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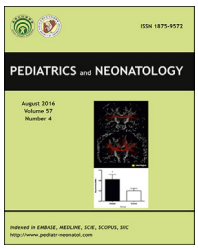

REVIEW ARTICLE

Early and Late Infections in Newborns: Where Do We Stand? A Review

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Neonatal sepsis still represents an important cause of mortality and morbidity among infants. According to the onset, we can distinguish "early onset sepsis" when microbiological cultures positive for external pathogens come from newborns during the first 7 days of life (maternal intrapartum transmission); "late onset sepsis" when microbiological cultures positive for external pathogens come from newborns after the first 7 days from delivery (postnatal acquisition). In this review we synthesize the incidence, risk factors, clinical manifestations, and methods of diagnosis and treatment of each type of neonatal infection, in order to better define such a pathological condition which is of great importance in common clinical practice.

1. Introduction

Neonatal sepsis still represents an important cause of mortality and morbidity among infants, above all in very-low-birth-weight (VLBW, birth weight < 1500 g) preterm infants, with an incidence ranging from 1–5/1000 live births to 49–170/1000 live births.[1]

It is defined by the presence of infections involving bloodstream, urine, cerebrospinal/peritoneal structures, and/or any other sterile tissues. Bacteria and viruses are the most frequent causative agents; at the same time, fungi and parasites play a minor but important role in neonatal sepsis etiology.[2]

According to the time and mode of infection, we can distinguish the following types: *early onset sepsis* (EOS), caused by maternal intrapartum transmission of invasive

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organisms and diagnosed in case of positive microbiological cultures during the first 7 days of life or during the first 72 hours of life in the case of VLBW infants[3] and *late-onset sepsis* (LOS) when infection is demonstrated in blood and cerebrospinal fluid cultures after 7 days from delivery, caused by a postnatal acquisition (nosocomial or community sources) of the pathogen.[4] This is a common complication of the prolonged hospitalization of preterm newborns into the Neonatal Intensive Care Units (NICUs). The aim of this review is to evaluate the literature data about neonatal sepsis. We separately considered EOS and LOS. Each category has been evaluated for its incidence, causative risk factors, clinical manifestations, as well as methods of diagnosis and treatment, in order to give a comprehensive overview about this worrisome clinical problem.

2. Pathogenesis

2.1. EOS

EOS is due to infections occurring during the intrapartum period or just before delivery, in agreement with a sort of "vertical transmission".

The incidence is ~1–2 per 1000 live newborns, reaching a mortality rate of ~3% among term newborns, and ~16% in VLBW infants.[5–7]

Babies can become ill before or during labor due to an ascending infection caused by bacteria colonization of the maternal perineum or due to the direct contact between these microorganisms and the body of the newborn during the delivery. Maternal hematogenous transmission and chorioamnionitis can further be considered as possible conditions able to induce EOS. Aspiration and digestion of infected amniotic fluid *in utero* or infected secretion in the birth canal can effectively produce pneumonia and/or sepsis.[6]

The most common source of pathogens is maternal vaginal bacterial flora; therefore, maternal antibiotic therapy could prevent newborns infection.[8] Nevertheless, the prophylactic administration of antibiotics is only allowed in case of a real probability of infection because of the potential risk for infants coming from maternal drugs administration.[9]

2.2. LOS

LOS is due to microorganisms acquired from the environment after the delivery (nosocomial community-acquired infections); preterm infants, especially if VLBW, are most involved. The recent advances in their management have resulted in a significant increase in survival, associated at the same time with prolonged hospitalization, mechanical ventilation, use of invasive procedures and devices (i.e., intravascular catheters and endotracheal tubes), which are all predisposing factors to LOS. Moreover, VLBW immaturity of the immune system makes them particularly susceptible.

In the Neonatal Research Network (NRN) cohort, 70% of infections were associated with Gram-positive organisms; coagulase-negative staphylococci (CoNS) contributed 48%, Gram-negative 18% and fungal 12%.[10] In late preterm newborns (gestational age, 34–37 weeks) the incidence is about 6–10%.[11] Mortality rates increase with postnatal age, reaching 36% in newborns aged 8–14 days and 52% in those aged 15–28 days.[10]

3. Risk factors

3.1. EOS

We can distinguish maternal and neonatal factors.

3.1.1. Maternal factors

Premature birth (< 37 weeks), premature and prolonged time (> 18 hours) of membranes rupture, maternal peripartum infection, and low socioeconomic status are strongly associated with EOS.

Chan et al[6] further differentiated the categories of predisposing factors into the following: maternal infection, maternal colonization, and risk factors for infection. They defined *maternal infection* according to the following criteria: the presence of laboratory confirmed bacterial infection [bacteremia, amnionitis, urinary tract infections, or chorioamnionitis; documented by positive cultures of biologic fluids; positive polymerase chain reaction (PCR) at the level of the amniotic fluid only; or histopathologically confirmed chorioamnionitis] or clinical signs of infection [intrapartum maternal fever, uterine tenderness, maternal tachycardia, malodorous vaginal discharge, elevated white cell count, elevated C-reactive protein (CRP), physician diagnosis of clinical chorioamnionitis]. *Maternal colonization* was determined if positive reproductive tract/genital bacterial cultures with or without signs or symptoms of infection were identified; and *maternal risk factors* included prelabor rupture of membranes (rupture of membranes before the onset of labour at ≥ 37 weeks of gestation), preterm prelabor rupture of membranes (rupture of membranes prior to onset of labour at < 37 weeks of gestation) and prolonged rupture of membranes (duration of rupture of membranes > 8–24 hours or undefined).[6]

The multivariate logistic regression analysis of a Chinese 1:4 case–control study[5] involving 147 EOS newborns and 588 controls showed that maternal age > 35 years [odd ratio (OR) = 4.835, 95% confidence interval (CI) = 1.170–19.981], cesarean section (OR = 0.103, 95% CI = 0.041–0.258), and premature rupture of membranes (OR = 0.207, 95% CI = 0.078–0.547) represent the major predisposing factors to neonatal sepsis. Furthermore, in the univariate analysis, fixed occupation of mothers (OR = 0.439, 95% CI = 0.289–0.668), urban residence (OR = 5.079, 95% CI = 2.899–8.990), abnormal fetal position (OR = 1.621, OR 95% CI = 1.340–1.962), fetal times (OR = 1.212, OR 95% CI = 1.041–1.412), parity (OR = 1.859, OR 95% CI = 1.188–2.908), amniotic fluid volume abnormalities (OR = 0.200, OR 95% CI = 0.054–0.745), pregnancy-induced hypertension (OR = 0.297, OR 95% CI = 0.122–0.726), and placental abnormalities (OR = 0.050, OR 95% CI = 0.006–0.428) seemed to predispose to neonatal infection, but these results were not confirmed by multivariate regression analysis evaluation.[5]