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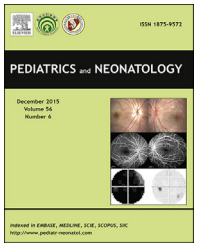

REVIEW ARTICLE

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]

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The role of the young maternal age (< 20 years old) is questioned although it was previously considered as an important predisposing factor to neonatal sepsis probably in relation to the higher rate of group B streptococcus (GBS) colonization into the maternal vagina.[3] Epidemiological studies showed an increased incidence of EOS in black newborns as compared to white ones, although the explanation seemed to be better related to the different socioeconomic conditions between the two ethnicities.[12]

Certain obstetric practices such as invasive fetal monitoring, membrane-stripping, and intrapartum vaginal exams may all promote early infections.[13]

3.1.2. Neonatal factors

Among neonatal factors able to promote EOS, the alterations of the innate immune response can play a significant role. As the adaptive response requires 5–7 days from delivery to develop, during this period infants are largely dependent on innate immune system (respiratory and intestinal) barriers and the skin, local immune sentinel cells, [macrophages, endothelium, epithelium, polymorphonuclear cells (PMN), and dendritic cells], antigen-presenting immune cells (monocytes, macrophages, and dendritic cells), host defense proteins and peptides (complements, cytokines, chemokines, active phase, and coagulation proteins), as well as passively acquired immunoglobulin from the mother. Defects of immunoregulatory genes (mainly X-linked) and prematurity (especially with LBW) are associated with an incomplete maturation and/or function of the innate immune system resulting in an increased likelihood of infections.[14]

Birth weight also determines a major susceptibility to EOS; preterm neonates, especially VLBW, showed incidence rates > 10 times higher than those born at term with a total mortality of about one-third.[15] Furthermore, prematurity (OR = 0.059, 95% CI = 0.010–0.329) and newborn jaundice (OR = 0.092, 95% CI = 0.021–0.404) seemed to predispose to EOS in a multivariate analysis of a recent case-control study.[5] Other neonatal risk factors include male sex, neonatal Apgar scoring at 1 minute and at 5 minutes, wet lung, fetal distress, anemia, intraventricular hemorrhage, hypothermia, and metabolic disorders.[2,6]

3.2. LOS

A review of studies from the NICHD Neonatal Research Network including VLBW registry data on infection showed that the likelihood of developing LOS was inversely related to gestational age and birth weight [highest in infants < 25 weeks gestation (46%) and 401–750 g (43%)].[10] Moreover, while maternal intake of corticosteroids was associated with a significant reduction in EOS (unadjusted OR 0.52; 95% CI, 0.31–0.88), it was also associated with an increased risk of LOS (unadjusted OR 1.29; 95% CI, 1.10–1.51) and of sepsis at any time in the hospitalization (unadjusted OR 1.22; 95% CI, 1.09–1.37). Nevertheless, the increased incidence of LOS in newborns having undergone antenatal administration of corticosteroids must be balanced with the significant reduction in death rates, intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, and risk of EOS observed after corticosteroids use.[10]

A Swedish retrospective case–control study demonstrated that the risk of LOS was directly related to duration of central/umbilical catheters and ventilatory treatment (OR 2.6 and OR 1.6, respectively). Premature rupture of membranes, fever during delivery, and days of continuous positive airway pressure treatment did not seem to predispose to LOS (p = not significant).[16] A retrospective, matched, case–control study performed on 164 Taiwanese case infants with bloodstream infections and as many controls showed that parenteral nutrition (OR 6.07; 95% CI, 1.14–32.32; $p = 0.034$) and intraventricular hemorrhage (OR, 2.68; 95% CI, 1.20–5.99; $p = 0.017$) were independently associated with bloodstream infections after multivariate analysis.[17]

Moreover, a retrospective United States (US) cohort study, evaluating NICUs patients with peripherally inserted central catheters from 2003 to 2010, showed that catheter removal due to adverse events is significantly associated with LOS and that antibiotic use before removal is not associated with a decline in sepsis rate.[18]

4. Microorganisms associated with EOS

EOS can be determined by bacteria, fungi, viruses, or protozoa; bacteria are the most frequent. *Streptococcus agalactiae* and *Escherichia coli* are the agents most commonly involved, followed by *Listeria monocytogenes*, *Streptococcus pyogenes*, *Viridans streptococci*, *Streptococcus pneumoniae*, *Haemophilus influenza*, *Staphylococcus* (S.) *aureus*, Enterococci, and *Pseudomonas aeruginosa*.[6,19]

4.1. GBS

Streptococcus agalactiae (Lancefield GBS) still represents the pathogen mainly responsible for neonatal sepsis (70% of GBS diseases) and meningitis despite the use of intrapartum antibiotic prophylaxis (IAP). Data from low and high income countries showed a total GBS EOS incidence of about 0.43% (95% CI 0.37–0.49), with the highest values in African patients (0.53%, 95% CI 0.15–0.92), followed by the Americans (0.50%, 95% CI 0.43–0.57), and Europeans (0.45%, 95% CI 0.34–0.56). Southeast Asia shows the lowest rates of incidence (0.11%, 95% CI 0.012–0.220).[20] The average mortality rate was 9.6% (95% CI 7.5–11.8), showing EOS from GBS (12.1%, 95% CI 6.2–18.3), a mortality rate twice that of LOS (6.8%, 95% CI 4.3–9.4).[21] The mortality rate was three times higher in low-income countries (12.6%, 95% CI 10.8–14.9) than in high-income ones (4.6%, 95% CI 2.1–9.1).[22]

The GBS serotype III is often associated with meningitis while types Ia, II, III, and V are associated with EOS.[20] Gastrointestinal and genitourinary maternal GBS colonization may be the sources for newborn contamination. Infection may occur within the first 7 days of life, although it can appear even within the first 12 hours from delivery in the form of sepsis and pneumonia.[21] Gestational age is tightly related to death in GBS EOS; a mortality rate of 20–30% among infants with gestational age < 33 weeks was detected, and this was 2–3% in full-term newborns.[22]

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Guidelines on the use of IAP to prevent neonatal GBS infections recommended universal screening for GBS colonization in pregnant women at 35–37 weeks of gestation and prophylactic administration of penicillin as the first-line antibiotic agent.[9,23]

The available data suggest that IAP is effective in preventing neonatal GBS infections.[24,25]

Recent estimates showed that chemoprophylaxis significantly reduced the incidence of early GBS infection compared to no treatment in developed countries (Relative Risk (RR), 0.17; 95% CI 0.04–0.74).[24]

Moreover, data from the US highlighted that IAP was associated with a reduction of invasive early-onset GBS disease by more than 80%, from 1.8 cases/1000 live births in the early 1990s to 0.26 cases/1000 live births in 2010, with over 70,000 prevented cases of early-onset GBS invasive diseases from 1994 to 2010.[25]

Vaccination of pregnant women is an alternative strategy for preventing neonatal sepsis. A trivalent GBS polysaccharide-protein conjugate vaccine (capsular epitopes from serotypes Ia, Ib and III) has completed Phase II trials.[26] An analytic model estimated that vaccination against GBS would prevent 4% of US preterm births and 60–70% of neonatal GBS infections.[27]

Moreover, a recent US cost-effectiveness study highlighted that the addition of routine GBS maternal vaccination to screening and IAP would prevent an additional 899 cases of GBS disease and an additional 35 deaths among infants, with estimated annual cost savings of $43.5 million.[28]

In particular, GBS vaccine could be a valuable tool in low- and middle-income countries, where chemoprophylaxis is often not feasible.

According to a recent a decision-analytic model in South Africa, GBS vaccination alone would prevent 30–54% of infant GBS cases as compared to doing nothing. IAP alone, compared to doing nothing would prevent 10% of infant GBS cases, and vaccine plus IAP 48% of cases.[26]

4.2. Escherichia coli

E. coli is a Gram-negative bacterium that commonly colonizes human urogenital and enteric tracts. It is considered the second most common pathogen related to EOS onset in term infants and the major determinant of neonatal sepsis in VLBW newborns.[12] Its antigenic structure has several virulence factors [adhesion molecules (F1, P, and S fimbriae), iron-sequestering systems, hemolysin, capsules (K1, K5), lipopolysaccharide O-antigen and others with unclear function (Tsh, IbeA, CNF1, CDT, TraT)], whose combination determines its pathogenic power. In particular, K1 and O18 strains are associated with a higher rate of neonatal meningitis and septicemia, as well as higher mortality rates.[29] The great resistance degree to ampicillin (85% of cases) increases its virulence.[30]

4.3. Other causal agents

GBS and *E. coli* are the most common agents inducing EOS, together accounting for about 70% of cases.[3,31] Nevertheless, other microorganisms should be considered. *L. monocytogenes* is a facultative anaerobic Gram-positive bacterium which can colonize the intestine. It is associated with invasive disease, spontaneous abortions, or stillbirth.[6] *Streptococcus pyogenes* and *viridians*, *Streptococcus pneumoniae*, *H. influenzae*, *S. aureus*, Enterococci, and *P. aeruginosa* are uncommon sources for EOS, but several reports documented neonatal infections determined by these agents.[32,33]

5. Microorganisms associated with LOS

According to NICHD Neonatal Research Network data, about 70% of the first episodes of LOS are caused by Gram-positive bacteria; CoNS were the most common pathogens (68% of Gram-positive infections and 48% of all infections), followed by *S. aureus* (8%), *Enterococcus* species (3%), and GBS (2%). Gram-negative organisms were responsible for 18% of LOS. The remaining 12% were caused by fungal organism, of which *Candida albicans* was the most represented (6%).[10]

The average incidence of LOS (7–89 d) is 0.24% (95% CI 0.17–0.30); the highest values were reached in Africa (0.71%, 95% CI 0.38–1.04), followed by the Americas (0.31%, 95% CI 0.16–0.89).[18]

5.1. CoNS

CoNS are a type of Staphylococci which are unable to produce coagulase. In nosocomial infections *S. epidermidis* is the most commonly found pathogen; *S. aureus* is isolated in 8% of cases, while *S. capitis*, *S. haemolyticus*, and *S. hominis* are rarely involved.[34] *S. epidermidis* commonly colonizes human skin and mucosal membranes and rarely causes infections in healthy tissues but is capable of adhering and proliferating on plastic surfaces of indwelling medical devices, thanks to its ability to form persistent multilayered agglomerations called biofilms, which are intrinsically resistant to antibiotics and a real barrier against the attacks of the immune system.[5,35] Immunocompromised patients and premature neonates are the most vulnerable individuals to be exposed to CoNS infections.[36]

Furthermore, resistance to antibiotics appears to be widespread for *S. epidermidis*, to methicillin in particular (methicillin-resistant *S. epidermidis*, MRSE). This type of resistance (90% of isolated *S. epidermidis*) is encoded by the *mecA* gene, located on mobile genetic elements, and therefore it is transferable to different bacterial strains. Vancomycin is used in MRSE cases.[5,35]

5.2. Other organisms

Gram-negative bacteria (i.e., *E. coli*, *Klebsiella*, *Pseudomonas*, *Enterobacter*, and *Serratia*) are responsible for approximately a quarter of LOS cases, while fungi (*C. albicans* the most common) account for about 12%. The related mortality rates are high.[11] Gram-negative infections usually occur by transmission from health care personnel, contamination of bladder and venous catheters, parenteral solutions and pediatric formulas.[37]

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As regards *C. albicans*, Benjamin et al[38] showed that birth weight, male sex, forms other than enteral nutrition, and antibiotic treatment with cefalosporins represent the main risk factors for neonatal infection.

6. Clinical manifestations

EOS and LOS present common and unspecific clinical manifestations. Medical diagnosis is particularly difficult in preterm and LBW infants due to the immaturity of the immune system that makes signs and symptoms misleading.

The degree of clinical manifestations is highly variable depending on the virulence of pathogens and on the mechanisms of host defense. Body temperature may be elevated, normal, or depressed; low temperatures with irregular fluctuations are often present in preterm newborns.[39] Motor functions are characteristically reduced; delayed weight gain, pale skin, and reduction of activity (movements, eating, crying) are often observed. Cyanosis, apnea, tachycardia, bradycardia, and hypotension represent warning signs for severe and rapidly evolving forms as they can be considered precursors of shock (cold extremities, decreased femoral pulses, congestive heart failure, and even disseminated intravascular coagulation). Jaundice may sometimes be the only manifestation, preceding encephalopathy in severe cases. All organs and systems may be affected; the central nervous system involvement can induce drowsiness, irritability, lethargy, convulsions, and increased tension at the fontanelle's level. Anorexia, regurgitation, abdominal distension, vomiting, diarrhea, and necrotizing enterocolitis are common symptoms of gastrointestinal lesions. Skin lesions are frequent; these include cutaneous and mucosal petechiae, impetigo, cellulitis and abscesses. Involvement of cardiovascular system (myocarditis, pericarditis, endocarditis, heart failure), septic shock with thrombotic-hemorrhagic manifestations, urinary tract infections, osteomyelitis, and deep infections are also possible.

7. Diagnosis

Serum inflammatory biomarkers (acute-phase reactants, inflammatory cytokines) may be helpful, although no laboratory test alone is sufficient for the absolute diagnosis. For this reason, delays may occur in the identification of affected infants. This delay in identifying affected infants may lead to prolonged and unnecessary therapy, the emergence of resistant microorganisms, the growth of health care spending, and especially a higher risk of complications such as cerebral palsy or intraventricular hemorrhage.

In order to make a diagnosis, several clinical and hematological parameters are generally considered together, although the correct combination is not well-established. Rodwell et al[40] formulated a hematologic scoring system (HSS), which was easy to perform and cost-effective, based on the following seven criteria: high values of total leukocytes count; high PMN level count; elevated immature PMN count; elevated immature-to-total-PMN ratio; immature-to-mature PMN ratio $\geq$ 0.3; platelet count $\leq$ 150,000/mm^3; and pronounced degenerative changes in PMNs. A score $>$ 2 means likelihood of sepsis, whereas $\leq$ 2 is related to 99% likelihood of sepsis absence.[40] Moreover, some new leukocyte parameters (neutrophil and monocyte volume, conductivity, scattering, and volume distribution width) may be useful in the differential diagnosis of newborn sepsis.[41]

Macrophage cytokines, which are produced in response to microorganism antigens and which stimulate the release of acute-phase reactants and hence the host inflammatory immune reaction, are usually used in clinical practice as indicators of both EOS and LOS.[42] Moreover, serum markers, increasing earlier than changes in hematological parameters, play a pivotal role in the diagnostic process, allowing detection of sepsis and its severity, differentiation of bacterial from fungal and viral agents, and monitoring of response to therapy.[43] The proinflammatory cytokine tumor necrosis factor-alpha (TNF-α) measured in cord blood seems to be increased in neonates with EOS (sensitivity, 78.0%; specificity, 41.2%).[44] Interleukin-6 (IL-6) and IL-8 plasma concentrations are considered to be sensitive and specific for the prediction of neonatal sepsis. These indicators can be detected in blood early but their short half-life, of about 12–24 hours, limits their use in clinical practice.[45]

CRP, a peptide synthesized by the liver in response to infection or inflammatory processes, was shown to be the best diagnostic marker of neonatal sepsis, with higher sensitivity and specificity than total PMN count and immature-to-total-PMN ratio.[46] However, it presents a low sensitivity during the early phases of infection due to the time needed for release (about 6 hours). Serial determinations improve the diagnostic accuracy and are useful for evaluating the response to treatment.[47]

The granulocyte colony-stimulating factor was shown to have sensitivity of 95% and negative predicting value (NPV) of 99% in detecting infection in neonates of all gestational ages when a cut-off level of 200 pg/mL was used.[48]

Moreover presepsin, a truncated form of soluble CD14, can be used as a reliable biomarker for LOS and treatment response in preterm infants.[49]

Procalcitonin (PCT), a peptide produced by monocytes and hepatocytes in response to systemic inflammation, seems to be more specific than CRP in bacterial infections.[50] In neonatal sepsis, its concentrations increase after 4 hours from proinflammatory action of bacterial endotoxins, reaching the peak after 6–8 hours, so a rise of PCT value is more precocious compared to CRP. In normal-birth-weight neonates, a PCT cut-off limit $>$ 0.5 ng/mL indicates a two-fold probability of nosocomial sepsis, while a value $>$ 2.4 ng/mL in infected VLBW infants suggests the need for an empirical antibiotic therapy.[51]

Leukocyte differentiation antigens, CD33, CD66b, and CD19, induced by inflammation secondary to bacterial infections, increase in preterm newborns with sepsis. In addition, an increased expression of PMN Fc-gamma-receptor I (CD64) has been demonstrated in newborns during the early phase of an acute bacterial infection.[52]

Weirich et al[53] proposed neutrophil CD11b as a precocious marker of neonatal infection. In their study, NPV, positive predicting value (PPV), sensitivity, and specificity were 100%, 99%, 96%, and 100%, respectively.[53]

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Table 1 Neonatal sepsis: summary table.

Types of neonatal sepsis	Early onset sepsis	Late onset sepsis
Definition	Neonatal infection during the 1st 7 d of life or during the 1st 72 h of life in case of VLBW infants.	Neonatal infection after 7 d from delivery.
Epidemiology	Incidence of 1–2 per 1000 live newborns.	Prevalence of ~25–30% in VLBW infants, incidence of ~6–10% in late preterm newborns (gestational age, 34–37 wk)
Mortality	3% among term newborns, & ~16% in VLBW infants	36% in VLBW babies aged between 8 d & 14 d & 52% in those aged between 15 d & 28 d
Physiopathology	Vertical transmission from mother: infection contracted from bacteria colonizing the maternal perineum, maternal hematogenous transmission or chorioamnionitis.	Infection is acquired after the delivery; preterm & VLBW infants are most frequently involved.
Predisposing factors	Maternal factors: premature birth (< 37 wk), premature or prolonged time (> 18 h) of membranes rupture, maternal peripartum infection, a low socioeconomic status, maternal age < 20 y & > 35 y, cesarean section, black ethnicity, obstetric practices, having previously had an infant with GBS infection. Neonatal factors: alterations of the innate immune response, defects of immunoregulatory genes, prematurity, birth weight, newborn jaundice, male sex, neonatal Apgar scoring, wet lung, fetal distress, anemia, intraventricular hemorrhage, hypothermia, & metabolic disorders.	The risk is inversely related to gestational age & birth weight, other risk factors are maternal intake of corticosteroids, antenatal administration of corticosteroids in babies, prolonged hospitalization, mechanical ventilation, invasive procedures, & devices implantation.
Causative microorganisms	*Streptococcus agalactiae* & *Escherichia coli* are the agents most commonly found, but all microorganisms may be responsible.	About 70% of the 1st episodes of LOS are caused by Gram-positive bacteria; CoNS are the most common pathogens. Gram-negative organisms are responsible for 18% of cases. The remaining 12% are caused by fungal organisms.
Clinical manifestations	Clinical manifestations are common & unspecific: fever, cyanosis, apnea, tachycardia, bradycardia, hypotension, jaundice, drowsiness, irritability, lethargy, convulsions, anorexia, regurgitation, abdominal distension, vomiting, diarrhea, skin lesions, involvement of cardiovascular system, septic shock, urinary tract infections, osteomyelitis, & deep infections.	
Diagnosis	• Serum inflammatory biomarkers (acute-phase reactants, inflammatory cytokines, alterations in blood tests); • Identification of causative agent through molecular genetics techniques (amplification of target DNA/RNA fragments); • Microbiological exams on biological samples (blood, urine, cerebrospinal fluid).	
Prevention	Universal GBS screening of all pregnant women at 35–37 wk of gestation & in case of positive test, intrapartum antibiotic prophylaxis at least 4 h before the delivery.	Reduce, as far as possible, the sources of contamination (ensuring a sterile environment in NICUs, minimizing the invasive procedures)
Therapy	• Empiric therapy as 1st line: ampicillin & an aminoglycoside are recommended • Then, target antibiotic therapy on the base of culture exams.	• Empiric therapy as 1st line: vancomycin & an aminoglycoside are recommended • Then, target antibiotic therapy on the base of results of culture exams.

CoNS = coagulase-negative Staphylococci; GBS = group B-streptococcus; LOS = late-onset sepsis; NICUs = neonatal intensive care units; VLBW = very low birth weight.

In preterm neonates with EOS, a prenatal immune response with increased umbilical plasma levels of cytokines (TNF-α, CRP, IL-1β, IL-6, IL-8, p55, p75, and IL-1 receptor antagonist) has been demonstrated.[54] IL-1β, IL-6, and IL-8 were the most specific55 in this clinical setting. Recent proteomics-based technologies provided novel biomarkers for identifying pregnancies at risk for intrauterine infection and prenatal fetal damage.[55]

Molecular genetics techniques can further help physicians in the diagnosis of neonatal sepsis by identifying specific fungal, bacterial and viral genes in neonatal blood through amplification of target DNA/RNA fragments. The

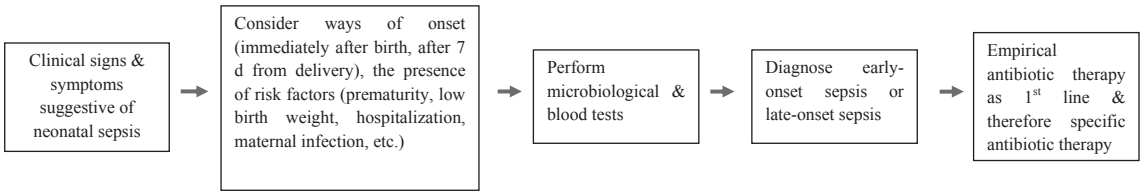

Figure 1 The management of neonatal sepsis step by step.

amplification of 16S rRNA gene with PCR had 100.0% sensitivity, 95.4% specificity, 77.2% PPV, and 100.0% NPV as compared to blood culture.[56]

A recent comparative study highlighted that the 16S rDNA PCR assay was more sensitive than blood culture in diagnosis of EOS; the combination of high sensitivity-CRP, PCT, and IL-6 was better than single markers, and among them PCT had the greater diagnostic value.[57] As regards instrumental evaluation, echocardiography and ultrasound assessments of peripheral vessels[58] are not really of help to physicians in early detection of EOS or LOS onset. The involvement of the cardiovascular system represents, in fact, a late and often irreversible manifestation of advanced stages of the septic state, and the ultrasound evaluation can only confirm this condition.

To the best of our knowledge, the definitive diagnosis is still microbiological as cultural exams on biological samples (blood, urine, cerebrospinal fluid) are considered the gold standard for the detection of bacteremia or fungemia, despite their limitations of low sensitivity (sepsis due to bacterial endotoxins induce negative cultures) and the time required for results (48—72 h), which can retard the beginning of antibiotic therapy and compromise the life of newborns.[59]

8. Prevention and treatment

The primary objective to be achieved is the correct prevention of neonatal sepsis. Recent guidelines recommended the universal GBS screening of all pregnant women at 35—37 weeks of gestation.[9,23] Furthermore, they specified the IAP by using penicillin, ampicillin, cefazolin, or clindamicin (in case of documented, anamnestic penicillin allergy) at least 4 hours before the delivery.[23]

Other prophylactic strategies included breastfeeding, prevention of health care-associated infections, administration of lactoferrin, antistaphylococcal monoclonal antibodies, immunoglobulin, granulocyte-macrophage colony-stimulating factors, probiotics, and fluconazole (in case of Candida infections).[60]

In the presence of symptoms and signs suggestive of neonatal sepsis, empiric therapy should be undertaken pending the identification of the causative agent: ampicillin and an aminoglycoside are recommended as empiric therapy for EOS; vancomycin and an aminoglycoside for LOS; and cephalosporin if Gram-negative meningitis is suspected. The specific therapy for the causative pathogen should be adopted as soon as possible based on cell culture results. The duration of treatment varies from 7 days to 21 days, depending on the type of pathogen and the site of infection (meningitis, cerebritis, osteomyelitis, and endocarditis). The pharmacological treatment is stopped when no pathogen is identified and no signs and symptoms of infection can be observed.[60]

The summary table (Table 1) and the flow chart (Figure 1) respectively summarize the main features and the clinical approach to neonatal sepsis.

9. Conclusion

Neonatal sepsis continues to be an important cause of morbidity and mortality worldwide due to the lack of adequate preventive and therapeutic strategies in low income settings and due to the increased survival of preterm and low-weight newborns with lengthy stays in NICUs in high-income countries. Much remains to be done in order to minimize the neonatal mortality rates.

Conflicts of interest

The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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