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Neonatal sepsis: A review

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Abstract
Neonatal sepsis (NS) is a dysregulated host response to a systemic viral, bacterial, or fungal infection in the first 28 days of life that is potentially fatal and could turn life-threatening in both term and preterm newborns. Neonatal sepsis is categorized into two major groups: early-onset sepsis (EOS) and late-onset sepsis (LOS) depending on the time of infection, mode of transmission, and causative organisms.

Keywords: Neonate, sepsis, early-onset sepsis (EOS)

Introduction
Neonatal sepsis (NS) is a dysregulated host response to a systemic viral, bacterial, or fungal infection in the first 28 days of life that is potentially fatal and could turn life-threatening in both term and preterm newborns [1]. Neonatal sepsis is categorized into two major groups: early-onset sepsis (EOS) and late-onset sepsis (LOS) depending on the time of infection, mode of transmission, and causative organisms [2]. EOS describes a vertically transmitted infection in the first three days of life (72 hours), and LOS is a horizontally transmitted infection (after 72 hours of life) commonly caused by a microorganism in hospital settings. Although some researchers consider seven days as a cutoff limit for differentiating EOS and LOS, most epidemiological studies recommend 72 hours as a reference [3]. Moreover, a third group, very late-onset neonatal sepsis (VLOS), has also been described by some as a third classification. VLOS mainly occurs in infants hospitalized in the neonatal intensive care unit (NICU); it usually occurs after 30 days of hospitalization till discharge [4].

Aims and Clinical Relevance
Neonatal sepsis is responsible for approximately 8% of neonates' deaths and is a predominant cause of neonatal mortality and long-term morbidity, especially in low- and middle-income countries [5, 6]. Although the epidemiology of NS is constantly changing, approximately 1.3 to 3.9 million new cases are reported annually by the Global Burden of Disease (GBD). An estimated 24% of deaths among this vulnerable group of infants are caused by severe infections [5, 6]. A recent systematic review and meta-analysis indicated that the approximate EOS incidence is 2,496 per 100,000 live births, which was 2.6 times more common than LOS, 946 per 100 live births [7]. However, the overall incidence of EOS has been declining throughout the years, from 1990 to 2015, because of universal group B streptococcus screening and intrapartum antibiotic prophylaxis. Incidence has declined from 1.37 to 0.23 per 1,000 live births. Nonetheless, the incidence of LOS has remained nearly unchanged, at 0.31 per 1,000 live births [8, 9]. The prevalence of sepsis is significantly higher in both preterm and low-weight newborns, with a reported mortality of 17.6% [5].

Pathophysiology
Neonatal sepsis is a clinical syndrome that is characterized by signs and symptoms of infection usually associated with bacteremia, which leads to a systemic inflammatory response syndrome that further leads to multiorgan dysfunction [10, 11]. Early-onset neonatal sepsis includes gram-positive bacteria like Streptococcus agalactiae and *Escherichia coli*, Staphylococcus aureus, Enterococcus, and Streptococcus pneumonia [2]. Late-onset neonatal sepsis includes gram-negative bacteria, coagulase-negative staphylococci (CONS), Klebsiella pneumoniae, Acinetobacter baumannii [2, 12], and viral pathogens which

include echovirus, enterovirus, parechovirus, coxsackie virus, adenovirus, parainfluenza virus, rhinovirus, and coronavirus [13]. Fungal causes are uncommon, with the most common fungal cause being Candida [13].

Maternal risk factors include prolonged rupture of membranes, chorioamnionitis, and poor prenatal care. Neonatal risk factors include prematurity of the fetal immune system, congenital dermatologic abnormality, and birth asphyxia which disrupts host defenses and predisposes to infection [10]. Moreover, preterm infants are shown to be exposed to bacteria in utero, while term infants are most probably exposed to bacteria in the birth canal during labor [14]. During the early stage of sepsis, host immunity plays a major role in pathogenesis, and the innate immune system acts as a defense, while adaptive immunity still requires maturity. Innate barriers are skin and mucosal barriers that act by producing acidic pH, mucus, and cilia [15]. However, neonates have less acid production and motility and low-level productive mucous; respiratory epithelia produce mucociliary clearance. In preterm neonates, there are more goblet cells compared to normal and the reduced mucociliary clearance results in an inability to clear bacterial debris; thus, they are prone to sepsis.[16] Gastrointestinal epithelia including Paneth and intestinal lymphoid cells produce interleukin 17 that helps activate adaptive immunity [16].

EOS pathophysiology can be categorized from least to most common as follows: retroperitoneal accession via the fallopian tube, vertical bacterial transmission from the mother before birth (when pathogens from the vagina ascend to the uterus and reach the fetus through hematogenous transmission), and contamination of the fetus's mucous membranes during vaginal birth by microorganisms from the birth canal, maternal genitourinary tract colonizers, and perineal area, potentially affecting the lungs or intestines [17-19].

Symptoms

The clinical symptoms of neonatal septicemia are often non-specific, and blood culture is the gold standard for the diagnosis of septicemia, but blood culture cannot produce immediate results. Some children have used antibiotics before blood culture, which brings some difficulties to early diagnosis. WBC count, neutrophil classification and CRP elevation are not specific to septicemia, so scholars at home and abroad are committed to exploring more sensitive indicators for early diagnosis. Clinical manifestations range from subtle symptoms to profound septic shock. Signs and symptoms of sepsis are nonspecific and include temperature instability, mostly fever, irritability, lethargy, tachypnea, grunting, hypoxia, poor feeding, tachycardia, poor perfusion and hypotension [20].

Treatment

1. Antibiotic Therapy

Selecting appropriate antibiotics according to the results of blood culture and drug sensitivity tests is an ideal method for the treatment of neonatal septicemia, but bacterial culture cannot get results quickly. Antibiotics are often selected on the basis of experience in the clinic. It is inevitable that the pertinence is not strong [21].

Staphylococci were the first pathogen of neonatal septicemia, of which Coagulase-negative *Staphylococcus* (CNS) was the main pathogen. However, CNS is generally resistant to penicillin, ampicillin, oxacillin and erythromycin, and has an increasing resistance rate to ceftriaxone and cefazolin. Although it is highly sensitive to vancomycin, vancomycin-resistant *Enterococci* have been detected, so ortho-cloxacillin is the first choice for CNS infection. Vancomycin should be used on the premise of an etiological basis. Methicillin-resistant CNS (MRCNS) and methicillin-resistant Staphylococcus aureus (MRSA) infections are resistant to many antibiotics, sensitive to vancomycin, and partially sensitive to amikacin, gentamicin, rifampicin, tetracycline and ofloxacin. However, due to the limitation of neonatal medication, only vancomycin can be used as the first choice for MRCNS and MRSA infection [22].

The third-generation cephalosporins such as cefotaxime, ceftazidime and ceftriaxone can be used for Gramnegative bacilli that do not produce extended-spectrum B-lactamase (ESBLS). For those producing ESBLS, compound dosage forms with synergists, such as cefoperazone/sulbactam, or other antibiotics stable to ESBLS, such as imipenem, meropenem, etc, were used, but these drugs were expensive and were not used as first-line drugs [23-24].

Group B *Streptococcus* and *Escherichia coli* are the most common causes of both early- and late-onset sepsis, approximately two-thirds of early-onset infections. The combination of ampicillin and gentamicin is effective in treating most common organisms. In the case of neonates with suspected meningitis the addition of expanded-spectrum cephalosporin like cefotaxime to ampicillin and gentamicin [25].

Early-onset pneumonia before seven days of age is treated with empiric coverage with ampicillin and gentamicin. Third-generation cephalosporin should generally not be used for early-onset sepsis or pneumonia. carbapenems are not used generally due to carbapenem-resistant Enterobacteriaceae [26].

2. Emollient Therapy

One randomized clinical trial showed that the application of topical emollient reduces the chance of bloodstream infection in preterm infants. But it does not affect mortality and is insignificant in the prevalence of sepsis. It shows local irritation and is not further recommended [27, 28].

Conflict of Interest

Not available.

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