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NEONATAL SEPSIS, CLINICAL MANIFESTATION, DIAGNOSIS AND TREATMENT

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Abstract

Sepsis is a severe illness during the neonatal period. Despite significant advances in the care of newborn infants, sepsis remains a leading cause of neonatal morbidity and mortality. The overall incidence of neonatal sepsis ranges from 1 to 5 cases per 1,000 births and case fatality rates (CFRs) range from 2 % to 60 %. Both rates depend on multiple factors, such as pathogen distribution, gestational age, Streptococcus agalactiae (group B Streptococcus, GBS) carriage rates and prevalence of other common specific pathogens.

Most types of microorganisms can cause sepsis, including bacteria, fungi, viruses and parasites, such as those that cause malaria. Bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella* and *Neisseria meningitidis* are the most common etiological pathogens. Manifestations of sepsis and septic shock can be the fatal frequent pathway of infections with seasonal influenza viruses, dengue viruses and highly transmissible pathogens of public health concern such as avian and swine influenza viruses, severe acute respiratory syndrome coronavirus, Middle East respiratory syndrome coronavirus and most recently, Ebola and yellow fever viruses.

It is descriptive, non-experimental study. The aim of it is to specify the etiologic factors, clinical manifestation, diagnostic criteria and treatment of sepsis.

Based on the results of the study conclusion is that the use of non-culture based diagnostics and sepsis scores to predict and diagnose septic neonates are areas of active investigation. The next frontier for antibiotic stewardship in the neonatal intensive care unit must be development of strategies to decrease antibiotic use and minimise adverse effects by a thorough study of duration of therapy.

Key words. Neonatal sepsis, complete blood count, blood culture, antimicrobial therapy.

Sepsis arises when the body's response to infection injures its own tissues and organs. It can lead to septic shock, multiple organ failure and death, if not recognized early and managed promptly [1].

An international consensus has recently recommended that sepsis should be defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection" and septic shock as "a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone" [2]. Both definitions are accompanied by clinical criteria to translate them into practice to support diagnosis and clinical management during patient care.

Sepsis is a severe illness during the neonatal period. Despite significant advances in the care of newborn infants, sepsis remains a leading cause of neonatal morbidity and mortality, particularly among very low-birth-weight (VLBW) preterm infants. The overall incidence of neonatal sepsis ranges from 1 to 5 cases per 1,000 livebirths [3] and case fatality rates (CFRs) range from 2 % to 60 %. Both rates depend on multiple factors, such as pathogen distribution, gestational age, Streptococcus agalactiae (group B Streptococcus, GBS) carriage rates and prevalence of other common specific pathogens [4, 5]. Children admitted to the NICU are normally in a serious condition or premature; the prevalence of sepsis amonglong-term hospitalized children may be as high as 30%,with a mortality rate as high as 50%, and survivors experience serious sequelae [6 – 8].

Most types of microorganisms can cause sepsis, including bacteria, fungi, viruses and parasites, such as those that cause malaria. Bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Escherichia coli, Salmonella* spp. and *Neisseria meningitidis* are the most common etiological pathogens. Manifestations of sepsis and septic shock can be the fatal frequent pathway of infections with seasonal influenza viruses, dengue viruses and highly transmissible pathogens of public health concern such as

avian and swine influenza viruses, severe acute respiratory syndrome coronavirus, Middle East respiratory syndrome coronavirus and most recently, Ebola and yellow fever viruses [1].

The Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Network and theVermont Oxford Network define neonatal early-onset sepsis (EOS) as the onset of signsand symptoms of sepsis with an associated positive culture result at or before age 72 hours. Late-onset sepsis (LOS) is defined as the onset of signs or symptoms of sepsis after age 72hour [9]. EOS is further divided into very early onset (VEOS, 0–2 days) and other EOS (3–6 days), while LOS is sometimes further divided to age groups of 7–30 days and 31–90 days [10]. Another acceptable classification differentiates between hospital-acquired and community acquired sepsis [11]. The incidence of EOS in the United States is estimated to be 0.98 cases per1,000 live births overall and 10.96 cases per 1,000 live births among VLBW infants [12]. In addition, more than one-fifth (21%) of VLBW infants have at least one episode oflate-onset culture-proven sepsis [13].

Vulnerability of the Neonate are:

- Immature innate immune system: Reduced phagocytic and opsonisation activity, low complement levels, and immature cell mediated and humoral immunity.

- Poor barrier to infection: Fragile immature skin easily susceptible to invasion of organism, immature mucosal barriers and reduced levels if secretory immunoglobulins, immature ciliary function with reduced ability to clear secretions and poorly developed blood brain barrier.

Presence of the following risk factors has been associated with an increased risk of EOS.

- Low birth weight (<2500gms) or prematurity.
- Febrile illness in the mother 2 weeks prior to delivery.
- Foul smelling and / or meconium stained liquor.
- Prolonged rupture of membrane (>24 hours).
- More than 3 vaginal examinations during labor.
- Prolonged and difficult delivery with instrumentation [14].

The burden of LOS is significant in developed [15,16] and developing nations of the world [17]. The incidence of LOS varies inversely with gestational age and birth weight. The important risk factors for LOS in preterm infantsare intravascular catheters, delayed commencement of enteral feeds, prolonged use of parenteral nutrition, prolonged ventilation, and surgery.1 Although the predominant organism causing LOS is coagulase-negative

staphylococci, other organisms such as *Staphylococcus aureus*, Gramnegative bacteria, and fungi also are important [18].

Neonatal sepsis (NS) is an inflammation-induced systemic inflammatory response syndrome and an important cause of neonatal deaths, this condition comprises systemic poisoning symptoms caused by alarge number of toxins produced by bacteria upon entry into the blood stream, growth, and reproduction. As the neonatal blood–brain barrier is not completely developed,purulent meningitis is easily contracted and represents agreat threat to the life and health of children, particularly preterm children [3].

Neonates with bacterial sepsis might show non-specific signs and symptoms or focal signs of infection, including temperature instability, hypotension, poor perfusion with pallor and mottled skin, metabolic acidosis, tachycardia or bradycardia, apnoea, respiratory distress, grunting, cyanosis, irritability, lethargy, seizures, feeding intolerance, abdominal distention, jaundice, petechiae, purpura, and bleeding (table 1).

Table 1: Initial signs and symptoms of infection in newborn infants

Symptoms	
General	Fever, temperature instability; “not doing well”, poor feeding, or oedema
Gastrointestinal system	Abdominal distention, vomiting, diarrhoea, or hepatomegaly
Respiratory system	Apnoea, dyspnoea, tachypnoea, retractions, flaring, grunting, or cyanosis
Renal system	Oliguria
Cardiovascular system	Pallor, mottling, cold, clammy skin, tachycardia, hypotension, or bradycardia
CNS	Irritability, lethargy, tremors, seizures, hyporeflexia, hypotonia, abnormal Moro reflex, irregular respirations, full fontanel, or high-pitched cry
Haematological system	Jaundice, splenomegaly, pallor, petechiae, purpura, or bleeding

Initial symptoms might be few and could include apnoea alone or tachypnoea with retractions, nasal flaring, grunting, or tachycardia. Later complications of sepsis might include respiratory failure, pulmonary hypertension, cardiac failure, shock, renal failure, liver dysfunction, cerebral oedema or thrombosis, adrenal haemorrhage or insufficiency, bone

marrow dysfunction (neutropenia, thrombocytopenia, anaemia), and disseminated intravascular coagulation.

Non-infectious presentations of organ failure might mimic the clinical presentation of neonatal sepsis. Additionally, infectious and non-infectious causes might coexist in the same host. For example, clinical observations have shown that respiratory distress syndrome secondary to surfactant deficiency might be present with bacterial pneumonia [19].

Adequate and timely diagnosis of neonatal sepsis remainsan important challenge to the clinician especiallyin developing countries. Blood culture, which is the gold standard for definitive diagnosis, takes at least 48hours up to 6 days, by which time the infection may have progressed with consequences on the morbidity and mortality of the neonates. Some gold standard tests (eg, positive bacterial or viral cultures) may take some time to become available or may be very expensive, which can increase the value of a test that can be performed in expensively and rapidly [20].

It should be stated, however, that blood culture sampling often yields false-negative results, and clinical signs of infectionare often unspecific. It is therefore a huge challenge to diagnose sepsis correctly in early disease states, which would be necessary to initiate prompt antimicrobial treatmentand to reduce case fatality rates.

The complete blood count (CBC) is used by 99% ofthe clinicians as part of their initial sepsis evaluation. However, no single marker possesses adequate sensitivity to rule out late-onset sepsis in VLBW infants [21]. CBC parameters previously associated with late-onset sepsis include a total white blood cell count (WBC) < 5000/mm3, an immature neutrophil/total neutrophil (I/T) ratio > 0.10 and a platelet count lower than < 100,000/uL [22]. The use of CBC in combination with CRP for late onset sepsis evaluation in VLBW infants could potentially be more sensitive than each individual test. It is also possible that the variation in time (from T0 to T24)of these tests could be clinically useful even when the absolute test results are below the cut-off of abnormal values.

Inflammatory markers such as procalcitonin, C –reactive proteins (CRP) and haematological indices have also been used in diagnosing neonatal sepsis [23].

The advantage of CRP includes its very low serum level in normal infants and rapid rise within 6 to 8 hours after the onset of sepsis [24]. Previous studies have shown that quantitative serial CRP levels 12 – 24 hours offer the most sensitive and reliable information [25]. And can therefore be used as an adjuvant tool to guide physicians.

Several information sources argue that haematological scoring system (HSS) based on total leukocyte count, neutrophils and platelets have also been used to predict neonatal sepsis

[23, 24]. In resource limited settings, where blood culture is notroutinely done, relatively in expensive screening tools suchas CRP and HSS can be utilized as a screening tools, potentially serving lives [26].

Several studies have investigated different molecular methods for the diagnosis of NS since they have an increased sensitivity and the capacity of rapid detection of pathogens. To assess their diagnostic accuracy, a systemic review of literature was performed by Cochrane. The meta-analysis of 35 studies found a mean sensitivity and specificity of 0.90 and 0.93%, respectively. Based on the results, the authors suggest that the molecular tests for the diagnosis of NS are unlikely to be used as a triage test (a test that select neonates to undergo cultures) because false-negative can delay performance of culture and postpone treatment but may perform well as an "add-on" test (a test performed concurrently with cultures) since they lead to a rapid detection of pathogens (results are available in 6–8 hours) that may help in optimizing treatment [27].

Management of a neonate with sepsis includes providing aggressive supportive care, antimicrobial therapy and adjuvant therapies.

Supportive Care consists of:

- Maintenance of thermo-neutral environment, prevention of hypo or hyperthermia.
- Maintenance of normoglycemic status (45 to 120 mg/dl).
- Maintenance of Oxygen saturation (91 to 94%).
- Maintenance of tissue perfusion and blood pressure using colloids and inotropes.
- Maintenance of adequate nutrition by enteral feeding if not feasible by parenteral nutrition.
- Blood products to normalize the coagulation abnormalities, correction of anemia and thrombocytopenia.

Antimicrobial therapy of neonatal infections can be divided into the suspected (empirical) or known (definitive) pathogens. Consideration of early-onset or late-onset presentation and exposures (community versus hospitalised status at the time of symptom onset) affects antimicrobial choice. The most important components are a thorough and complete history and physical examination as well as cultures of clinical specimens [19].

The indications for starting antibiotics in neonates at risk of EOS include:

- Presence of >3 risk factors for early onset sepsis.
- Presence of foul smelling liquor.
- presence of 2 antenatal risk factor and a positive septic screen and `

– Strong clinical suspicion of sepsis.

The indications for Starting Antibiotics in LOS Include

– Positive septic screen.
– Strong clinical suspicion of sepsis [14].

Although it is preferable to obtain cultures before the initiation of antimicrobial therapy to optimize recovery of organisms, antimicrobial therapy administration should not be unduly delayed for specimen collection in severely ill neonates in septic shock. In general, empirical therapy should be guided by the antimicrobial resistance patterns of bacterial isolates commonly detected in the neonatal intensive care unit or in community settings. Initial empirical treatment of early-onset bacterial infections should consist of ampicillin and an aminoglycoside (usually gentamicin), with third-generation or fourth-generation cephalosporin drugs reserved for suspected Gram-negative meningitis. Infections due to extended-spectrum β-lactamase-producing Gram-negative bacilli require treatment with carbapenems, such as meropenem. Treatment with piperacillin–tazobactam and ampicillin–sulbactam is being used increasingly among infants admitted to hospital in the neonatal intensive care unit; however, the penetration of tazobactam into the CNS is unreliable and should not be used for treatment of meningitis. However, the β-lactamase inhibitor sulbactam, when combined with ampicillin, does seem to achieve high concentrations in the CSF [28].

Health-care-associated infections acquired in a neonatal intensive care unit are more likely to be caused by coagulase-negative staphylococci, and less often due to *S aureus* and Gram-negative bacteria. Although bloodstream infections due to coagulase-negative staphylococci in preterm infants are associated with substantial short-term morbidity as well as long-term neurodevelopmental impairment, they are not associated with increased mortality. With improvement in blood culture techniques that provide real-time culture results, narrow empirical therapy with a β-lactam antistaphylococcal antibiotic such as nafcillin combined with an aminoglycoside, could be initiated in infants not colonised with MRSA and altered if pathogen recovery suggests alternative antimicrobial coverage. Such a strategy has been shown to reduce vancomycin use in the neonatal intensive care unit [29].

Fungal infections including candidiasis, aspergillosis, and zygomycoses, should be aggressively managed when they are suspected and diagnosed. Empirical antifungal therapy with amphotericin deoxycholate can be considered in high-risk infants with risk factors for invasive candidiasis. Involvement of a paediatric infectious disease physician, a pharmacist with expertise in neonatal infections, and use of a guide containing neonatal dosing by weight and gestational age optimises antimicrobial use. Peak and trough measurements of

antimicrobials might be useful to minimise toxicity if the antimicrobial will be administered for more than 2–3 days and in the treatment of particular infections such as meningitis where CSF penetration is needed. Trough measurements might be indicated in infants with compromised kidney or liver function [19].

It can be concluded that despite the fact that the burden of early-onset sepsis attributed to GBS has been reduced because of the widespread implementation of prenatal screening and administration of intrapartum antibiotics, missed opportunities for diagnosis and intervention still exist. The widespread use of antibiotic prophylaxis raises questions about the emergence of resistance among co-colonising organisms and continued active surveillance will be important to monitor this concern. The significance of coagulase-negative staphylococci as colonising organisms versus pathogens in the neonate remains an important area of investigation, especially with concern for emergence of vancomycin resistance.

The use of non-culture based diagnostics and sepsis scores to predict and diagnose septic neonates are areas of active investigation. The next frontier for antibiotic stewardship in the neonatal intensive care unit must be development of strategies to decrease antibiotic use and minimise adverse effects by a thorough study of duration of therapy. As knowledge of the neonatal microbiome emerges, the importance of minimising antibiotic exposure to decrease necrotising enterocolitis, as well as other sequelae such as asthma, obesity, inflammatory bowel disease, and neurological disorders is paramount.

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