pediatric populations over povidone iodine, although its use is still controversial in neonates. The U.S.

Federal Drug Administration has not approved CHG for cutaneous use in infants less than 2 months of age. Nevertheless, off-label use of CHG in NICUs is common: more than 60% of U.S. neonatology staff reported using CHG in their NICUs[29]. The concentration of CHG used for neonates is lower than that used for adults (0.5% vs. 2.0%), although its effectiveness is possibly reduced[30]. Garland et al.[31] reported severe contact dermatitis with the use of a CHGimpregnated patch that was placed over catheter sites after insertion.

Most episodes occurred in neonates who were <1 week old and <28 weeks' gestation at birth. Garland et al.[25] suggested that occlusion, pressure created by the dressing, CHG, or a combination of all 3 factors was responsible for severe contact dermatitis of the dressing site.

In a randomized clinical trial, prophylactic use of a heparinized saline containing vancomycin 25 ug/mL (antibiotic lock technique) markedly reduced the incidence of CRBSI in VLBW infants with PICCs and did not promote no vancomycin-resistant enterococci or CoNS[32]. However, several issues still need to be resolved before the routine use of antibiotic lock to prevent CRBSI. They include ideal dwell times and drug concentrations, progressive reduction of antibiotic activity, compatibility between antibiotics and heparin, antimicrobial resistance and risk of systemic toxicity, and universal application of antibiotic lock technique awaits validation by larger clinical trials[33].

Conclusion

Since CVC have been used as a routine tool for administration of the hyperosmolar fluid or medications to VLBW infants, catheter-related infection remains a leading cause of healthcare associated infections in NICUs. The incidence of each pathogen isolated from catheter was individualized on NICUs, even though two-thirds of micro-organisms implicated in infections arise from gram-positive cocci, including CoNS and *Staphylococcus aureus*. Because CRBSI/CLABSI contribute to increased morbidity, mortality, and prolonged hospitalization, NICU staffs have tried to reduce these infection rates with the control of risk factors and strict adherence of protocols for the insertion and maintenance of CVC. Strategies to reduce CRBSI include: 1) precaution during line insertion and maintenance of CVC and tubing set; 2) reduction of the duration of time that CVC is used; 3) vancomycin prophylaxis for CVCs; 4) prompt removal of the CVC when there is a positive culture and you no longer need, and re-evaluation of catheter necessity.

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