Neonatal nosocomial infections

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Abstract

Objective: to review the current medical literature on neonatal nosocomial infections, emphasizing aspects of neonatal colonization, immune system and infection mechanisms, modes of transmission, epidemiology, surveillance and prevention of these infections, in addition to assessing peculiarities about etiologic agents and prophylactic recommendations.

Sources: electronic search in the Medline and Lilacs databases, with selection of the most relevant articles published within the last ten years.

Summary of the findings: the several peculiarities that cause greater susceptibility to infection in newborns, and the survival of preterm infants due to the invasive procedures and treatment with broad spectrum antibiotics at intensive care units are responsible for prevalence rates of neonatal nosocomial infections between 9.3 and 25.6%. Neonatal nosocomial infections affect at least 50% of newborns who weigh less than 1500 g, which ends up increasing mortality rates. Full-term newborns frequently have skin and soft tissue lesions caused by gram-positive organisms. In neonatal intensive care units, sepsis and pneumonia are frequently diagnosed (especially those caused by S. aureus, S. epidermidis, E. coli, K. pneumoniae, and E. cloacae). An increasing frequency of resistance to several antimicrobial drugs has been observed. A nosocomial infection surveillance program tailored to the characteristics of the neonatal unit allows the identification of infection outbreaks, the rational use of antibiotics and the application of preventive measures.

Conclusions: neonatal nosocomial infections are a relevant problem. Their control can only be achieved if adequate measures concerning pregnant women, hospital environment, nursing staff, and newborns are adopted. Although new prophylactic measures are being proposed for preterm infants, they are costly and do not preclude continued epidemiological surveillance and control in neonatal units.


Introduction

Reports of infections acquired in places where patients are treated date back to the middle ages. The inherent risks of hospital assistance as to what concerns morbidity and mortality are also known since the origin of hospitals in the 18th century.1 Important milestones for the understanding of factors involved in transmission of hospital infections are represented in the observations of Holmes2 and of Semmelweis,3 who verified a relation between occurrence of puerperal infection and inadequate washing of the hands by the staff who assisted the parturients.

Currently, the cumulative knowledge on the incidence, presentation, associated factors, consequences, and prevention of infections acquired in the hospital or up to 73
hours after discharge allows for identification, surveillance, and control of nosocomial infections.

Hospital infections are more frequent and, generally, more severe in newborn infants than in older children or adults. The peculiar characteristics of this period of life allow for greater susceptibility to infections. In addition, another factor responsible for infections being more severe in these patients is the increased survival of premature newborn infants, following prolonged neonatal ICU stay, use of invasive procedures and of wide spectrum antimicrobials.

The prevention and control of neonatal bacterial infections represent a challenge for all professionals involved in hospital care of newborns. Infection outbreaks in nurseries and that result in deaths have been widely reported by the Brazilian press. In other countries, hospital infections are associated with 7 to 73% of neonatal mortality. Neonatal hospital infections, in addition to being the cause of a significant number of perinatal, neonatal, and postnatal deaths, are also associated with increased healthcare costs. This is because hospitalization of infected children is up to threefold longer than that of noninfected children. It is our objective to review the main aspects of this broad theme.

Colonization, infection, and mechanisms of defense in newborn infants

Colonization is the presence of a microorganism in or on a host, with growth and multiplication but without any overt clinical expression or detected immune response in the host at the time it is isolated. A developing fetus is protected from the microbial flora of the genital tract of the mother. Normal colonization in newborns and of the placenta begins during the birth process, after rupture of the amniotic membrane and through subsequent contacts with the inanimate or animate environments until a delicately balanced normal flora is established; subsequently, the precise components of a neonatal endogenous flora evolve. Many factors can influence the acquisition of normal flora: maternal genital flora; type of nutrition of the newborn; hospital staff and people in direct contact with the newborn; and environment, including the flora of objects and other newborns.

In general, newborns that remain in contact with the mother and are naturally breastfed can be colonized on the skin and mucous surfaces (nasopharynx, oropharynx, conjunctive, umbilical chord, external genitalia) several days after birth. The main microorganisms, in this sense, are alpha-hemolytic Streptococcus, negative-coagulase Staphylococcus (skin, upper respiratory mucosa, umbilical stump), lactobacillus, other anaerobic microorganisms, and E. Coli (gastrointestinal tract). Other common bacteria are Candida albicans (gastrointestinal tract, vagina, perineal area) and Staphylococcus aureus (skin and mucous surfaces).

The presence of normal flora and of mildly virulent microorganisms protects the newborn from potentially pathogenic microorganisms, such as gram-negative bacillus. That is because the microorganisms in the normal flora spread to different sites and compete with pathogenic organisms, but rarely causing disease.

Infections, which are the invasion by a microorganism that multiplies and causes lesions, usually occur as a direct extension of the sites of colonization or of bloodstream infection with the resulting dissemination of the infection. Infections also depend on the virulence of the microorganism, of the inoculum, and of the pathogen-host interaction. In most cases, the pathogens invade the newborn through the conjunctive, the respiratory and gastrointestinal tracts, and the skin.

The decreased production and function of local and systemic defense (of both innate and specific responses) depend on the antigen and contribute to greater susceptibility to infection during the neonatal period.

That is the reason for local natural barriers against bacterial infections being compromised in newborn infants. The skin, and especially that of preterm newborn infants, is immature and has increased permeability, which is partially caused by the production of free fatty acids and alkaline pH. Moreover, skin integrity can be affected by environmental aggressions. The umbilical chord can be another source of infection due to is proximity to the bloodstream, to the increased permeability, and to the potential colonization by pathogens. Also, the production of secretory immunoglobin A is absent during the first days of life; thus, the respiratory and gastrointestinal epithelium are more vulnerable.

The lack of innate immune response (granulocytes, mononuclear phagocytes, and humoral factors such as the complement, fibronectin, and colectin), which is activated in the first hours or days of contact with microbes, plays a critical role in the susceptibility to infection by pyogenic bacteria and fungi. The antigen-specific response, in turn, does not develop until 5 to 7 days after the initial exposure to microorganisms.

In general, in newborn infants, the ability to accelerate production of neutrophils as a response to infection is restricted, the chemotaxy of neutrophils is decreased as a response to a variety of stimuli, and these cells are less adherent, deformable, and survive less. As to what concerns the mononuclear phagocytes, despite the delayed and attenuated inflow of these cells to the site of inflammation, some studies have suggested that newborns present microbicidal activity against certain bacteria that is similar to that of adults. In turn, in term newborns, the production of mediators that contribute to the recruitment of neutrophils to the site of infection differs 25 to 50% in relation to that of adults (GM-CSF, TNF, IL-8, leukotriene B4); whereas the production of C-CSF and of IL-1 is similar to that of adult life. Also, newborn infants and especially preterm newborn infants present deficiencies in both pathways of
the complement system and in fibronectins. In this sense, the fractions of the alternative pathway of the complement present smaller concentrations than those of the classical pathway. Consequently, there is a deterioration of the lyse of bacteria (complement factor 9 - C9), especially of those that are gram-negative, and a reduction of opsonization (C3b), especially of those that are capsulated.

The immature innate response of newborns is partially compensated by transplacental transfer of immunoglobulin G from the mother. The specific antibodies acquired from the mother, in this sense, can promote more efficient opsonization and phagocytosis. However, the absence of type-specific antibodies acquired from the mother can be a predisposing factor to infection by certain agents independently of the production of antibodies by the newborn infant.

The ability to respond to specific antigens develops chronologically and in a distinct manner provided that the response occurs independently of the help of T lymphocytes, or that this help is necessary. With the exception of polysaccharide antigens, the response to most specific antigens is dependent on T cells. In newborn infants, the production of antibodies by the lymphocytes B and thymus-dependent antigens is similar to that of adults. Considering that many pyogenic bacteria are capsulated and, consequently, the response is thymus-independent, the production of antibodies by newborns will be limited and contribute to greater susceptibility.

Despite the fact that the causes of increased susceptibility of newborns to intracellular pathogens such as virus, T. gondii, and M. tuberculosis are still not well understood, there is evidence of involvement of defects in innate immune system cell function, such as: delayed recruitment of monocytes and macrophages to the tissues; reduction of cytokine production, which increases cell immunity; and reduction of citotoxicity of NK cells and of production of gamma-interferon. Moreover, there are other factors that can contribute to slower differentiation of T cells, such as: less efficient dendritic cells; greater dependence of dendritic cells on T cells; greater dependence of dendritic cells on the levels of cytokines for their induction and proliferation, and, also, differentiation for T cells. Consequently, this allows for facilitated replication of intracellular pathogens.

### Hospital infections

**Definition**

In general, hospital infections include any infection that are not present or incubated at the moment of hospital admission and, thus, are acquired during hospitalization or up to 72 hours after discharge.

Though all infections acquired by babies born in hospitals can be considered nosocomial infections, infections that become overt early (during the first week of life) are frequently caused by microorganisms transmitted by the mother to the newborn. These infections present a characteristic epidemiology, different from that of hospital infections acquired later in the neonatal period. Usually, neonatal infections are divided into early-onset (less than 3 to 7 days of life), originated by the mother, and late-onset (greater than 3 to 7 days of life), which are those acquired after birth and thus not originated by the mother.

The Center for Disease Control and Prevention (CDC) considers that hospital infections includes those acquired intrapartum, during hospitalization, or up to 48 hours after hospital discharge. The exception includes transplacental infections (syphilis, toxoplasmosis, rubella, cytomegalovirus infection, hepatitis B, herpes simplex, HIV infection, and so on). Infections that occur up to 48 hours of life are considered hospital infections originated by the mother and those that occur after 48 hours of life are considered hospital infections originated by the environment.

In Brazil, the Ministry of Health (portaria 2616/98) has presented guidelines for the control of hospital infections. These guidelines classify all neonatal infections as hospital infections with the exception of those acquired through the placenta or those associated with rupture of amniotic membranes for more than 24 hours before delivery.

### Epidemiology of hospital infections

The rates of incidence of nosocomial infections vary considerably. These rates depend on the type of hospital, on the characteristics of the newborn patients (gestational age, postnatal age, associated conditions), on the methods for diagnosis of infections and for epidemiological surveillance.

Term newborn infants admitted to appropriate care, admitted to rooming-in environments, and breastfed rarely acquire postnatal infections. Studies have reported that term newborns acquired infections at rates of 0.6 per 100 to 16.9 per 100 infants. In turn, infections in newborns in neonatal ICUs are increasingly more frequent.

The most comprehensive studies on epidemiology of hospital infections at neonatal ICUs were carried out by the CDC, by means of the National Nosocomial Infection Surveillance System (NNISS), which reported 13,179 nosocomial infections at US neonatal units; and by the National Institute of Child Health and Human Development (NICHD), which reported data from a cohort of 7,861 babies with birth weights of 401 to 1,500 g.

The overall rates of nosocomial infections per patient (total number of infections per 100 patients) at US neonatal units range from 1.8 to 15.3. In the case of newborn infants with less than 750 g, the incidence of hospital infections is of at least 42%. There are no comprehensive studies available in the Latin American or Brazilian literature. A study carried out by the Brazilian Ministry of Health, in 1994, in 99 tertiary hospitals located in Brazilian capitals indicated an overall hospital infection rate of 14.4% in neonatology. A study carried out at the Hospital São
infections. The predisposition to infection in these newborns involves frequent use of the hands. In general, newborn infants presenting good clinical status have a short hospital stay and are not submitted to invasive procedures. In this sense, the exposure to hospital staff is the most important risk factor for these patients. Conversely, newborn infants admitted to neonatal ICUs have prolonged hospital stay, and frequent exposure to invasive procedures and to a great number of people responsible for the care of the baby. The care of these newborns involves frequent use of the hands. In general, low weight at birth is the most influential factor for hospital infections. The predisposition to infection in these newborn infants is due to a combination of several risk factors as a consequence of immature immune defenses and of the use of life support systems, in the sense that the latter promotes breakdown of the normal defense barriers. These systems submit the newborn to use of endotracheal cannulas and mechanical ventilators, which interfere on local pulmonary defenses; to use of catheters that allow for spreading of microorganisms from the cutaneous flora into the bloodstream; to the use of mechanisms that reduce gastric acidity, such as H2 blockers, parenteral hyperalimentation (can convey pathogenic agents to the patient); and to prolonged and frequent use of antimicrobials such as cephalosporines and aminoglycosides, whose selective pressure promotes colonization with resistant pathogens. Moreover, prolonged neonatal ICU stay facilitates the colonization with potentially pathogenic, gram-negative bacterial flora of the environment and hands of hospital staff. This colonization can be of strains of *Staphylococcus aureus* (repeatedly recovered from the hands and nostrils of 30 to 50% of hospital personnel) and, thus, facilitate infection especially in overcrowded, understaffed units.

The main pathways for acquiring microorganisms that can cause infections are airborne transmission; direct contact (direct physical transmission from an infected or colonized person to a host by the hands or secretions); indirect contact (physical transmission from inanimate objects such as transducers, thermometers, stethoscopes, manometers, suction catheters, and water); common conveyors (contaminated fluids, IV solutions, milk, blood, and derivatives); and by vectors (flies and cockroaches). The exposure to these sources will contribute to the establishment of an endogenous flora of the newborn; in other words, bacterial colonization of the skin, the mucosa, and the gastrointestinal and respiratory tracts that, in turn, are also frequently the source of microorganisms that cause infection. Infections originated by the patient’s own reservoirs are classified as of endogenous transmission. Table 1 presents the types of transmission of infections caused by certain etiological agents.

The main risk factors for infection of newborns can be divided into intrinsic and extrinsic factors. The intrinsic factors include characteristics such as gestational age, sex, birth weight, severity of the disease, and immunologic development. The extrinsic factors include hospital stay; use of invasive procedures, such as arterial and venous catheters, tracheal cannulas, gastric or gastric-duodenal probe, ventriculo-peritoneal shunt, chest drains, and so on; exposure to hospital environment and staff, such as nurse:patient ratio and physical space (overcrowding and understaffing), staff training, hygiene and hospital infection control techniques; and use of antimicrobials.

In general, newborn infants presenting good clinical status have a short hospital stay and are not submitted to invasive procedures. In this sense, the exposure to hospital staff is the most important risk factor for these patients. Conversely, newborn infants admitted to neonatal ICUs have prolonged hospital stay, and frequent exposure to invasive procedures and to a great number of people responsible for the care of the baby. The care of these newborns involves frequent use of the hands. In general, low weight at birth is the most influential factor for hospital infections. The predisposition to infection in these newborn

### Acquiring microorganisms and the predisposing factors for infection

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### Infection sites

Infections of term newborns and at normal nurseries are primarily cutaneous and of soft tissues, including omphalitis, pocks, abscess, and bullous impetigo. Outbreaks of conjunctivitis and bacterial or viral gastroenteritis can spread very rapidly in these nurseries.

In the case of neonatal ICUs, bacteremia and sepsis are the most frequent infections and account for 30 to 50% of hospital infections; these infections are followed by pneumonia; eye, ear, nose, and throat infections; skin and soft tissue infections; and gastrointestinal and surgical site infections. There are variations in these sites of infection according to weight at birth and to the characteristics of the unit.

### Etiology

The microorganisms that cause hospital infections include bacteria, fungi, and virus; it is also possible to include all commensal pathogens and organisms of humans. In normal nurseries, the *Staphylococcus aureus*, the...
Table 1 - Major modes of transmission of some nosocomial infections

<table>
<thead>
<tr>
<th>Mode of transmission</th>
<th>Nosocomial infection</th>
<th>Infectious reservoir</th>
<th>Source of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>Measles, pulmonary tuberculosis</td>
<td>Infected individuals</td>
<td>Air-borne particles</td>
</tr>
<tr>
<td>Direct contact</td>
<td>Staphylococcal neonatal infection</td>
<td>Colonized / infected</td>
<td>Hands containing secretions from infected wounds</td>
</tr>
<tr>
<td>Indirect contact</td>
<td>Respiratory Syncytial Virus</td>
<td>Infected individuals</td>
<td>Hands and fomites</td>
</tr>
<tr>
<td></td>
<td>Antibiotic-resistant bacteria</td>
<td>Colonized/ infected</td>
<td>Hands and fomites</td>
</tr>
<tr>
<td>Droplets</td>
<td>Whooping cough, invasive meningococcal disease, Streptococcal infection - group A</td>
<td>Colonized / infected</td>
<td>Large respiratory droplets</td>
</tr>
<tr>
<td>Endogenous</td>
<td>Bacteremia caused by coagulase-negative Staphylococcus</td>
<td>Skin at the insertion site of the vascular catheter</td>
<td>Intravascular catheter</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection caused by <em>Escherichia coli</em></td>
<td>Periurethral skin and mucous membranes</td>
<td>Urinary catheter</td>
</tr>
<tr>
<td>Common source</td>
<td>Bacteremia caused by gram-negative bacteria Posttransfusion infection with HIV, HBV, HCV, CMV</td>
<td>Liquid substances in the environment</td>
<td>Contaminated IV fluids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infected individuals</td>
<td>Donor’s contaminated blood products</td>
</tr>
<tr>
<td>Vectors</td>
<td>Salmonellosis</td>
<td>Infected / colonized</td>
<td>Contaminated food</td>
</tr>
<tr>
<td></td>
<td>Enteric infection</td>
<td>infected individuals</td>
<td>Flies, ants</td>
</tr>
</tbody>
</table>

HIV: human immunodeficiency virus; HBV: hepatitis B virus; HCV: hepatitis C virus; CMV: cytomegalovirus.

enteropathogens, and the respiratory virus are the main infection agents. At high-risk nurseries, there is a broad spectrum of infection agents that includes microorganisms normally nonpathogenic for term newborns, such as *negative-coagulase staphylococci* and Candida. In the assessment of the etiology of neonatal hospital infections it is important to consider that it also depends on birth weight; on characteristics of the unit; on use of invasive procedures; on maternal or nonmaternal origin of the infection; and on temporal evolution of etiological agents in the unit. It is fundamental that each institution register the microbiological ecology of its units through epidemiological surveillance.

Table 3 presents the etiology of hospital neonatal infections of two selected studies.

Next, we will comment some of the aspects of the main etiological agents and the most frequent clinical manifestations according to different agents.

**Gram-positive bacteria**

The Staphylococcus is the main gram-positive infection agent of hospital infections of the newborn; the most important being negative-coagulase Staphylococci such as *Staphylococcus epidermidis*, which frequently affects low
Table 2 - Reports of nosocomial infection at neonatal units, possible modes of transmission, and associated factors

<table>
<thead>
<tr>
<th>Reference #</th>
<th>Country/region</th>
<th>Agent</th>
<th>Probable mode of transmission / associated factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>New York, USA</td>
<td><em>P. aeruginosa</em></td>
<td>Nurses' false nails</td>
</tr>
<tr>
<td>25</td>
<td>Netherlands</td>
<td><em>Multiresistant Enterobacter cloacae</em></td>
<td>Digital electronic thermometer</td>
</tr>
<tr>
<td>37</td>
<td>Washington DC, USA</td>
<td><em>Enterobacter cloacae</em></td>
<td>Endogenous flora</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Horizontal transmission</td>
</tr>
<tr>
<td>38</td>
<td>Boston, USA</td>
<td>Several causing sepsis</td>
<td>Broviac catheter</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Parenteral nutrition</td>
</tr>
<tr>
<td>28</td>
<td>South Africa</td>
<td><em>Multiresistant Klebsiella pneumoniae</em></td>
<td>Cockroaches</td>
</tr>
<tr>
<td>31</td>
<td>Madrid, Spain</td>
<td><em>Enterobacter cloacae</em></td>
<td>Inadequate hygiene, overcrowding</td>
</tr>
<tr>
<td>39</td>
<td>Southeast of India</td>
<td><em>Klebsiella pneumoniae</em></td>
<td>Intravenous dextrose solution</td>
</tr>
<tr>
<td>40</td>
<td>Ottawa, Canada</td>
<td><em>coagulase-negative Staphylococcus aureus</em></td>
<td>Enteral nutrition through nasogastric tube</td>
</tr>
<tr>
<td>41</td>
<td>New York, USA</td>
<td><em>Vancomycin-resistant Enterococcus</em></td>
<td>Prolonged antibiotic therapy and low birthweight</td>
</tr>
<tr>
<td>42</td>
<td>St-Ettiene, France</td>
<td><em>Serratia marcencens</em></td>
<td>Transducers with built-in tachograph</td>
</tr>
<tr>
<td>26</td>
<td>Brussels, Belgium</td>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Water bath used to thaw frozen plasma</td>
</tr>
<tr>
<td>43</td>
<td>Bahamas</td>
<td><em>Acinetobacter spp.</em></td>
<td>Aerosols and air-conditioners</td>
</tr>
<tr>
<td>27</td>
<td>Roraima, Brazil</td>
<td>endotoxins clinical sepsis and 35 deaths</td>
<td>Intravenous solutions</td>
</tr>
<tr>
<td>44</td>
<td>Netherlands</td>
<td><em>Stenotrophomonas maltophilia</em></td>
<td>Tap water</td>
</tr>
</tbody>
</table>

The *Staphylococcus aureus* is also a concern for most nurseries around the world. Cutaneous lesions and invasive procedures are predisposing factors for occurrence of focal lesions, bacteremia, meningitis, or pneumonia. The main reservoir of this bacterium is the hospital staff and contamination usually occurs through the hands.

The *Enterococcus spp* can be acquired by the mother, but it is turning into a prevalent agent in nosocomial infections. The most common source of infection is the gastrointestinal tract of the newborn. There is also possibility of colonization of the mouth, respiratory tract, cutaneous lesions, and of contamination by objects and surfaces of the environment. Preterm newborns who remain hospitalized for more than 30 to 60 days, with prolonged use of venous catheters and exposed to multiple antimicrobials, are especially predisposed to infections by *Enterococcus*. These infections can be severe and include: necrotizing enterocolitis, sepsis, pneumonia, meningitis, and endocarditis.
**Table 3** - Frequency (%) of pathogens causing early-onset (maternal origin) and late-onset (environmental origin) nosocomial infection at neonatal intensive care units in selected studies

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>USA, NNISS 1986-1994</th>
<th>USA, NICHD 1991-1993</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>maternal origin</td>
<td>environmental origin</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Gram-positive Bacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>2.6%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Coagulase-negative Staphylococcus</td>
<td>12.3%</td>
<td>14.7%</td>
</tr>
<tr>
<td>Streptococcus - group B</td>
<td>46.4%</td>
<td>31.8%</td>
</tr>
<tr>
<td>Enterococcus (Streptococcus - group D)</td>
<td>2.1%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Other streptococci</td>
<td>10.0%</td>
<td>6.8%</td>
</tr>
<tr>
<td>Gram-negative Bacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>10.2%</td>
<td>7.4%</td>
</tr>
<tr>
<td>Klebsiela species</td>
<td>3.2%</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas species</td>
<td>2.9%</td>
<td></td>
</tr>
<tr>
<td>Enterobacter</td>
<td>0.5%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Fungi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida species</td>
<td>1.2%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Other</td>
<td>14.7%</td>
<td>23.9%</td>
</tr>
</tbody>
</table>

n= number of infants diagnosed with infection.

**Gram-negative bacteria**

Gram-negative bacteria are the cause of approximately 19% of cases of nosocomial sepsis, and of over 30% of pneumonias. These infections are severe and present high lethality rates (40 to 90%). Nonmaternal strains of *Escherichia Coli* (other patients or environment) can cause invasive diseases. The main reservoir of *Klebsiela* and *Enterobacter* are the gastrointestinal tract of the patient, invasive procedures, and catheters. Several gram-negative bacillus have been associated with outbreaks of hospital infections at neonatal units, especially those associated with environmental contamination, such as: *Pseudomonas aeruginosa*, *Serratia marcencens*, *Acinetobacter spp.*, *Stenotrophomonas maltophilia*, among others.

**Fungi**

Similarly to infections by gram-negative bacteria, those by fungi are increasingly prevalent in neonatal units. These infections are associated with prolonged exposure to antibiotics, with parenteral hyperalimentation, with tracheal intubation, and with IV infusion of lipids. Different *Candida* strains (albicans, tropicalis, parapsilosis) account for most hospital infections. The most common presentation is fungemia. However, the fungi can spread and cause meningitis, spleen or kidney abscess, endophtalmitis, osteomyelitis, or invasive dermatitis with mortality rates as high as 25 to 50%.

**Virus**

Despite the fact that they are usually not identified, viral nosocomial infections are very common. Hospital staff, family members, and other infected patients represent the main conveyors of viral infections in neonatal units. The most frequent viral nosocomial infections are caused by respiratory syncytial virus and by rotavirus.

Nosocomial transmission of respiratory syncytial virus can result in increased morbidity and mortality for all
Epidemiological surveillance

Epidemiological surveillance is a set of activities aimed at active, systematic and continuous observation of collection, analysis and assessment of data regarding infection. The main objectives of surveillance of neonatal hospital infections, which is fundamental for prevention, are:

1. to determine the epidemiological profile of hospital infections evaluating etiological agents, microbial sensitivity, and affected sites;
2. to observe the endemic levels of infection and early detection of outbreaks;
3. to define risk factors according to type of patient and procedures used;
4. to prioritize control and prevention measures, as well as the evaluation of necessary strategies of intervention.

Hence, the development of a surveillance program involves choosing a surveillance method, establishing uniform criteria for hospital infections, for identification of types of infection, and rationalizing control and use of antimicrobials.

There are several methods of epidemiological surveillance of hospital infections. The method of choice will depend on the characteristics of the hospital, on the available resources, on the type of patient, and on the most frequently identified infections. This allows for choosing between global hospital surveillance and site or type of infection surveillance, or a combination of both; both types involve evaluation of risk factors through microbiological data. In epidemiological surveillance, it is possible to collect data passively, actively, or by review of medical records. In any of these methods, following the isolation of the etiological agent, it is necessary to characterize the susceptibility to antimicrobials.

A traditional method of epidemiological surveillance is based on the calculation of cumulative incidence of infections. The numerator of the formula of this calculation is the number of identified cases, which can be either the number of infected newborns or of hospital infections; the denominator is the number of admissions, births, or discharges of the unit (discharge and deaths). In this method of surveillance, the concept of cumulative incidence of infections assumes that there is an equivalent risk for infection for each patient, thus not taking into consideration the duration of exposure to important risk factors.

Cumulative incidence of infections

\[
\text{number of infected newborns or of hospital infections in all sites} \times 100
\]
\[
\frac{\text{number of admissions/births/discharges}}{1000}
\]

The data should be analyzed and assessed monthly. The calculated rate can be used for assessment of endemic patterns and for early detection of possible outbreaks. The results should be distributed to the staff involved in healthcare of newborns with the objective of involving all professionals in the problem of hospital infections and in the carrying out of control measures.

The National Nosocomial Infection Surveillance System (NNISS) is an epidemiological surveillance system for hospital infections with the use of protocols called surveillance components. This method is widely used in ICUs. It was developed in the United States during the 1970s and is based on nosocomial infection rates being associated with risk factors such as average hospital stay in units and number and duration of invasive procedures (central catheters, artificial ventilators, and so on). Based on these observations, the notion of incidence density rates was introduced for the calculation of nosocomial infection rates. The numerator of the formula of this calculation is the number of hospital infections, and the denominator is the factor of duration of exposure. Thus, the denominator for incidence density is based on patient-day and device-day (catheters-day and ventilators-day). The rates for epidemiological surveillance provided by this methodology are divided into rates of use of devices, of infections, and of average length of stay (ALOS) of patients, stratified according to weight at birth: less than 1,000 g; 1,000 to 1,500 g; 1,501 to 2,500 g; and greater than 2,500 g. These rates should be calculated monthly for high-risk neonates who fulfill the following criteria: birth weight less than 1,500 g; use of central catheter; use of ventilatory support; use of antifungal therapy; and postoperative period (up to 30 days after surgery). Next, we will present the formulas for calculating some of the NNISS rates.

Device utilization rates

\[
\text{number of devices (central catheter; ventilator)-day} \times 100
\]
\[
\frac{\text{number of patients-day}}{1000}
\]

Global nosocomial infection rates

\[
\text{number of hospital infections in all sites} \times 100
\]
\[
\frac{\text{number of patients-day}}{1000}
\]
Bloodstream infection rates associated with central catheter

\[
\text{Number of bloodstream infection rates associated with central catheter} \times 1000
\]
\[
\text{Number of catheters-day}
\]

Pneumonia rates associated with ventilator

\[
\text{Number of pneumonias associated with ventilator} \times 1000
\]
\[
\text{Number of ventilators-day}
\]

Average length of stay (ALOS)

\[
a + b + c
\]
\[
d + e
\]

a = sum of the number of days of hospitalization for all patients in the unit on the first day of the month
b = sum of the number of days of hospitalization for all patients in the unit for the month (patients-day)
c = sum of the number of days of hospitalization in the unit on the last day of the month
d = sum of the number of patients in the unit on the first day of the month
e = sum of the number of patients admitted in the unit during the month

Investigation and control of hospital infection outbreaks in nurseries

Hospital infection outbreaks occur in cases of significant increase of infections (above the upper endemic limit of the neonatal unit). The increase in infection rates in specific sites or by a specific microorganism calls for measures aimed at identifying the agent, the reservoir, and the risk factors for transmission of the infection. Moreover, the occurrence of infections caused by unusual pathogens that are associated with high morbidity and/or lethality rates in newborns call for special concern with, and investigation of, the matter.

In cases of suspected outbreaks, all infection control measures should be reviewed. Special attention should be given to the washing of the hands of the staff between handling of newborn infants, to the sterilization and disinfecting routine procedures, to the preparation of formulas, and to the asepsis techniques for invasive procedures.

The origin of cases of outbreak due to unusual microorganisms is probably on the nonobservance of infection control measures, such as overcrowding, understaffing, hygiene, and so on.

If only one microorganism is responsible for the outbreak, infected or colonized patients, as well as the staff should be located in a cohort. The cohort can be located in a separate or marked area inside the neonatal unit with newborn infants isolated inside incubators.56

The collection of cultures for identification of reservoirs in staff or equipment is indicated only in cases in which preliminary epidemiological investigation is suggestive of association with the outbreak. One of the typical examples is that of outbreaks caused by S. aureus resistant to oxacillin and in which culture from the nasal mucosa indicates colonization of the staff. The topic use of mupirocin to the anterior nares is indicated.57

Use of antimicrobials and hospital infection: the need for rationalization and control

Antimicrobials can save lives in the treatment of infected children; whereas in the case of newborns, there are substantial risks, such as: superinfection and infection by microorganisms resistant to toxicity and drugs. That is because antimicrobials interfere in both the endogenous and pathogenic microbiota.

The use of antibacterials is frequent in newborns, especially in those admitted to ICUs. The reported data indicates that the use of these drugs varies from 4.4% to 10.5% for all newborns, and from 42% to 60.4% for all preterm newborns.20 At ICUs, at least 75% of all newborns are administered antibacterials for at least 40 hours, with rates of use as high as 92% for preterm newborns with less than 1,500 g.58 In general, the frequent use of antibacterials is justifiable by the risks and high lethality rates of bacterial infections in newborns. However, it has not been demonstrated that the prophylactic use of antibiotics prevents nosocomial infections. Moreover, newborns whose normal flora is still not established and who are treated with antibiotics can develop colonization of microorganisms not detected in normal children. It has been reported that these microorganisms include those that are resistant to antibiotics. These microorganisms were selected from numerous patients on antibacterials and are part of the flora of the unit.20 In this sense, bacterial invasions are generally resistant to antibacterials used in the specific unit.

Multiresistance to antibacterial drugs has been identified with frequency. In this sense, over 80% of Staphylococcus epidermidis strains and at least 60% of Staphylococcus aureus strains that cause nosocomial infections in neonatal units are methicillin/oxacillin resistant; in other words, resistant to beta-lactamic antibiotics (including penicillin, cephalosporin, and carbapenem) and to a combination of
drugs with beta-lactamas inhibitors. The appearance of strains of enterococcus resistant to vancomycin has been reported in ICUs. This could be a problem since these bacteria are resistant to all available antibiotics and have the potential of being reservoirs for glycopeptide-resistant genes that can be transferred to other more virulent pathogens.

As to the gram-negative bacteria, studies have reported that the appearance of resistance to antibacterials of Klebsiela and Enterobacter strains has caused problems and nosocomial outbreaks. The resistance, which is mediated by plasmid, induces extended-spectrum beta-lactamas (ESBLs) protection providing resistance to penicillin, cephalosporin, and monobactam to both microorganisms. This resistance can also be transferred to other microorganisms and can develop during antimicrobial therapy.

Consequently, it is fundamental to rationalize the use of antimicrobials during the neonatal period. In the choice of antibacterials, priority should be given to drugs that are safer and present more successful in therapeutics or prophylaxis; well-tolerated and that cause less adverse effects; less toxic and cause less selective induction on the endogenous microbiota of the patient; and more cost-effective.

In addition, the understanding of the prevalence of bacteria sensitivity to antibacterials with epidemiological surveillance at each hospital unit, as well as that of the modifications in this sensitivity that occur with time are fundamental for the designing of empirical recommendations of antibacterial therapy and for a more rational use of antimicrobials.

Prevention and control of nosocomial infections

Nosocomial infection prevention and control measures are aimed at minimizing the exogenous and endogenous transmission of pathogenic microorganisms. These measures are directed to the pregnant woman, to the hospital environment, to the hospital staff, and to the newborn him or herself.

Pregnant and parturient woman

In order to understand the factors that determine the prevention of maternally acquired neonatal bacterial infection in the view of current knowledge, we should review and discuss several aspects involved in this process: premature labor, bacterial colonization and invasion in pregnant women by potential neonatal infection agents, premature and/or prolonged amniorrhaxis in different gestational ages, obstetric and perinatal risk factors for early-onset neonatal bacterial infection, maternal antibiotic therapy, intrapartum antibiotic prophylaxis, handling of newborns presenting risks for infection, among others. In this paper, we will limit ourselves to aspects of bacterial infection prevention that do not have a maternal origin. For more information, readers can consult the literature on the matter.

Hospital environment

In relation to hospital environment, some factors associated with the acquisition of infections are physical area, nurse:patients ratio, and equipment. In our setting, with the aim of reducing the indexes of nosocomial infection, the Society of Pediatrics from São Paulo delivered to all neonatal units of the state specific recommendations related to the physical space required between incubators, to the adequate number of sinks and to the ideal nurse:patients ratio in high, medium, and low-risk units. The same publication recommends that the nursery be located close to the obstetric unit and count on internal divisions, with beds for intermediary and intensive care. According to these recommendations, the intermediary care unit should have an area of 3.5 m² for each bed and a 60 cm distance between the cradles; for the Intensive Care Unit, these measures should be of 5 m² and 80 cm, respectively. The rooming-in environments should have an area of 6 m² for the mother and the newborn, with, at the maximum, six rooms in each unit. Concerning sinks, one sink is necessary to every five patients in medium and high-risk nurseries.

Besides these routine procedures, the publication also establishes measures related to the asepsis of equipment. It is recommended that every material in direct contact with the newborn’s skin or mucosa be decontaminated or sterilized between its use with different patients. Materials such as thermometers and stethoscopes should be of individual use or cleaned with alcohol or iodophor every time it is used with a different patient. Water may also be a source of bacterial proliferation (examples are Pseudomonas spp and Serratia spp); thus it is recommended that sterile liquids be used in nebulizers and humidifiers, and that the liquid that condenses in the ventilator circuit be thrown away, in order to prevent it from returning to the nebulizer. Ventilators should be cleaned externally with sterilized soap and water, and the circuits should be changed every 48 hours and disinfected with glutaraldehyde at 2% (the nasal cannula should also be disinfected using this solution). Similarly, equipment used in neonatal resuscitation, such as balloons, masks, and laryngoscopes should be cleaned every time they are used, according to the hospital protocol. Cradles and incubators should be washed with water and liquid soap every day, and terminal cleaning should be performed every 7 days or after the bed is disoccupied. The floor, walls, windows, and other surfaces should be cleaned every day using methods that minimize the spread of dust, using chlorinated and quaternary ammonium compounds. The use of phenolic compounds is not indicated in neonatal units due to their absorption by the skin and to the risk for hyperbilirubinemia in newborns.
Another concern in terms of measures for the prevention of nosocomial infections is related to the presence of visitors in the neonatal unit. The risks for transmission of pathogens through family visits are probably small, although some studies suggest that neonatal colonization and infection do not increase with the presence of visitors. However, visits to the Neonatal Intensive Care Unit should follow some rules: the visitor cannot have been recently exposed to infectious or contagious diseases, such as chickenpox, rubella, and measles; the visitor should not present fever or acute respiratory, gastrointestinal, or cutaneous infections; the visitor should not have contact with the other newborns present in the unit and should not touch any equipment. Another prevention measure is the limitation of number of visitors and of duration of visits.

**Hospital staff**

The recommendations related to the hospital staff advocate an adequate number of personnel for the continuous observation of the newborns, as well as a enough time to wash the hands between the handling of patients. In the medium-risk nursery, the presence of one nurse for every ten patients and one nursing assistant for every four beds is recommended. In the high-risk unit, one nurse and one nursing assistant for every two beds is recommended.

Some routine procedures are recommended for the prevention of nosocomial infection. Among them, **washing of the hands** is the most effective measure, avoiding bacterial transmission and propagation. The hands have a resident flora, composed by low-virulence microorganisms, and a transitory flora, with potentially pathogenic microorganisms; the latter is especially important in the hospital environment. Washing of the hands removes transitory flora microorganisms and controls the growing of resident flora. When entering the unit, the staff member should fasten long hair, remove watch, rings, and bracelets, as well as wash hands, forearms and nails for approximately 3 minutes. After this, between the manipulation of one patient and another, hands can be washed with water and soap for a period of 15 seconds; this time is then enough to remove the transitory flora. Washing hands with water and soap acts effectively in the removal of microorganisms. The use of a specific antiseptic agent will be based on the bacterial prevalence at each unit. However, the use of antiseptic agents with residual antibacterial activity is recommended in neonatal units. The antiseptic agents most commonly used are iodophors, iodine compounds combined with a solubilizing agent (bactericidal activity), and chlorhexidine (a colorless, odorless, and basic salt, which has a bacteriostatic action when in low concentrations and a bactericide action when in high concentrations). Iodophors are more irritative to the skin of the hospital staff; this makes the appearance of desquamation and dermatitis more common and may provoke an increase in bacterial colonization. This disadvantage makes the chlorhexidine become the most used antiseptic agent in nurseries.

The **wearing of aprons** in neonatal units has given raise to controversy. The routine use of aprons by the hospital staff has not shown to be an important measure in the control of nosocomial infections, since the transmission of microorganisms usually occurs through the hands. Several studies showed that the use of aprons does not alter the bacterial colonization of the newborn or the rate of infection in neonatal units. The use of aprons is indicated in the performance of invasive procedures and in some situations of contact isolation. Wearing gloves is indicated as part of universal prevention measures whenever there is the possibility of the professional getting in contact with the patient’s blood and secretions.

Still concerning the hospital staff, immunity for rubella and hepatitis B should be investigated, and vaccination is recommended whenever necessary. Annual immunization against prevalent strains of the influenza virus is highly recommended, because the neonates, especially preterms or those with chronic pulmonary disease, are particularly vulnerable to complications when they acquire infections; vaccination of the staff presents a very good cost-benefit ratio.

Individuals presenting a clinical viral status or contagious respiratory diseases, such as tuberculosis, should be temporally kept away from the unit; any other potentially contagious condition should be carefully evaluated.

**Newborn**

The basic measures for the prevention of nosocomial infection in newborns include the colonization of the newborn with nonpathogenic bacterial flora; the main procedures are the prophylaxis for neonatal ophthalmia and care with the newborn’s skin and umbilical stump.

The prevention of gonococcal ophthalmia is recommended, and the agents used for this are silver nitrate at 1%, erythromycin ointment at 0.5%, and tetracycline ointment at 1%. The use of erythromycin and tetracycline-based preparations prevents chemical conjunctivitis, which commonly occurs as a result of the instillation of silver nitrate. However, these preparations are not superior to others in terms of prophylaxis for ophthalmia caused by Chlamydia trachomatis.

Simple techniques with the skin and the umbilical stump are able to prevent infection. After the stabilization of the newborn’s temperature, the first bath should be carried out with warm water and individual neutral soap. This procedure is recommended during the whole stay of the newborn at the unit. Several substances, such as bacitracin, the triple stain, and sulfadiazine are used in American nurseries for the care of the umbilical stump. However, none of these substances showed great advantages in terms of limitation of pathogenic bacterial colonization. In our setting, Fogliano et al. carried out a study comparing four different antiseptic solutions used in the umbilical stump care of term newborns:
ethyl alcohol at 70%; iodinated alcohol at 2%; povidone iodine; and alcoholic chlorhexidine. These authors observed a decrease in bacterial colonization (mainly by S. aureus) with the use of chlorhexidine. However, the use of antiseptic agents both in the umbilical stump care and in the newborn’s daily bath has been restricted to situations in which high rates of colonization are associated with a high frequency of staphylococcal infection at the unit. In this case, the application of chlorhexidine is preferred, since iodophors may impair the thyroidal function when absorbed by the newborn’s skin and hexachlorophene may lead to neurotoxicity in the neonatal period.

Besides the care with the newborn’s skin and umbilical stump, attention should be given to the breast milk and the milk-based formula. When a sick newborn is not able to be breastfed, the breast milk should be carefully stored in order to prevent bacterial contamination. The mother’s hands should be washed with antiseptic agents, and the milk should be collected and stored in sterilized feeding-bottles. When a breast pump is used to collect the milk, all components that get in contact with the breast milk should be washed with water and soap after each collection; they should also be sterilized every day. Breast milk should be stored in the refrigerator for 24 to 48 hours or frozen at -20 ºC for a maximum period of 6 months. When milk-based formulas are used, the utensils involved in its preparation should be sterilized, and the water should be boiled during 5 minutes. The formula should be stored in individual feeding-bottles and refrigerated for a maximum period of 24 hours; after being taken out of the refrigerator, the formula should be consumed within 4 hours. In cases of milk administration through probes, these should be changed every 24 hours, and the syringe, every 4 hours. Routine microbiological monitoring is not recommended neither for breast milk nor for milk-based formulas, except for cases in which the newborns present gastrointestinal intolerance and sepsis, among other pathologies. It is important to emphasize that one of the main prevention measures for nosocomial infection at neonatal units is the incentive to rooming-in environments and to breastfeeding.

On the other hand, the use of central venous catheters in critically ill newborns is a potential source of nosocomial infection. One of the factors associated with the increase in catheter-related infections in the blood flow is its insertion method. The risk for sepsis with central venous catheters inserted surgically is three times higher in the neonatal period when compared to peripherally inserted catheters. Based on these data, percutaneous catheters have been more often used than surgical catheters. The main prevention measures for infections related central venous catheters are the use of maximum barrier precautions, such as the use of surgical caps, masks, aprons, gloves, sterilized areas and materials, skin disinfection with alcoholic chlorhexidine, and a team specialized in the insertion and maintenance of the catheter.

Recent proposals for the prevention of nosocomial infection in preterm newborns in Intensive Care Units

Besides basic care, some measures have been proposed to reduce the risk for nosocomial infection in preterm newborns, mainly those presenting low weight and gestational age. In general, the usefulness of these measures has not been proved yet, and they are usually expensive. Some examples are mentioned below.

Emollient lotions

Some studies suggest that the prophylactic application of emollient lotions, such as AquaphorTM and EucerinTM, in preterm newborns may protect the stratum corneum, increasing the epidermal barrier function and, consequently, contributing to the improvement of skin integrity and decreasing the risk for nosocomial infection. However, these results were observed in studies with a small number of patients, and the groups were heterogeneous. Campbell et al. showed that the use of emollients in preterm newborns increased the incidence of systemic candidiasis. Therefore, the routine prophylactic indication of emollient lotions for the prevention of nosocomial infections still seems to be controversial, and further controlled studies with a higher number of patients are necessary in order to determine the impact of this strategy in the prevention of the neonatal nosocomial infections.

Use of intravenous immunoglobulin

Considering that preterm newborns, mainly those with a gestational age below 32 weeks, receive low concentrations of maternal immunoglobulin G, and that the administration of IgG may improve the opsonic activity, activate complement, and promote citotoxicity, the administration of intravenous immunoglobulin has been assessed for the prevention of nosocomial infections. In a recent systematic review of 15 clinical controlled studies with placebo in preterm newborns (<37 weeks), Ohlsson & Lacy verified a significant reduction of one or more episodes of severe infection during a 8-day or longer hospitalization. This administration resulted in a reduction of 3–4% in the number of episodes of severe infection and was not associated with short-term side effects. There was no reduction in incidence of other diseases, hospitalization time, or mortality. The decision about the prophylactic use of immunoglobulins will depend on the cost, and it is important to observe that 24 to 32 children have to be treated so that nosocomial infection is prevented in one child.

Low-dose vancomycin infusion

Considering that late-onset sepsis occurs in at least 50% of the <1000 g newborns, and that coagulase-negative staphylococci are the most frequent agents, several studies have assessed the efficacy of low doses of vancomycin administrated through continuous infusion, in parenteral...
solutions, or through intermittent intravenous infusion. These studies were recently revised by the Cochrane Neonatal Review Group, which concluded that the use of vancomycin reduces the incidence of nosocomial sepsis caused by Staphylococcus. However, in view of the risk for developing resistant organisms and the few clinical benefits shown, these authors suggest that the routine use of vancomycin should not be practiced.84

Isolation measures in the neonatal unit

The routine isolation strategies used in neonatal units are based on the CDC and the American Academy of Pediatrics recommendations.65 This isolation system is extremely complex, which makes its implementation in our setting more difficult, due to the lack of medical and nursing personnel. The recommendations of Feferbaum & Rugolo,85 presented in Tables 4 and 5, seem to adapt better to our practical needs.

In conclusion, we would like to say that even considering a great number of measures aimed at controlling and preventing nosocomial infections, at the hospital environment, at the hospital staff and the newborn, and associated with the frequent overcrowding of neonatal units and with the clinical severity of the hospitalized patients, often any act of carelessness in the practice of these measures may cause increased rates of nosocomial infection. Therefore, only with an active, systematic, and continuous process of collection, analysis, and assessment of data, as in epidemiological surveillance, we will be able to detect failures and implement adequate intervention strategies.

Table 4 - Isolation techniques and precaution measures used at the neonatal unit

<table>
<thead>
<tr>
<th>Type of isolation / Precaution measure</th>
<th>Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total isolation</td>
<td>Private room, use of apron, mask, and gloves</td>
</tr>
<tr>
<td>Respiratory isolation</td>
<td>Private room, use of mask for contact with newborns</td>
</tr>
<tr>
<td>Contact isolation (fluids, dejecta, and infectious material)</td>
<td>Use of mask, apron, and gloves for contact with newborns</td>
</tr>
<tr>
<td>Enteric precautions, and precautions with drainage/secretions</td>
<td>Use of apron and gloves for contact with body fluids and blood</td>
</tr>
<tr>
<td>Standard precautions</td>
<td>Use of apron, gloves, and eye protection for contact with blood and secretions</td>
</tr>
</tbody>
</table>

Adapted from Feferbaum R, Rugolo LMSS. Rev Paul Pediatria 1996;14:194.

Table 5 - Types of isolation and precautions against neonatal infections

<table>
<thead>
<tr>
<th>Type of isolation</th>
<th>Neonatal infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>Chickenpox</td>
</tr>
<tr>
<td>Contact</td>
<td>Herpes simplex, rubella, and multiresistant bacteria</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Pertussis, respiratory syncytial virus, and influenza</td>
</tr>
<tr>
<td>Enteric precaution</td>
<td>Hepatitis A, cytomegalovirus, diarrheal disease, and necrotizing enterocolitis</td>
</tr>
<tr>
<td>Standard precaution</td>
<td>Hepatitis B, HIV, syphilis, sepsis, meningitis, pneumonia, skin infection</td>
</tr>
</tbody>
</table>

References


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