

REVIEW

NOSOCOMIAL INFECTIONS IN THE NEONATAL INTENSIVE CARE UNIT

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ABSTRACT

Neonates admitted for intensive care are a highly vulnerable population of patients, susceptible to infections. In newborns, the nosocomial infections have characteristics that are not seen in any other group of patients. The incidence rate of nosocomial infections in newborns is one of the highest and there are differences in this rate between developed and developing countries. The etiology of nosocomial infections in intensive care units is diverse and the causative agents might be bacteria, viruses or fungi. There are numerous risk factors associated with the characteristics of the patients, the hospital-stay and the level of care provided, that might increase the risk of nosocomial infections.

Keywords: nosocomial infection, neonate, etiology, incidence, risk factors.

List of abbreviations:

CDC- Center for Diseases Control and Prevention
CoNS- Coagulase-negative Staphylococcus
CRIB- Clinical Risk Index for Babies
ESBL- extended-spectrum beta-lactamase producing
HAI- hospital-acquired infection

RÉSUMÉ

Infections nosocomiales dans l'unité de soins intensifs néonataux

Les nouveau-nés admis dans l'unité de soins intensifs constituent une population particulièrement vulnérable de patients sensibles aux infections. Chez les nouveau-nés, les infections nosocomiales (IN) ont des caractéristiques que l'on ne retrouve dans aucun autre groupe de patients. Le taux d'incidence des IN chez les nouveau-nés est l'un des plus élevés et il existe des différences entre ces taux dans les pays développés et ceux en cours de développement. L'étiologie de NI est diverse et les agents responsables peuvent être des bactéries, des virus ou des champignons. Il existe de nombreux facteurs de risque associés aux caractéristiques de la population de patients, au séjour à l'hôpital et au niveau de soins fournis qui pourraient augmenter le risque d'infection nosocomiale.

Mots-clés: infection nosocomiale, nouveau-né, étiologie, l'incidence, facteurs de risque.

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NEC- necrotizing enterocolitis
NI- nosocomial infection
NICU- neonatal intensive care unit
RSV- respiratory syncytial virus
SENIC- Study on the Efficacy of Nosocomial Infection Control
SNAP- Score for Neonatal Acute Physiology
VAP- ventilator-associated pneumonia
WHO- World Health Organization

INTRODUCTION

The improvements in antenatal management during recent years have changed the prognosis of preterm neonates. This has led to a shift of the main population of newborns that are hospitalized and taken care of in the neonatal intensive care units (NICUs). Newborn infants, especially those born prematurely and needing intensive care, are at greater risk of nosocomial infection (NI). They are relatively immunocompromised, often require a prolonged stay in the hospital, and are victims of invasive therapeutic and diagnostic procedures¹. The infections in the neonatal period have characteristics that do not occur in any other group of patients.

Nosocomial infection, also known as hospital-acquired infection (HAI), is defined by the Centers for Disease Control and Prevention (CDC) as a localized or systemic condition resulting from an adverse reaction to an infectious agent or its toxins, without evidence that the infection was present or incubating at the time of admission to the acute care setting².

Nosocomial infections increase the costs of neonatal intensive care, prolong hospitalization and are responsible for almost 50% of the deaths that occur under 2 weeks of age³. According to extensive studies on the consequences of NI on the national health-care system, based mainly on Study on the Efficacy of Nosocomial Infection Control (SENIC), 6% of all nosocomial infections could be prevented by minimal infection control efforts, and 32% of all nosocomial infections could be prevented by well organized and highly effective infection control programmes⁴. In the present article we present some of the aspects of neonatal NI, such as etiology, incidence and risk factors.

ETIOLOGY OF NOSOCOMIAL INFECTIONS IN NEONATAL INTENSIVE CARE UNITS

The organisms causing NI include bacteria, viruses and fungi. In healthy term babies the predominant bacterial pathogens are *Staphylococcus aureus*, enteropathogens and respiratory viruses. In high-risk

nurseries there is a broad spectrum of infectious agents that includes microorganisms normally non-pathogenic for term-newborns, such as *Coagulase negative Staphylococcus* (CoNS) and *Candida*⁵.

Gram-positive bacteria

In the developed countries, up to 70% of the nosocomial infections in the NICUs are caused by Gram-positive microorganisms⁶. The *Staphylococcus spp.* is the main Gram-positive agent of hospital infection in the newborn, the most important being CoNS. It frequently affects low birth weight newborns with prolonged hospital stay, with venous catheters, and administration of parenteral lipids⁷. According to the literature, CoNS causes 50-70% of the cases of late-onset sepsis⁵.

Staphylococcus aureus is a common pathogen in nurseries around the world. It causes bloodstream infections, cutaneous and wound infections, osteoarthritis, meningitis and ventriculitis³. The main reservoir of this bacterium is the hospital staff and contamination usually occurs through the hands⁸.

The most common source of *Enterococcus spp.* is the gastrointestinal tract of the newborn⁷. There is also the possibility of colonization of the mouth, respiratory tract, cutaneous lesions, and of contamination by objects and surfaces of the environment⁹. Enterococci are an occasional cause of infections in the NICU. Overall, 6% of late-onset sepsis cases, 5% of pneumonias, and 9% of surgical infections are caused by enterococcal species³. Preterm newborns who remain hospitalized for over 30 to 60 days, with prolonged use of venous catheters and exposed to multiple antimicrobials, are especially predisposed to infections by *Enterococcus*⁷.

Gram-negative bacteria

According to the literature, approximately 19% of cases of sepsis and 30% of pneumonias are caused by Gram-negative bacteria^{5,10}. These infections are associated with high lethality rates. Commonly isolated bacteria are *E. coli*, *Klebsiella spp.*, *Pseudomonas aeruginosa*, *Enterobacter spp.*, *Serratia marcescens*.

Non maternal strains of *E. coli* (from other patients or environment) can cause invasive diseases¹¹. Studies document that *E. coli* causes 9% of all nosocomial infections¹² and 5-13% of the late-onset bloodstream infections and is one of the leading pathogens in ventilator-associated pneumonia (VAP) alongside with *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*¹³.

Klebsiella spp., particularly *K. pneumoniae* and *K. oxytoca* are well-established pathogens in NICU patients that cause sepsis, urinary tract infections, and pneumonia³. In recent years in the NICUs, extended-spectrum beta-lactamase-producing (ESBL) *Klebsiella spp.* have been identified that are resistant to third-generation cephalosporins.

Serratia spp. is mostly nosocomial pathogen and it may cause sporadic cases of pneumonia, meningitis or little epidemic outbreaks with high lethality rate, especially in prematurely born infants¹⁴.

Pseudomonas aeruginosa is a well-known causative agent of sepsis, conjunctivitis and endophthalmitis and is associated with high mortality rates³. This pathogen is the leading causative agent of ventilator-associated pneumonia (VAP) in premature neonates¹⁵. The epidemiologic importance of this microorganism is supported by its biologic features: production and proliferation of new hospital strains, high antibiotic resistance and ability to persist in a humid environment, including medical equipment for prolonged mechanical ventilation^{16,17}.

Fungi

Different *Candida* strains (*albicans*, *tropicalis*, *parapsilosis*) account for most hospital infections. *Candida spp.* cause candidemia, particularly catheter-related bloodstream infection, and less commonly urinary tract infections, endocarditis, osteomyelitis and meningitis⁷.

Viruses

The most frequent viral nosocomial pathogens are respiratory syncytial virus (RSV) and rotavirus. Hospital staff, family members, and other infected patients represent the main conveyors of viral infections in the neonatal units. The nosocomial viral respiratory infections increase the need for mechanical ventilation, prolong the hospital stay and cause higher medical costs.

INCIDENCE OF NOSOCOMIAL INFECTIONS IN NEONATAL INTENSIVE CARE UNITS

The reported incidence of nosocomial infections depends on a number of factors. In some studies,

both perinatal and nosocomial infections are included¹⁹, while others exclude infections occurring in the first days of life. Other factors are the level of intensive care provided – small units providing care mainly to normal term babies report lower rates than level III intensive care units in which care for critically ill infants is provided²⁰. The rate of nosocomial infections is the highest in NICUs compared to other hospital wards, including pediatric and adult intensive care units¹⁸. The rates of incidence differ depending on the type of hospital, the characteristics of the newborn patients (gestational age, birth weight, associated conditions), on the methods used for the diagnosis of infections and for epidemiologic surveillance⁷.

The most frequent infections in NICUs are bloodstream infections, pneumonia, and necrotizing enterocolitis (NEC); less frequent complications are infections of the eyes, mouth or skin^{21,22}.

Significant differences exist between the NICUs and the incidence of nosocomial infections in the group of infants with very low birth weight may vary between 6.7% to 74.5%, whereas in the group of infants with low or normal birth weight the incidence is between 0.1% to 17%²³. Another factor that might influence the incidence rate is the methodology used for the diagnosis of infection. In some studies, the researchers included only microbiologically proven infection while in others are included both clinically and microbiologically diagnosed infections. In addition, different methods might be used for calculating the incidence. Usually, the incidence is calculated dividing the number of infected patients by 100 hospitalized patients. In the last years more frequently used and accurate is the calculation of the incidence rate using the number of infections in the nominator and in the denominator is the hospital stay/1000 patient-days.

There are differences in the incidence of nosocomial infections between the NICUs in developed and developing countries (Table 1). In the developing countries, the nosocomial infections remain the major reason for preventable morbidity and mortality. Countries in sub-Saharan Africa and South Asia have the highest neonatal mortality caused by nosocomial infections²⁴. The main reasons for high morbidity and mortality in those countries are overcrowding, lack of preventive measures, lack of control and inadequate use of the scarce financial resources. An observational study of the incidence of nosocomial infections in developing countries determined that bloodstream infections in those countries are 3 to 20 times more common than in industrial countries²⁵.

Table 1. Nosocomial infections incidence published in different studies from developed and developing countries.

<i>Authors</i>	<i>Study Design</i>	<i>Number of patients</i>	<i>Period, Place of the study</i>	<i>Results</i>
Klevens et al. ²⁶	National nosocomial infection surveillance system (NNIS)	3,789,310 neonates	1990-2002 USA	6.88/1,000 patient-days
Gill et al. ²⁷	Prospective multicenter	3180 neonates with birth weight <1000 gr	2002-2004 Australia, New Zealand	5.02/1,000 patient-days
Aziz et al. ²³	Cohort, Prospective, Multicenter	3253 neonates with weight <1500 gr. 13244 neonates with weight >1500gr.	January 1996- October 1997. Canada	23.5% in neonates with weight <1500 gr 2.5% in neonates with weight >1500 gr
Zingg et al. ²⁸	Point-prevalence ECDC	6750 neonates	2011-2012 29 EU country members, Iceland Norway Croatia	10.7%
Orsi et al. ²⁹	Cohort prospective	575 neonates	2003-2006 Italy	13.2% 7.8/1000 patient-days
Djordjevic et al. ³⁰	Cohort prospective	381 neonates	1 January- 31 December 2012 Serbia	19.4% 9.1/1000 patient-days
Basiri et al. ³¹	Point-prevalence retrospective	1000 neonates	October 2012- March 2013 Iran	5.1% 7.2/1000 patient-days
Urzedo et al. ³²	Cohort prospective	4615 neonates	1997-2012 Brazil	14.45/1000 patient-days
Mohammed et al. ¹³	Cohort prospective	418 neonates	March 2012- February 2013 Egypt	38.5%
Kilic et al. ³³	Cohort prospective	352 neonates	July 2011- June 2012 Turkey	10.5% 11.5/1000 patient-days

RISK FACTORS FOR NOSOCOMIAL INFECTIONS IN NEONATAL INTENSIVE CARE UNITS

The risk factors for hospital-acquired infections (HAI) can be divided in two groups: intrinsic and extrinsic. The intrinsic factors include characteristics such as gestational age, birth weight, severity of the disease, immunologic maturity. These risks are usually outside of the control of the hospital and vary from hospital to hospital, but are important factors in determining whether the patients will develop an infection. Extrinsic risk factors may reside in the patient care staff (practices of an individual care-giver) or the institution (practices in an entire hospital). The extrinsic factors include hospital-stay, use of invasive devices, medications, exposure to hospital environment and hospital staff, hygiene and hospital infection control practices.

Intrinsic risk factors

• **Immunologic immaturity**

The immunologic deficits in the newborns affect all aspects of the immune system³⁴. The levels

of neutrophils and immunoglobulins are lower compared to adults. In premature infants, the antibodies have lower opsonic function for potential pathogens and their ability to produce antibodies under the influence of polysaccharide antigens is reduced. The T-cell function is also disturbed in infants born prematurely.

• **Birth weight**

The birth weight is used as one of the most important and stable predictive factor for the expected severity of the disease. The risk of infection is inversely proportional to the birth weight. It also serves as a marker for the immunologic immaturity and underdeveloped mechanical barriers³⁴. The strong correlation between low birth weight and the risk of nosocomial infection has been proved in numerous studies^{1,13,22,30}. The risk of infection increases by 3% with every reduction of the birth weight with 500 grams³⁵. The strongest correlation between birth weight as risk factor and nosocomial infections has been established for the group of infants with weight between 750-999 grams³⁶.

- **Gestational age**

The risk of nosocomial infection is inversely proportional with the gestational age. Premature birth and birth weight are considered the two most important risk factors for HAI^{29,35}. The highest incidence is recorded in children born before 32 weeks of gestation³⁵. When considering gestational age as a risk factor for NI, some authors recommend the rate of NI to be corrected based on gestational age, to facilitate a better comparison of data³⁷.

- **Severity of illness**

Substantial variations in outcomes among infants of the same birth weight have been observed in different NICU's. In order to have better predictors for outcome, neonatal severity of illness scores have been developed. These scores assess underlying physiologic factors that can contribute to outcome. These include the Score for Neonatal Acute Physiology (SNAP)³⁸ and the Clinical Risk Index for Babies (CRIB)³⁹, which assess physiologic derangements in each organ system at specified intervals during hospitalization (e.g. at admission, at day of life 7). The use of those scores is limited now to research studies, but they might be implemented routinely in everyday practice after validation in a non-research setting.

- **Extrinsic risk factors**

- **Intravenous catheters**

The use of umbilical venous catheters for more than 5 days could increase the risk of sepsis by 21 times, whereas considering arterial catheters the risk is 16 times higher⁴⁰. The prolonged use of central or peripheral venous catheters is considered one of the major and independent risk factors of catheter-related bloodstream infections³⁰.

- **Administration of lipids**

The lipid solutions provide high-caloric food intake for the premature infants. However, these emulsions facilitate the growth of microorganisms by suppressing the function of neutrophils and macrophages³⁵. The risk of CoNS bacteremia is mainly associated with the use of lipids⁴¹.

- **Mechanical ventilation**

Endotracheal intubation abolishes the cough reflexes, decreases ciliary motility and results in bacterial colonization of the endotracheal tube. This increases the risk of nosocomial pneumonia in the ventilated neonate²⁰. The prolonged mechanical ventilation is an independent risk factor for VAP^{31,35,37}. Researchers from China determined that ventilation for more than 5 days increases the risk of VAP by 4.8 times⁴².

- **Hospital stay**

It is generally assumed that prolonged hospital stay increases the risk of nosocomial infection^{30,35}. This is hardly surprising, as the sickest babies will stay in hospital longer and will be exposed to different procedures and variety of potential nosocomial pathogens.

- **Antibiotics**

Antibiotics and the duration of antibiotic use are associated with an increased risk of infection with multi-resistant microorganisms, invasive fungal infection, necrotizing enterocolitis, late-onset sepsis⁴³⁻⁴⁵. The use of third generation cephalosporins has been linked to the emergence of extended spectrum β -lactamase-producing *Klebsiella pneumoniae*⁴⁶.

- **Understaffing, overcrowding and design of the NICU**

Studies have demonstrated the direct link between ensuring well-trained medical personnel and the rate of infections in NICUs⁴⁷. The recommended nurse to patient ratio is 1:2⁴⁸. Decreasing the distance between incubators increases the risk of NI. The British Association of Perinatal Medicine recommends a distance of 2-4 meters, which ensures 12 m³ for a patient⁴⁹.

- **Practices in the nursery**

The newborns in the developing countries are additionally exposed to some external environmental factors, that put them at risk of infection, such as dangerous practices during childbirth. According to World Health Organization (WHO), only 68% of the women in developing countries receive antenatal care and only 35% in the most underdeveloped countries have access to trained medical personnel during childbirth⁵⁰. This leads to unhygienic practices, discontinuation of the umbilical cord with non-sterile instruments, inadequate care for the skin of the newborn⁵¹. The hospitals in developing countries are the main source of neonatal infection for hospital-born infants²⁵.

CONCLUSIONS

Nosocomial infections are one of the leading causes of morbidity and mortality in the neonatal period. There are substantial variations in the reported incidence rates of NI in developed and developing countries. Knowing the risk factors and the leading etiological agents of NI is an important step in the development of systems for epidemiologic surveillance and programs for infection control and prevention.

Authors contributions

V.R. conceived the original draft preparation. V.R., A.K., M.K., were responsible for conception and design of the review. V.R. and A.K. were responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. V.R., A.K. and M.K. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article“

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