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Review

Risk Factors for Nosocomial Infections in the Neonatal Intensive Care Unit (NICU)

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Abstract

Nosocomial infections are one of the major cause of morbidity in the neonates and they have characteristics not found in any other group of patients. There are a number of risk factors for infection in neonates including birth weight, gestational age, practices in the ward, prescription of antibiotics etc. Understanding the risk factors is crucial for developing strategies to reduce the incidence of nosocomial infections in the NICU.

Keywords: Neonate, Neonatal intensive care unit, Nosocomial infection, Risk factors

INTRODUCTION

Nosocomial infections (NIs) are one of the major causes of mortality and morbidity in the neonatal intensive care units (NICUs) (Borghesi and Stronati, 2008). NI is an infection during hospitalization that was not present or in incubation at the time of admission that has an impact on the healthcare system as it increases the use of medical resources, duration of hospitalization, as well as increased cost of treatment in both developed and developing countries (Kawagoeet al., 2001). The knowledge gained so far about the risk factors, the spread and the manifestation, consequences, and prevention of healthcare-associated infections (HAI) in the NICU allows their possible identification, monitoring and control. In newborns, nosocomial infections have characteristics not found in any other group of patients. Newborns,especially those born prematurely are immune deficient compared to the elderly patients and their antibody levels reflect the immunological memory of the mother. Imperfect defense mechanisms and risk factors during hospitalization as a result lead to a high incidence of infections associated with medical care, significantly exceeding that of other patient populations.

There are a number of risk factors for infection in neonates hospitalized in neonatal intensive care units. Understanding the risk factors associated with NI is crucial for developing prevention strategies. The most commonly reported risk factors associated with NI in the neonatal period are the following:

Birth weight

Birth weight is defined as the most important and constant predictor of the expected severity of the disease. The risk of infection is inversely proportional to birth weight. It also serves as a marker for immunological immaturity and underdeveloped mechanical barriers (Saiman L, 2002). Numerous studies have reported a strong correlation between low birth weight and the risk of NI (van der Zwet, Kaiser, and van Elburg 2005; Stoll et al., 2002; Mohammed and El Seifl, 2014; Djordjevic et al., 2015).

There is a 3% increase in the risk of infection with each decrease of 500 grams of birth weight. It is 2.2 times higher in newborns weighing less than 1500 g compared to those weighing more than 1500grams (Nagata, Brito, and Matsuo, 2002). The strongest association between weight as a risk factor and nosocomial infections was found in the group of children weighing between 750 and 999 grams (Różańska, Wójkowska-Mach, Adamski, 2015) According to data covering more than 20 years of follow-up by the National Institute of Child Health and Human Development, 20 to 25% of very low birth weight infants who survived more than 3 days had 1 or more episodes of microbiologically proven sepsis, with the predominant pathogens are from the group of Gram (+) microorganisms, mainly *Coag (-) Staphylococcus* (Ramasethu, 2017).

Gestational age

The risk of developing a nosocomial infection is inversely related to gestational age. Premature birth along with weight are considered to be the most important risk factors for HAI (Stoll et al, 2002; Djordjevic et al., 2015; Nagata, Brito, and Matsuo, 2002). The highest incidence of NI was recorded in children born before 32 weeks of gestation(Nagata, Brito, and Matsuo, 2002; Jeong and Choi, 2006; Auriti et al., 2003). Premature birth is a potential risk factor for late-onset sepsis (Yancey et al., 1996; Sarvikivi, Kärki, and Lyytikäinen, 2010). A study of 248 neonatal intensive care units in the United States between 1996 and 2007, covering patients born at 34 to 36 weeks of gestation, recorded 6.3 episodes of late-onset sepsis in 1,000 hospitalized patients (Cohen-Wolkowiez, 2009).

When it comes to gestational age as a risk factor for the occurrence of NI, some authors advise that the calculated NI values be adjusted according to gestational age so that the data can be more easily compared between departments (Stoll et al., 2002; Schwab et al., 2007).

Immunology of the neonate

Immune deficiencies in newborns affect almost all aspects of the immune system (Saiman, 2002). T cell function is impaired in both pretermand term infants. The production of several lymphokines-cytokines- and colony stimulating factors by neonatal cells is decreased (Lewis and Wilson, 2001). These include Interleukin (IL) -3,-4,-5, and -6, Interferonλ, tumor necrosis factor λ, and granulocyte-macrophage colony stimulating factor. Furthermore, the preterm neonate's antibodies may have reduced opsonic function for potential pathogens such as coagulase negative staphylococci (CONS) (Fleer and Gerards, 1988) and preterm infants have an impaired ability to produce antibodies, particularly in response to polysaccharide antigens

Mechanical barriers

The skin of premature infants is thin and deficient in keratin because stratus corneum develops after 26 weeks of gestation (Harpin and Rutter, 1983). The skin of the hospitalized newborn is further damaged and dried by phototherapy, which is used to treat hyperbilirubinemia, by adhesive tapes used for heart monitors, to maintain catheters, or for surgical wounds. Even small violations of the integrity of the skin can be a gateway for potential bacterial or fungal pathogens. Preterm infants have a higher risk of surgical wound infections after surgery (Madden et al., 1988).

Intravenous catheters

Central venous catheters are often used in neonatal intensive care units to provide nutrition and fluids, blood products, and medications. Because most catheters have 1 lumen, it is common practice to inject lipid solutions, blood products, and medications through the same central venous catheter, which results in frequent manipulation and increases the risk of contamination. Central venous catheters and the timing of their use are very important risk factors for late-onset sepsis in neonatal patients, especially those with very low birth weight (Kung et al., 2016; Hornik et al., 2012). Placement of a central venous catheter in children weighing less than 1,500 grams increases the risk of nosocomial sepsis by 1.7 times and this risk is higher in umbilical catheters. The use of an umbilical venous catheter for more than 5 days can increase the risk of sepsis by up to 21 times, while with an arterial catheter this risk is 16 times higher (Mullett, Cook, and Gallagher, 1998). In catheter-related blood infections as a major and independent riskfactor in addition to low birth weight, small gestational age, prolonged mechanical ventilation and parenteral nutrition is established and prolonged presence of a central or peripheral venous catheter (Djordjevic et al., 2015; Auriti et al., 2003).

Infusion of lipid solutions

Lipid solutions provide a continuous supply of high-calorie food to premature infants. But this type of emulsion facilitates the growth of many microorganisms due to the suppression of the function of neutrophils and macrophages (Nagata, Brito, and Matsuo, 2002). The risk of bacteremia with coagulase-negative Staphylococcus is primarily associated with the use of lipid solutions (Auriti et al., 2003; Avila-Figueroa et al., 1998). In 1990, Freeman and colleagues (Freeman et al., 1990) reported that infants with a peripheral venous catheter had a 14.9% attributive risk of bacteremia caused by *Coag. (-) Staphylococcus* and these patients were 5.8 times more likely to have received lipid solutions before the onset of bacteremia. Since then, a number of other studies have shown that central venous catheters and intravenous lipid emulsions are independent risk factors for bloodstream infections during hospitalization in the neonatal intensive care unit (Auriti et al., 2003; Avila-Figueroa et al.,1998).

Mechanical ventilation

In many studies, mechanical ventilation (MV) is one of the invasive procedures most often associated with an increased risk of developing HAI (Djordjevic et al., 2015; Auriti et al., 2003; Orsi et al.,2009). Prolonged MV is an independent risk factor for the development of VAP (Stoll

et al., 2002; Nagata, Brito, and Matsuo, 2002; Basiri et al., 2015). Researchers from China found that mechanical ventilation for more than 5 days increased 4.8 times the risk of ventilation pneumonia (Yuan, Chen, and Yu, 2007). In adults (Torres et al., 1995) and children (Elward, Warren, and Fraser, 2002), reintubation has also been shown to be a risk factor for the development of NI. There is still no consensus on the need to change the breathing circuits, the frequency of such manipulations and the risk associated with them for patients, and the data obtained so far are contradictory.

Duration of hospitalization

Data from the literature indicates that the longer the hospital stay in NICU, the higher is the risk of developing HAI (Djordjevic et al., 2015; Nagata, Brito, and Matsuo, 2002; Ramasethu, 2017). The prevailing opinion is that the average diagnosis of HAI is made 2 weeks after treatment. A study from Canada (Aziz et al., 2005) found 15-19 days, South Korea-15-18 days (Jeongand Choi, 2006), and South America - 14-17 days (Efird et al., 2005).

Antibiotics

Antibiotics are the most commonly prescribed drug in neonatal intensive care units (Schulman et al., 2015). The positive effects of proper and timely antibiotic therapy are undoubted. However, overuse of antibiotics is associated with side effects, such as an increased risk of infection with multidrug-resistant microorganisms, invasive fungal infection, bronchopulmonary dysplasia, necrotizing enterocolitis, late-onset sepsis, and death (Tsai et al., 2014; Cotton et al., 2006; Novitsky et al., 2015; Kuppala et al., 2011).

The frequency and duration of antibiotic use are risk factors that are often associated with the incidence of sepsis in preterm infants (Calil et al., 2001). Newborns admitted to the intensive care unit often receive antibiotics, especially those born with very low weight. A study by the Canadian Neonatology Association found that 85% of the 13,738 children born with very low birth weight admitted to the neonatal intensive care unit between 2010 and 2014 were treated with antibiotics during their hospital stay (Ting et al., 2016). The high incidence of early and late onset sepsis in preterm infants, associated with increased mortality and morbidity, and the difficulty in differentiating the clinical signs of sepsis from other non-infectious symptoms may explain the empirical antibiotic treatment.

Insufficient staff and overcrowding of the wards

The lack of sufficient staff, the overcrowding of the wards and the lack of sinks and products for hygienic disinfection are risk factors for nosocomial infections in neonatal intensive care units. Studies have shown a direct link between the provision of qualified staff and the level of infections in neonatal intensive care units (Rogowski et al., 2013; Gray et al., 2013). Longitudinal studies suggest that the design of the neonatal ward may increase the risk of HAI, especially when there is an overcrowding of the ward (Goldmann, Durbin, and Freeman, 1981). As the distance between the individual incubators decreases below the recommended values, and the frequency of NI also increases.

Practices in the maternity ward

According to the WHO, only 68% of women in developing countries receive antenatal care and only 35% of women in the least developed countries have access to trained medical staff at birth (World Health Organization Department of Reproductive Health and Research, 2008). This often leads to unhygienic practices during childbirth, rupture of the umbilical cord with non-sterile instruments, poor skin care and more. At the same time, useful practices such as colostrum use and breastfeeding have been ignored (Stoll, 2006).

Health facilities in developing countries are a major source of neonatal infections for children born in hospital (Zaidi et al., 2005). There is a shortage of consumables and sometimes basic sanitation in maternity wards, such as gloves, sinks, soap, running water, and medical staff are rarely trained in infection control. Non-compliance with the rules of asepsis in invasive procedures, inadequate sterilization of reusable devices and over-crowding of maternity wards make most hospitals in developing countries fertile ground for infections.

Risk Factors in Indicator HAI

Risk factors for catheter-associated bloodstream infections

The main risk factor for bloodstream infections is the presence of a central venous catheter. Central venous catheters (CVCs) can sometimes be life-saving and are widely used in intensive care units. Unfortunately, they are also often the cause of catheter-associated bloodstream infections. Newborns are one of the most vulnerable groups of patients in terms of this NI, due to immature or damaged defense mechanisms, invasive procedures to which they are subjected, suppression of the immune system and others. Low birth weight (Auriti et al., 2003; Geffers et al. 2010), low gestational age (Auriti et al., 2003, de Brito et al., 2010) and the presence of metabolic disorders (Advani et al., 2011) have been identified as risk factors for catheter-associated blood

infections. Catheter-associated bloodstream infections are often due to improper placement technique, omissions in hygienic protocols, and poor catheter care. Evidence suggests that the catheter hub is often contaminated with microorganisms and may be the cause of subsequent infection. The risk also increases with increasing catheterization time and frequency of venous manipulations through it (Stoll, 2002; Kung et al., 2016; Touveneau and Pittet, 2011). However, no consensus has been reached so far on what should be the period after which the central venous catheter should be replaced if prolonged venous access is required.

One of the most discussed risk factors for catheter-associated bloodstream infections is parenteral nutrition. It has been shown to be an independent significant risk factor for NI in a number of studies that can increase the risk of blood infection by up to 6-fold (Kawagoe et al., 2001; Kung et al., 2016). Emphasis is placed on the importance of lipid solutions used in parenteral nutrition as the element that predisposes to bloodstream infections, although the exact mechanism has not yet been elucidated (Freeman et al., 1990). Previous studies in intensive care units, including neonatal intensive care units, have revealed an increased risk of catheter-associated bloodstream infections in patients with gastrointestinal disorders (Niedner et al., 2011; Coffin et al., 2014). Disruption of the integrity of the colon wall for some reason may contribute to the translocation of the gastrointestinal microbiota to the bloodstream and the development of a bloodstream infection (Graham et al., 2006).

Risk factors for ventilator-associated pneumonia

One of the most important risk factors associated with VAP is the duration of mechanical ventilation and the presence of an endotracheal tube (Yuan, Chen, and Yu, 2007; Foglia, Meier, and Elward, 2007; Al-Alaiyan and Binmanee, 2017). The intubation procedure itself independently further increases the risk of VAP (Kollef et al., 1997). Early extubation and early transition to enteral feeding may reduce the risk of VAP. Sedation with opiates, frequent endotracheal aspirations and reintubation increase the risk of VAP. Some features of newborns may also serve as risk factors for VAP, such as relative immunosuppression in preterm infants, shorter airways, and the possibility of congenital malformations or immunodeficiencies (Manzoni, Mostert, and De Luca, 2013).

A meta-analysis of eight observational studies involving 370 cases of VAP and 1,071 controls identified 10 risk factors associated with neotal VAP (Tan et al., 2014). The identified risk factors according to the odds ratio are as follows: length of hospital stay (OR 23.45), reintubation (OR 9.18), enteral nutrition (OR 5.59), mechanical ventilation (OR 4.04), blood transfusion (OR 3.32), low birth weight (OR 3.16), premature birth (OR 2.66), parenteral nutrition (OR 2.30), bronchopulmonary dysplasia (OR 2.21) and tracheal intubation (OR 1.12).

Risk factors for necrotizing enterocolitis

One hypothesis for NEC is that the main risk factor is abnormal intestinal colonization, due to the fact that this disease is diagnosed at the earliest 8-10 days after birth, when anaerobic bacteria have colonized the stomach (Claud and Walker, 2001). The authors are of the opinion that any process that leads to hypoperfusion and subsequent damage to the gastrointestinal tract, such as sepsis, polycythemia, intrauterine exposure to cocaine, peri or postnatal asphyxia, respiratory distress syndrome, congenital heart disease, the presence of an umbilical catheter, may predispose the newborn to necrotizing enterocolitis (Lin and Stoll, 2006; Kliegman, 1990; Panigrahi, 2006). In addition, the immature digestive system, digestion and absorption of nutrients, imperfect barrier functions predispose premature infants to intestinal problems (Martin and Walker, 2006). In this group of patients, the secretion of gastric juice is reduced and may be compromised by the introduction of H2 blockers and this further increases the risk of NEC (Guillet et al., 2006).

CONCLUSION

Neonatal nosocomial infections are still a poorly studied problemglobally.They are particularly significant problem due to the serious health and social burden on patients and society. The present review reveals that factors such as low birth weight, prematurity, duration of hospitalization, the use of a central venous catheter and mechanical ventilation are significantly associated with increased incidence of nosocomial infections. Making effective, clear and targeted preventive measures and systems for routine epidemiological surveillance based on risk factors would help reduce morbidity and the serious cost of treatment for occurrence of such an infection.

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