Egypt. J. Chem. Vol. 67, SI: M. R. Mahran, pp. 729-742 (2024)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Nursing Interventions and Biochemical Markers in Early Detection of Neonatal Sepsis

Nawaf Sharqi Khalaf Alanazi[1], Bandar Sharqi Khalaf Alanazi[1], Khalid Sharqi Khalaf Alanazi[1], Ahmed Ibrahim Mohammed Habadi[2], Amnah Aziz Alsubaie[3], Noora Mohammed Alnaji[4], Fahad Abdu Shoei Humedi[5], Ghadah Saud Alanazi[6], Ashwaq Faleh Mater Anzy[6], Atif Ogiby Alkhayri[6], Fatimah Ali Hakami[6], Fahd Nasser Alshakarah[7], Saleh Mohammed Alklywy[6], Salhah Ali Ibrahim Saddeg[8], Shrouq Kassim Ahmed Moharram[9]

[1]Nursing, Northern Area Armed Forces Hospital. King Khalid Military City, PO Box 10018, Hafr Al Batin 31991 , Kingdom of Saudi Arabia.
[2]Nursing technician, Prince Mohammad bin Nasser Hospital in Jazan, Kingdom of Saudi Arabia.
[3]Specialist Nursing, Imam Abdul Rahman Al-Faisal Hospital, Riyadh First Health Cluster, Kingdom of Saudi Arabia
[4]Specialist Nursing, Baish General Hospital, Jazan 87597, Kingdom of Saudi Arabia
[5]Nursing technician, Eradah for mental health Hospital in Jazan, Jazan Cluster, Kingdom of Saudi Arabia.
[6]Ministry of health, Kingdom of Saudi Arabia
[7]Epidemiological observer, Compliance Department, Riyadh Health, Kingdom of Saudi Arabia.
[8]Nursing technician, Primary Health Care Center in Albaidh, Riyadh, Kingdom of Saudi Arabia
[9]Nursing technician, Riyad, Kingdom of Saudi Arabia

In Loving Memory of Late Professor Doctor ""Mohamed Refaat Hussein Mahran""

Abstract

Aim: This study aims to explore the role of nurses and the use of biochemical markers in the management of neonatal sepsis. **Methods:** A comprehensive literature review was conducted to analyze current research on the roles of nurses in neonatal sepsis management and the utility of biochemical markers such as C-reactive protein (CRP), procalcitonin (PCT), interleukins (IL-6, IL-8, IL-10), and soluble CD14 subtype presepsin (sCD14-ST) in diagnosing and monitoring neonatal sepsis. Studies focusing on clinical trials, observational studies, and meta-analyses published between 2000 and 2024 were included. **Results:** Nurses play a critical role in the early recognition and management of neonatal sepsis through vigilant monitoring, timely intervention, and effective communication with healthcare teams. Biochemical markers, particularly CRP and PCT, have shown promise in aiding early diagnosis and monitoring treatment response. IL-6, IL-8, IL-10, and sCD14-ST have also demonstrated potential as adjunctive markers in differentiating sepsis from non-infectious conditions. **Conclusion:** The integration of nurses in the multidisciplinary care team is crucial for improving outcomes in neonatal sepsis. Biochemical markers provide valuable adjuncts to clinical assessment, facilitating early diagnosis, appropriate antibiotic use, and monitoring of treatment efficacy. Further research is needed to standardize protocols for marker use, optimize diagnostic accuracy, and enhance the overall management of neonatal sepsis.

Keywords: Neonatal sepsis, nurses' role, biochemical markers, C-reactive protein, procalcitonin, interleukins, soluble CD14 subtype presepsin.

1. Introduction

Neonatal sepsis is a serious illness that is recognized as a global health concern because it dramatically increases the morbidity and death rate among infants (1-2). The American Academy of Pediatrics defines early-onset sepsis as occurring within 3 days, whereas the Centers for Disease Control define it as occurring within 7 days, using epidemiological research as support (3-4). According to 5, the prevalence of early-onset neonatal sepsis in North America is estimated to be between 0.76 and 0.77 cases per 1,000 live births, with a death rate of 24.4%. An estimated one million newborns worldwide perish from illnesses in underdeveloped nations each year, and those who survive are at a heightened risk of neurodevelopmental disabilities

*Corresponding author e-mail: no1717@hotmail.com (Nawaf Sharqi Khalaf Alanazi).
Receive Date: 12 July 2024, Revise Date: 16 August 2024, Accept Date: 21 August 2024
DOI: 10.21608/ejchem.2024.303722.9998

(6–9). Late-onset sepsis, which manifests at a time beyond three days of life and has a rate close to 36%, is more common in newborns in neonatal intensive care units (NICUs), especially premature extremely low birth weight infants (10). Timely identification is still a chronic and difficult problem in the care of infants or high-risk neonates in the NICU, despite recent advancements in managing neonatal sepsis, such as the use of powerful antibiotics and advanced biomarkers for diagnosis (11–13). A wide range of potential infectious organisms, from hospital-acquired infections to those acquired Transplacentally or during birth, interact with the immature immune systems of newborns and premature neonates, greatly limiting diagnostic capabilities and contributing to unfavorable outcomes in this population (14). Therapy delays raise the risk of death and morbidity in the absence of early, objective, and precise diagnostic indicators that persist abnormally long enough to enable the diagnosis of newborn sepsis (15).

Due to the fact that newborns frequently appear with modest and vague signs and symptoms, a number of variables, including the lack of specific clinical features, delay diagnosis and therapy commencement (16). Due to difficulties in diagnostic testing, a considerable percentage of newborns (up to 7%–13%) are routinely assessed and treated for potential neonatal sepsis, despite the low prevalence of culture-proven neonatal sepsis, which is estimated to be two per 1,000 live births (17). Conventional laboratory procedures that are frequently serum-based are used to determine typical diagnostic parameters. These tests include the white blood count (WBC), absolute neutrophil count (ANC), immature/total neutrophil (I/T) ratio, and C-reactive protein (CRP) that can be obtained in different ways (18-19). Nevertheless, the sensitivity and specificity of these traditional sepsis evaluation metrics are low, and they frequently exhibit elevated levels in response to other neonatal conditions like asphyxia, prolonged rupture of membranes, meconium aspiration, and the birth process (6, 8, 17, 20–22). According to recent data, age-specific ratio nomograms, as opposed to predefined normal ranges, may enhance the diagnostic accuracy of WBC, ANC, and I/T parameters (23). The gold standard for diagnosing sepsis is based on the isolation of pathogenic bacteria in blood cultures, although this method is not very sensitive and does not have the time to affect when antibiotic therapy is started (24). The blood culture approach has additional drawbacks, such as a higher rate of false negative results because of small amounts of blood used for the culture and the potential impact of prenatal antibiotic usage on later bacterial growth (17). Because of this ambiguity, early antibiotic therapy is frequently started for suspected infections or postponed, which raises the risk of illness.

Neonatal sepsis (NS) continues to be a major cause of morbidity and mortality even with recent advances in outcomes (25). Early-onset sepsis (EOS) is defined as illnesses detected in the first 72 hours of life, usually acquired during pregnancy, whereas late-onset sepsis (LOS) develops after day four and can come from hospital or community settings (26). The frequency of epilepsy in newborns born at or after 34 weeks gestational age (GA) varies from 0.3 to 0.8 per 1,000 live births (27-28). Lower gestational age (GA) is associated with a much higher risk of perinatal infection. Specifically, 4.8%–16.9% of preterm newborns exposed to chorioamnionitis acquire culture-positive EOS, while only 0.47%–1.24% of similarly exposed children delivered at ≥35 weeks GA experience the same risk (29). Neurological morbidities and bronchopulmonary abnormalities are linked to LOS (30-31). Since both EOS and LOS frequently exhibit vague clinical indications that closely resemble common noninfectious illnesses including transitory tachypnea and apnea of prematurity, diagnosing NS can be difficult. Although early and intensive antibiotic therapy is essential, overuse of these drugs has serious negative effects on health and finances. In susceptible preterm newborns, broad-spectrum antibiotics increase the risk of invasive fungal infections (32) and necrotizing enterocolitis (NEC) (33). Term newborns receiving antibiotic therapy frequently need to spend some time apart from their mothers at a critical phase of bonding (34). Moreover, early antibiotic usage has been associated with a higher risk of obesity (35-37), inflammatory bowel disease, and asthma (38-39). Accurate biomarkers are still essential for enabling prompt and accurate diagnosis of NS. When it comes to responding to infection and therapy, the perfect biomarker should show a steady and dependable pattern. While specificity is required to avoid treating unaffected children needlessly, high sensitivity is essential to prevent missing instances. In addition to identifying the pathogen, providing prognostic information, and being conveniently evaluated with a quick turnaround, an ideal biomarker would also need a small volume of blood if a serum sample were required (40).

As a result, neonatologists continue to face significant challenges in diagnosing neonatal sepsis accurately, quickly, and with high precision. This underscores the need for timely and reliable diagnostic biomarkers that will help clinicians identify sepsis risk early on, effectively manage antibiotics based on the causative organisms, and provide valuable guidance for therapy during the recovery phase. Examining the advancements in biomarkers for the detection and management of newborn sepsis is the goal of this review. One of the main causes of morbidity and death in both industrialized and developing nations is neonatal

sepsis. Determining the causative agent is essential to lowering the neonatal septicemia mortality rate. The disease's severe consequences can have a major impact on a newborn's life. Through the use of basic nursing care, nurses are essential in the prevention of newborn sepsis. Sepsis presents a serious risk to the community in the absence of treatment. There are several difficulties here. A biomarker's normal range may vary depending on GA or postnatal age, as well as because of concurrent noninfectious illnesses. Clinicians are frequently hesitant to rule out infection in a sick newborn with a negative blood culture, despite the fact that a positive blood culture is the gold standard and is sensitive to relatively low bacterial loads (41-42). Diverse definitions of "culture-negative" or "clinical sepsis" among research, in addition to variations in measurement methods, sample collection schedules, and threshold levels, all contribute to study heterogeneity and make it more difficult to derive conclusive findings from meta-analyses.

Neonatal Sepsis:

Within the first 28 days of an infant's existence, a common infection known as neonatal sepsis can strike, greatly increasing the morbidity and fatality rate of the young (45-46). Early-onset neonatal sepsis (EOS) continues to be a leading cause of newborn morbidity and mortality worldwide, even if its prevalence has decreased recently (47). EOS usually manifests 72 hours after birth and is frequently caused by contaminated amniotic fluid or vertical transfer during vaginal delivery from organisms in the mother's genital canal (48). It is typified by meningitis, pneumonia, and bacteremia. It can have lethal consequences or cause chronic issues like hearing loss, seizures, and delayed neurodevelopment in survivors (49). In rich nations, the death rate from EOS can reach 30%, while in underdeveloped nations, it can approach 60%. Numerous Gram-positive and Gram-negative bacteria as well as certain fungi are the cause of EOS (50). The most frequent pathogen, Group B Streptococcus (GBS), is present in half of the cases. Escherichia coli is detected in 25% of the cases. Common offenders include Staphylococcus aureus, Listeria monocytogenes, coagulase-negative Staphylococcus (CoNS), and other Gram-negative bacteria. E. Coli is more common than GBS in infants with extremely low birth weights (51-52). Making an accurate diagnosis is a major problem in managing this infection. Due to their low sensitivity and varied normal ranges throughout the neonatal era, traditional diagnostic tests have limited utility and are challenging to interpret (53). Although blood culture is still the gold standard for diagnosing EOS, its positive rate is low and depends on a number of parameters, including the volume of blood obtained, the severity of the infection, the use of antibiotics previously, and laboratory competence. The majority of cases in impoverished countries are caused by culture-negative sepsis (54-55). Smaller blood samples are needed for the new, non-culture-based techniques that have been developed recently to improve diagnosis (55). In light of this, there has been a great deal of interest in determining certain EOS biomarkers. Any measurable characteristic that offers comprehensible information regarding the diagnosis of EOS is referred to in this context as a biomarker (56). These biomarkers' sequential rise and fall during sepsis may make it possible to incorporate them into multiplex kits for the stage-specific detection of newborn infections.

Because of their immature immune systems, newborns are more vulnerable to sepsis, regardless of gestational age. When labor problems or maternal comorbidities complicate a birth, or when a newborn has preterm or other innate risk factors, the risk of infection rises (57). Differentiating sepsis from other illnesses is difficult due to the vague nature of diagnostic features, which frequently causes a delay in receiving the necessary therapy (58). It is challenging to identify sepsis early due to these overlapping symptoms. Gestational age and birth weight have an impact on the overall incidence of early-onset sepsis (EOS) and late-onset sepsis (LOS), which is predicted to be 1 to 2 per 1,000 infants (59). Compared to term newborns (0.98 per 1,000 births; 60-62), preterm infants have higher infection rates (4.4 to 6.3 per 1,000 births). Because of their undeveloped immune systems and the need for survival treatments that expose them to infectious organisms, very-low-birth-weight (VLBW) newborns (less than 1,500 g) are more susceptible to sepsis (63).

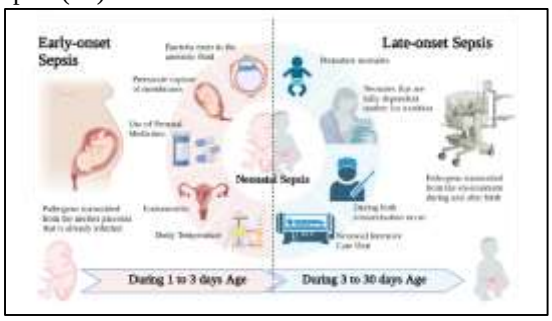

Figure 1: Neonatal sepsis.

Most often, vertical transmission of contaminated amniotic fluid or maternal microorganisms during the intrapartum period is the cause of EOS, which can become severely ill in newborns very quickly (64). Prenatal testing for Group B Streptococcus (GBS) and prophylactic antibiotic administration during labor have resulted in a considerable reduction in the incidence of EOS from GBS (65). But GBS continues to be the most common cause of neonatal sepsis, so medical professionals must keep a close eye on babies who are at risk. In a nationwide research, GBS-positive moms had received intrapartum antibiotics in half of the EOS cases, while 81% of mothers of term children with sepsis had negative GBS culture results

(62). Additionally, newborns are susceptible to infections during delivery that could be aggravated by chorioamnionitis. Sepsis is more likely to occur in babies whose moms had a fever during childbirth, especially if it happens early. Compared to babies whose moms were not treated for chorioamnionitis, premature newborns of mothers who received treatment are more likely to suffer from neonatal infection (66). Between 2007 and 2014, the percentage of live births in the US with preterm births dropped from 10.41% to 9.54% (66). One in ten newborns were delivered prematurely in 2015, despite a minor increase in preterm deliveries (Centers for Disease Control and Prevention, 2017). Premature birth rates are 48% higher among Black women than among all other women, demonstrating the persistence of racial and ethnic inequities (67). More babies are at danger when preterm and infection exposure occur during childbirth.

According to Stoll et al. (2002), LOS is frequently linked to horizontal variables that arise during prolonged NICU stays. With a 20% sepsis-related death rate, VLBW babies are especially vulnerable to sepsis (62). They are especially susceptible to sepsis because of their immature immune systems, underdeveloped central nervous systems, and requirement for central venous access for treatment (63). The length of hospital stay, and the complexity of the newborn's health status have a significant impact on the incidence of length of stay (LOS). According to Nizet and Klein (2010), LOS is linked to several conditions that impact ill newborns during extended hospital stays, including hypoxia, acidosis, hypothermia, and hypoglycemia. Neonates are particularly susceptible during these events, and normal medical procedures such as repeated blood draws and central line access provide entry points for infection (69). They may be continuously at risk due to the continual cycle of care for VLBW infants and intensive care events. Positive blood culture results are necessary for a final diagnosis of sepsis (70). It is difficult to identify small changes in the infectious process early on because of factors including the infant's age, the adjusted gestational age, and the care setting. For example, neonates weighing less than 2,500 g or fewer than 26 weeks gestation are frequently observed in high-surveillance NICU environments, which may result in temperature swings. Nurses may find it challenging to spot early signs of disease in neonates in typical newborn settings, such as mother-baby units (MBUs), because the babies' mothers may wrap or hold them close to their bodies. Although sepsis is not common in term newborns, it does occur more frequently in those with maternal risk factors, including positive GBS cultures, herpes simplex virus, temperature over 100.4 F, and ruptured membranes lasting more than eighteen hours (71). Suspicion of sepsis should be guided by laboratory results, clinical events, and established risk factors in addition to the need to differentiate clinical signs and symptoms from other illnesses (69).

The signs of early sepsis are poorly characterized. Waiting to start treatment until a neonate exhibits many physiological indications of sepsis raises the risk of morbidity and fatality. At the bedside, where nurses are more qualified than parents to spot early changes in the first few days after giving birth, sepsis surveillance takes place. Sepsis diagnosis in the NICU is a persistent worry that might be difficult to identify (72). In a qualitative research, nurses bemoaned the slow decline of newborns suffering from sepsis and thought that early, subtle alterations suggested sepsis before clear indications materialized (72). Early intervention might be facilitated by identifying a cluster of indications and symptoms. Few predictive methods and models have been effectively implemented for the early detection of sepsis (73-74). Rubarth (2007) created the 13-item Newborn Scale of Sepsis, which consists of five laboratory tests and eight clinical indications. Its limited diagnostic utility resulted from testing it on 62 newborns, which revealed high sensitivity (93%) but low specificity (47%) and positive predictive value (29%). Okascharoen et al. (2005) used derivation analysis with 1,870 newborns hospitalized for longer than 72 hours to construct a bedside prediction model for late-onset neonatal sepsis. The following seven factors contributed to the explanation of late-onset sepsis: lethargy, neutrophil bandemia, thrombocytopenia, aberrant body temperature, respiratory insufficiency, and duration of umbilical venous catheter use. The model's positive predictive value ranged from 43% to 56%, but its negative predictive value was high (90% to 96%). The Neonatal Trigger Score (NTS) was assessed by Holme et al. (2013) as a means of diagnosing sick infants. When the NTS was used to identify babies needing NICU admission, it demonstrated 77% sensitivity and 97% specificity in 485 neonates older than 35 weeks gestation. The NTS is encouraging, but it hasn't received external validation (75).

Role of Nurses in Neonatal Sepsis:

Updated recommendations for the medical treatment of sepsis are provided by the Surviving Sepsis Campaign guidelines, which are evidence-based guidelines for the management of sepsis. The 68 international experts from 30 organizations who contributed to these guidelines have evaluated the quality of the evidence and the strength of the recommendations using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) methodology. The recommendations are divided into three primary categories: (1) high-priority general care issues; (2) pediatric considerations; and (3) management of severe sepsis (76-77).

Initial Diagnosis and Resuscitation

The guidelines stress how crucial it is to diagnose and treat sepsis as soon as possible in order to lower death rates. Using a protocolized approach to resuscitation is crucial for patients who have tissue hypoperfusion caused by sepsis (hypotension that persists after the initial fluid challenge or blood lactate concentration ≥4 mmol/L). This strategy should be implemented as soon as possible, even prior to ICU admission, as it will have an impact on the treatment given in general clinical units and emergency departments (76-77).

Objectives for Grade 1C Initial Resuscitation (within the First 6 Hours):

- 8–12 mm Hg is the central venous pressure.
- ≥65 mm Hg is the mean arterial pressure (MAP).
- Output of urine: ≥0.5 mL/kg hr
- 70% for central venous oxygen saturation (superior vena cava) and 65% for mixed venous oxygen saturation

The guidelines also include aiming for the fastest possible normalization of lactate levels (grade 2C) and use blood lactate levels as a measure of tissue hypoperfusion. When sufficient intravascular volume replacement is achieved but central venous oxygen saturation (<70%) or mixed venous oxygen saturation (<65%) continues, dobutamine infusion (up to 20 μg/kg per minute) or transfusion of packed red blood cells to reach a hematocrit of at least 30% are the choices available. Clinician competency and the scarcity of equipment are obstacles to early quantitative resuscitation. The use of oxygen saturation and central venous pressure as resuscitation endpoints has generated debate, yet regimens incorporating these metrics are simple to set up in both emergency and intensive care unit settings. The influence of additional technologies on clinical outcomes in early resuscitation for assessing flow and volumetric parameters is minimal (76-77).

Bundles for Sepsis

The guidelines directly affect nurse care by offering detailed suggestions for managing sepsis through sepsis bundles. Nurses are frequently in charge of giving antibiotics and vasopressor therapy, as well as drawing blood samples for cultures and assessments of lactate levels. Sepsis bundles must be started as soon as possible when sepsis is diagnosed. Sepsis screening can increase early detection and lower mortality from sepsis as part of a process to enhance performance (78-79).

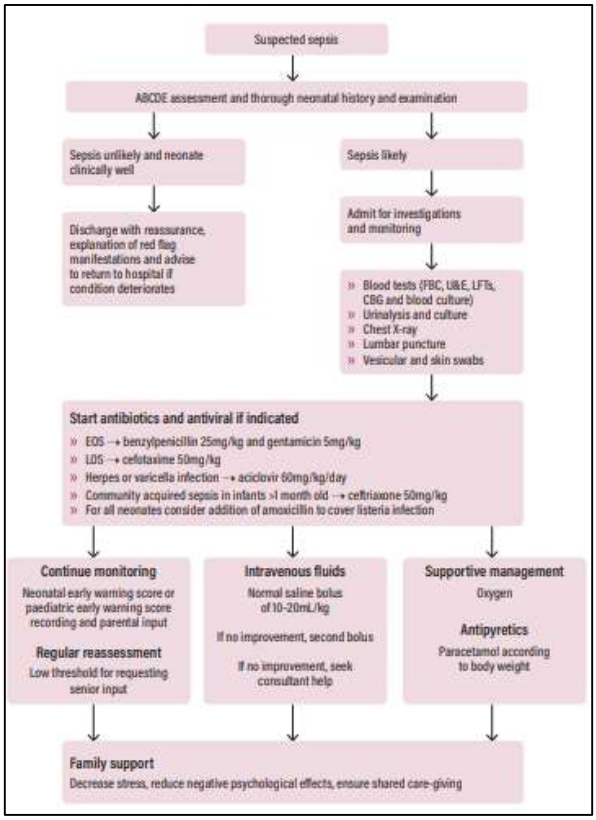

Figure 2: Management of Neonatal sepsis and role of nursing.

In order to accomplish goals in sepsis care, a multidisciplinary team comprising physicians, nurses, pharmacists, respiratory therapists, dieticians, and administrators is needed, as well as multispecialty collaboration including emergency medicine, surgery, and medicine. The identification and implementation of the new recommendations, which emphasize multidisciplinary and multispecialty engagement, can be improved through nurse-driven quality improvement projects that target sepsis (78-79).

Cultures and Antimicrobial Therapy

Before initiating antimicrobial therapy, it is recommended to obtain appropriate cultures, provided this does not delay administration longer than 45 minutes (grade 1C). To optimize identification of causative organisms, at least two sets of blood samples (both aerobic and anaerobic bottles) should be cultured before starting antibiotics. One blood sample should be obtained percutaneously and one through each vascular access device, unless the device was inserted less than 48 hours earlier. Other potential infection sources, such as urine, respiratory secretions, wounds, or other body fluids, should also be cultured if it does not significantly delay antibiotic administration (grade 1C). Nurses play a crucial role in obtaining samples for culture and administering antibiotic therapy. Obtaining samples from different sources maximizes the potential for positive culture results, and using appropriate techniques prevents contamination. If

cultures from different sites show the same organism, it enhances the likelihood that the organism is causing severe sepsis (78-79).

Source Control

Identifying the infection source is essential to manage sepsis and contain inflammatory responses. Appropriate interventions should be undertaken within the first 12 hours after diagnosis (grade 1C). Measures include surgical debridement for an abscess, removal of infected intravascular devices, or other actions to eliminate the infection source. Regular patient assessments can help identify potential infection sites, such as areas of redness, inflammation, or drainage from catheter sites (80).

Infection Prevention

Careful infection control practices, including hand hygiene, barrier precautions, catheter care, head-of-bed elevation, comprehensive oral care, and subglottic suctioning, should be maintained to prevent complications. Selective oral decontamination and selective digestive decontamination can reduce the incidence of ventilator-associated pneumonia (grade 2B). Oropharyngeal decontamination with oral chlorhexidine gluconate is also suggested to reduce this risk in ICU patients with severe sepsis (grade 2B). Infection prevention measures are critical for patients at risk of sepsis, focusing on education, surveillance, hand hygiene, and prevention of respiratory, central catheter–related, surgical site, and urinary tract infections (80).

Hemodynamic Support and Adjunctive Therapy

Fluid Therapy

Crystalloids are recommended as the initial fluid of choice for resuscitating patients with severe sepsis and septic shock (grade 1B). The use of hydroxyethyl starches is not supported (grade 1B). Albumin can be used when substantial amounts of crystalloids are needed (grade 2C). Fluid challenges should continue as long as hemodynamic improvement is observed, measured by dynamic (e.g., pulse pressure variation) or static (e.g., arterial pressure) variables (80).

Vasopressors

Vasopressor therapy should target a mean arterial pressure (MAP) of 65 mm Hg (grade 1C). Norepinephrine is recommended as the first-choice vasopressor (grade 1B). Epinephrine can be added if needed (grade 2B). Vasopressin up to 0.03 units per minute can be added to norepinephrine. Dopamine is an alternative only in selected patients (grade 2C). Phenylephrine is not recommended except in specific circumstances (grade 1C). Low-dose dopamine should not be used for renal protection (grade 1A). Arterial catheter placement is recommended for patients requiring vasopressors (grade 1C) (80).

Inotropic Therapy

A trial of dobutamine infusion up to 20 μg/kg per minute is recommended for myocardial dysfunction or ongoing hypoperfusion despite adequate volume and MAP (grade 1C). Increasing cardiac index to supranormal levels is not recommended (grade 1B) (80).

Steroid Therapy

Intravenous hydrocortisone (200 mg per day) is recommended only for hemodynamically unstable patients not responding to fluids and vasopressors (grade 2C). The corticotropin-releasing hormone stimulation test is no longer supported for identifying patients for steroid therapy (grade 2B) (80).

Administration of Blood Products

Red blood cell transfusion is recommended only for hemoglobin levels <7 g/dL to target 7.0 to 9.0 g/dL in adults (grade 1B). Erythropoietin is not recommended for treating anemia associated with severe sepsis (grade 1B). Fresh frozen plasma is not recommended to correct laboratory clotting abnormalities unless there is bleeding or planned invasive procedures (grade 2D). Platelet therapy is recommended for counts ≤10,000/mm³ in the absence of bleeding or ≤20,000/mm³ with a significant risk of bleeding. Higher platelet counts (≥50,000/mm³) are advised for active bleeding, surgery, or invasive procedures (grade 2D) (80).

Nursing Considerations

Nurses play a vital role in administering fluids, monitoring patient response, managing vasopressors, and ensuring proper techniques in obtaining cultures to prevent contamination. They also oversee infection prevention practices and educate other healthcare providers. Awareness and implementation of these guidelines in nursing practice are crucial for improving patient outcomes in sepsis management (80).

Supportive Therapy for Severe Sepsis

Mechanical Ventilation in Patients With Sepsis-Induced Respiratory Distress Syndrome

- **Tidal Volume**: A tidal volume of 6 mL/kg predicted body weight is recommended over 12 mL/kg for patients with sepsis-induced ARDS (grade 1A).
- **Plateau Pressures**: Maintain plateau pressures at ≤30 cm H2O (grade 1B).
- **PEEP**: Apply positive end-expiratory pressure (PEEP) to prevent alveolar collapse (atelectotrauma) (grade 1B).
- **Refractory Hypoxemia**: Use recruitment maneuvers for severe refractory hypoxemia (grade 2C) and prone positioning for PaO2/FIO2 ≤100 mm Hg (grade 2B).

General care principles include:

- **Head Elevation**: Maintain head of the bed elevation at 30º to 45º to limit aspiration risk and prevent ventilator-associated pneumonia (grade 1B).

- **Noninvasive Ventilation**: Use noninvasive mask ventilation in appropriate patients (grade 2B).
- **Weaning Protocol**: Implement a weaning protocol and conduct regular spontaneous breathing trials (grade 1A). Nurse-directed weaning has been shown to reduce the duration of mechanical ventilation. Nurses play a vital role in promoting adequate oxygenation, ventilation, and weaning patients off mechanical ventilation.

Sedation, Analgesia, and Neuromuscular Blockade in Patients With Sepsis

- **Minimizing Sedation**: It is recommended to minimize sedation in sepsis patients receiving mechanical ventilation, aiming for specific titration endpoints (grade 1B). This approach helps in reducing the duration of mechanical ventilation and lengths of stay in the ICU and hospital.
- **Neuromuscular Blocking Agents**: These should be avoided if possible or used in limited doses for less than 48 hours when necessary (grade 1C). Monitoring the depth of blockade using train-of-4 monitoring is recommended to prevent prolonged paralysis and its associated complications (80).
- **Monitoring**: Monitoring patients' response to sedation with validated scales like the Richmond Agitation Sedation Scale (RASS) is crucial. Strategies like daily sedation interruption, although initially promising, have shown no significant benefit in recent studies. Instead, protocols such as the ABCDE bundle (Awakening, Breathing Coordination, Delirium monitoring, Early mobilization) are effective in minimizing sedation, promoting early mobilization, and preventing complications like delirium.
- **Pain and Delirium Management**: Effective pain management and early detection and management of delirium using tools like the Confusion Assessment Method for the ICU (CAM-ICU) are essential. These measures help in improving patient outcomes by reducing the risks associated with prolonged sedation and immobility (80).

Glucose Control

Protocolized Blood Glucose Management

- **Initiation of Insulin**: Insulin dosing should commence when two consecutive blood glucose levels exceed 180 mg/dL in ICU patients with severe sepsis. The target upper blood glucose level should be maintained at 180 mg/dL or lower, rather than aiming for tighter control (grade 1A) (80).
- **Monitoring**: Blood glucose levels should be monitored every 1 to 2 hours initially, until stable, and then every 4 hours thereafter (grade 1C). It's important to note that point-of-care testing of capillary blood may not always accurately reflect arterial or plasma glucose values, necessitating caution in interpretation.
- **Insulin Therapy Management**: A protocolized approach to insulin therapy is recommended to ensure consistent management of blood glucose levels. This approach, often managed by nurses, has been shown to be feasible, safe, and effective in maintaining glucose within target ranges (grade 1A).

Renal Replacement Therapy

- **Continuous vs. Intermittent Therapies**: Both continuous renal replacement therapies and intermittent hemodialysis are equally effective in severe sepsis and acute renal failure, yielding similar short-term survival rates (grade 2B). Continuous therapies are preferred in hemodynamically unstable patients to manage fluid balance effectively (grade 2D).
- **Nursing Role**: Nurses play a crucial role in managing renal replacement therapy in the ICU, including preparation, adjustment of settings, monitoring electrolytes, and recognizing and managing complications like circuit failure (grade 2B) (80).

Prophylaxis of Deep Vein Thrombosis

- **Pharmacoprophylaxis**: Patients with severe sepsis should receive daily pharmacoprophylaxis against venous thromboembolism (VTE) using subcutaneous low-molecular weight heparin (LMWH) (grade 1B). If creatinine clearance is less than 30 mL/min, alternative forms of LMWH or unfractionated heparin should be considered (grade 1A) (80).
- **Combination Therapy**: Combining pharmacologic therapy with intermittent pneumatic compression devices is beneficial when feasible (grade 2C). Mechanical prophylactic treatments should be considered if there are contraindications to heparin use (grade 2C).
- **Nursing Implementation**: Nurses administer pharmacoprophylaxis as ordered, initiate mechanical compression devices, and promote early mobilization to prevent deep vein thrombosis, which is critical in reducing complications like pulmonary emboli (grade 1B).

Stress Ulcer Prophylaxis

- **Medication Recommendations**: Proton pump inhibitors (PPIs) are preferred over

histamine 2 blockers for stress ulcer prophylaxis in sepsis patients with bleeding risk factors (grade 1B). Routine prophylaxis is not necessary for patients without risk factors (grade 2B) (80).

- **Nursing Role**: Administration of stress ulcer prophylaxis is a standard practice in the ICU to reduce gastrointestinal bleeding risks, which can significantly impact patient outcomes (grade 1B).

Nutrition

- **Feeding Recommendations**: Oral or enteral feeding should be initiated as tolerated within the first 48 hours of severe sepsis diagnosis, rather than fasting or relying solely on intravenous glucose (grade 2C). Low-dose feeding initially, advancing as tolerated, is recommended to achieve full caloric feeding (grade 2B) (80).
- **Nutritional Strategies**: Enteral nutrition is preferred over parenteral nutrition alone or in combination with enteral feeding in the early phase of sepsis (grade 2B). Specific immunomodulating supplementation is not routinely recommended (grade 2C).
- **Nursing Considerations**: Nurses play a key role in implementing enteral feeding protocols, assessing tolerance, and managing complications related to feeding, which is crucial for maintaining gut integrity and preventing bacterial translocation (grade 2C).

Setting Goals of Care

- **Importance of Discussion**: Early discussion of treatment goals and prognosis with patients and their families is crucial within 72 hours of ICU admission (grade 2C). This includes incorporating goals of care into treatment and end-of-life planning using palliative care principles when appropriate (grade 1B) (80).
- **Enhancing Communication**: Nurses contribute significantly to these discussions, helping families understand prognosis and treatment options, which improves satisfaction, reduces stress, and aids in making informed decisions (grade 1B) (80).

These guidelines underscore the comprehensive approach required in managing severe sepsis, involving precise protocols for glucose control, renal replacement therapy, thromboprophylaxis, stress ulcer prevention, nutritional support, and setting clear goals of care to optimize patient outcomes in the ICU setting (80).

Biochemical Markers for Neonatal Sepsis:

Acute Phase Reactants in Neonatal Sepsis

C-reactive Protein (CRP)

- **Structure and Function**: CRP is a pentraxin protein that rapidly increases in response to inflammation, primarily binding to phosphocholine on bacterial membranes. It activates the complement pathway, enhances phagocytosis, and promotes proinflammatory mediator expression (81).
- **Diagnostic Utility**: CRP levels increase significantly during the acute phase response, making it a widely accessible and cost-effective marker in neonatal intensive care units for detecting infections.
- **Sensitivity and Specificity**: Sensitivity ranges widely (29% to 100%) depending on various factors such as timing of sampling, reference values, and patient characteristics. Specificity also varies (6% to 100%) (81).
- **Clinical Use**: Serial CRP measurements, especially 12-24 hours after onset of symptoms, are preferred for monitoring response to treatment and determining antibiotic therapy duration.

Procalcitonin (PCT)

- **Biological Properties**: PCT, the precursor of calcitonin, is mainly produced in the liver and peripheral blood mononuclear cells in response to TNF-α and IL-6 stimulation.
- **Diagnostic Value**: PCT levels rise rapidly and significantly in bacterial infections compared to viral or inflammatory conditions. It peaks at around 6 hours and remains elevated for up to 24 hours (81).
- **Clinical Applications**: Serial PCT measurements are useful for monitoring response to antibiotic therapy and distinguishing between bacterial and non-bacterial causes of infection.
- **Limitations**: Elevated PCT levels can also occur in non-infectious conditions such as respiratory distress syndrome or after birth (81).

Serum Amyloid A (SAA)

- **Function**: SAA proteins, part of the acute phase response, play a role in cholesterol metabolism and stimulate immune responses during inflammation.
- **Diagnostic Accuracy**: SAA has shown better diagnostic accuracy than CRP in some studies for early-onset neonatal sepsis.
- **Clinical Utility**: SAA levels increase early in the course of EOS and may complement other markers in diagnosing infections (81).

Lipopolysaccharide-Binding Protein (LBP)

- **Role**: LBP transfers endotoxins to immune cells, primarily active in Gram-negative bacterial infections.
- **Diagnostic Value**: Elevated plasma LBP levels persist for more than 24 hours in

neonates with early-onset sepsis, providing a prolonged window for diagnosis.

Interalpha Inhibitor Proteins (IaIp)

- **Function**: IaIp are serine protease inhibitors involved in inflammation regulation and wound healing (81).
- **Diagnostic Accuracy**: Reduced levels of IaIp are associated with neonatal sepsis and mortality in severe sepsis cases.

Mannose-Binding Lectin (MBL)

- **Function**: MBL activates the complement system via the lectin pathway, enhancing phagocytosis of microorganisms (81).
- **Diagnostic Potential**: Low MBL levels at birth are associated with increased risk of early-onset sepsis, showing promise in identifying neonatal infections.

These acute phase reactants play critical roles in the systemic response to infection, aiding in diagnosis, monitoring treatment response, and predicting outcomes in neonatal sepsis. Their clinical utility varies based on timing of measurement, underlying conditions, and specific patient characteristics, highlighting the importance of using them in combination for comprehensive diagnostic and therapeutic strategies (81).

Cytokines in Neonatal Sepsis

Interleukin-6 (IL-6)

- **Function**: IL-6 is a pleiotropic cytokine produced in response to infections and tissue injury.
- **Diagnostic Utility**: Elevated IL-6 levels indicate inflammation and have been studied as a marker for fetal inflammatory response syndrome (FIRS) in EOS.
- **Clinical Applications**: IL-6 levels rise significantly during infections, although it has a narrow window for distinguishing infections. It is often used in combination with CRP for better diagnostic accuracy (81).
- **Sensitivity and Specificity**: Various cutoff points have been proposed, with sensitivity and specificity reported around 79% and 84%, respectively, for identifying neonatal sepsis.

Interleukin-8 (IL-8)

- **Function**: IL-8 is a proinflammatory mediator involved in leukocyte activation and migration.
- **Diagnostic Value**: IL-8 levels increase rapidly within hours of infection, making it a promising early-phase indicator for neonatal sepsis.
- **Clinical Use**: IL-8 assays show sensitivities ranging from 80% to 91% and specificities from 76% to 100% in detecting neonatal sepsis.
- **Cutoff Values**: Mean cutoff values range around 220.53 pg/ml with varying sensitivity and specificity, highlighting the need for standardized protocols (81).

Interleukin-10 (IL-10)

- **Role**: IL-10 is involved in regulating inflammatory responses and has been implicated in EOS and late-onset sepsis (81).
- **Diagnostic Accuracy**: IL-10 shows high sensitivity (92%) and specificity (84%) using cutoff points for identifying bacterial culture-positive or negative sepsis.

Interleukin-35 (IL-35)

- **Function**: IL-35 is an anti-inflammatory cytokine that regulates immune responses.
- **Diagnostic Potential**: IL-35 has shown promise as a prognostic marker for EOS, with good sensitivity (78.48%) and specificity (66.67%) using specific cutoff values.
- **Clinical Implications**: Further research is needed to establish its role in clinical applications for neonatal sepsis management (81).

Visfatin and Resistin

- **Visfatin**: Also known as PBEF, visfatin induces both proinflammatory and anti-inflammatory cytokines and shows good sensitivity (92%) and specificity (94%) for diagnosing neonatal sepsis at a cutoff point of 10 ng/ml.
- **Resistin**: Secreted by adipose tissue, resistin is involved in inflammation and autoimmunity, with cutoff values showing high sensitivity (93%) and specificity (95%) for detecting neonatal sepsis (81).

Granulocyte Colony Stimulating Factor (G-CSF)

- **Function**: G-CSF stimulates the production and differentiation of neutrophils, making it a sensitive indicator for neonatal infections.
- **Diagnostic Value**: G-CSF levels >200 pg/ml have high sensitivity (95%) and specificity (73%) for detecting early-onset neonatal bacterial and fungal infections.

Other Cytokines

- **TNF-α and IL-1 Family**: TNF-α and IL-1β are early mediators of inflammation, but their diagnostic utility in neonatal sepsis varies due to conflicting study results and methodological differences (81).
- **IL-12 (p70)**: Used alone or in combination with other tests, IL-12 offers potential benefits in screening and diagnosing neonatal sepsis.

Cytokines play crucial roles as biomarkers in diagnosing and monitoring neonatal sepsis, reflecting the inflammatory responses to infections. Their clinical utility depends on accurate

measurement methods, standardized cutoff values, and understanding their kinetics in different neonatal populations. Further research is essential to optimize their use in clinical practice and improve outcomes for neonates at risk of sepsis (81).

Cell Surface Markers in Neonatal Sepsis Detection

Neutrophil Markers

CD64 (FcγRI)

- **Function**: CD64 is a high-affinity immunoglobulin Fc receptor expressed on monocytes and to a lesser extent on neutrophils (PMNs). Increased CD64 expression on PMNs is associated with activation, indicating bacterial infections.
- **Diagnostic Use**: CD64 expression can distinguish bacterial infections from other inflammatory disorders and is a strong indicator for initiating antibiotic treatment.
- **Combination with Other Markers**: Combining CD64 with markers like IL-6 or CRP improves diagnostic accuracy. For late-onset infections, combinations have shown sensitivity and negative predictive value up to 100%, while for early-onset infections, sensitivity reaches 97% and negative predictive value 98% (81).

CD11b (Mac-1)

- **Function**: CD11b is a marker of neutrophil activation and is upregulated in response to infections.
- **Clinical Utility**: Combining CD11b with CRP enhances sensitivity and negative predictive value for detecting neonatal infections.

Other Cell Markers

- **Lymphocyte Markers**: Include CD3, CD19, CD25, CD26, CD71, and CD69, which show varying expression in response to infections in preterm newborns. Elevated levels of CD19, CD33, and CD66b have been noted, but their diagnostic efficiency requires further evaluation (81).
- **Neutrophil Markers**: Besides CD11b, markers like CD11c, CD13, CD15, CD33, and CD66b are also studied in the context of neonatal sepsis.

Soluble CD14 subtype presepsin (sCD14-ST)

- **Function**: CD14 exists in a soluble form (sCD14) and plays a role in recognizing bacterial products, triggering inflammatory responses.
- **Diagnostic Value**: sCD14-ST, also known as presepsin, is associated with the severity and course of sepsis. It distinguishes bacterial sepsis from other conditions more effectively than CRP.
- **Clinical Use**: Changes in sCD14-ST levels correlate with the effectiveness of antimicrobial therapy and patient outcomes. It is seen as a potential tool to enhance the management of neonatal sepsis in clinical settings (81).

Clinical Implications

These cell surface markers and soluble forms like sCD14-ST offer promising avenues for improving the early detection and management of neonatal sepsis. Their integration into clinical practice could enhance diagnostic accuracy, guide timely treatment decisions, and ultimately improve outcomes for neonates at risk of sepsis. Further research is crucial to establish standardized protocols and validate their utility across different clinical settings (81).

Pro-inflammatory cytokines	
IFN-γ	Interferon-γ: predominantly produced by Th1 cells and facilitates activation of pro-inflammatory cells, e.g., macrophages
IL-1β	Interleukin-1β: mainly produced by macrophages to help regulate the pro-inflammatory process
IL-6	Interleukin-6: predominantly produced by leukocytes and hepatocytes in response to infection and trauma
TNF-α	Tumour necrosis factor-α: mainly produced by macrophages in response to bacterial and other inflammatory products
Anti-inflammatory cytokines	
IL-4	Interleukin-4: predominantly produced by Th2 cells
IL-10	Interleukin-10: inhibits production of pro-inflammatory cytokines by Th1 cells
TGF-β	Transforming growth factor β: regulates cellular proliferation and differentiation, and suppresses T helper cell function
CC chemokines	
MCP-1	Monocyte chemoattractant protein-1: attracts natural killer cells and activates mast cells
RANTES	Regulated upon activation normal T cells expressed and secreted: attracts eosinophils, lymphocytes and monocytes
CXC chemokines	
GRO-α	Growth-related oncogene-α: attracts neutrophils and suppresses myeloid colony formation
IL-8	Interleukin-8: attracts neutrophils and stimulates phagocytic activity
IP-10	Interferon-γ-inducible protein-10: attracts activated T lymphocytes, and may be induced by interferon-γ. It has anti-tumour activity and a regulatory role in angiogenesis
MIG	Monokine induced by interferon-γ: biological activity similar to IP-10
Acute phase reactants	
CRP	C-reactive protein: an acute phase protein produced by the liver that increases in response to IL-6
IαIp	Inter-α-inhibitor proteins: a group of plasma proteins that inhibit serine proteases and possess anti-inflammatory properties
LBP	Lipopolysaccharide-binding protein: an acute phase protein that is mainly produced by the liver
PCT	Procalcitonin: the precursor of the peptide hormone calcitonin mainly produced by the liver and by monocytes
SAA	Serum amyloid A: a group of structurally related proteins that are released in response to injury and infection by a broad range of cell types, e.g., hepatocytes, smooth muscle cells, endothelial cells, monocytes
Leukocyte surface antigens	
CD11b	Cluster of differentiation 11b: a β_2-integrin adhesion molecule present on leukocyte cell surfaces and binds molecules such as complement components and lipopolysaccharide
CD64	Cluster of differentiation 64: a receptor found on leukocyte cell surfaces that binds the Fc portion of IgG antibodies with high affinity

Figure 3: Biochemical markers of neonatal sepsis.

Conclusion:

Neonatal sepsis remains a significant challenge in healthcare, characterized by rapid onset and potentially devastating consequences if not promptly diagnosed and treated. The role of nurses in its management is pivotal, as they are often the first to observe subtle clinical signs and implement timely interventions. Their vigilance in monitoring vital signs, assessing clinical status, and promptly escalating concerns to medical teams is crucial for early recognition and intervention. Biochemical markers play a crucial role in the diagnosis and management of neonatal sepsis. Among these, C-reactive protein (CRP), procalcitonin (PCT), and various cytokines such as interleukin-6 (IL-6) and soluble CD14 subtype presepsin (sCD14-ST) have gained prominence. These markers offer valuable insights into the inflammatory response, aiding in the differentiation of sepsis from other causes of neonatal illness. Their use in conjunction with clinical assessment helps guide decisions on initiating or adjusting antibiotic therapy, monitoring response to treatment, and predicting outcomes. Nurses' involvement extends beyond bedside care; they contribute significantly to the multidisciplinary approach essential for managing neonatal sepsis. Their roles encompass patient advocacy, family support, meticulous documentation, and adherence to infection control protocols to prevent nosocomial infections. Education of parents on signs of infection and preventive measures further enhances their impact in mitigating risks associated with neonatal sepsis. Effective management of neonatal sepsis requires a coordinated effort involving healthcare providers across disciplines. Nurses, through their direct and continuous patient care, facilitate early detection of sepsis and prompt initiation of treatment, thereby improving outcomes and reducing mortality rates. Continued research into the optimization of biochemical markers and nursing protocols is essential to further enhance the management of neonatal sepsis, ensuring that infants receive timely and appropriate care tailored to their unique clinical needs.

References:

1. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics. 2002;110(2 Pt 1):285–291.
2. Tsai MH, Chu SM, Lee CW, et al. Recurrent late-onset sepsis in the neonatal intensive care unit: incidence, clinical characteristics and risk factors. Clin Microbiol Infect. 2014.
3. Polin RA. Committee on Fetus and Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics. 2012;129(5):1006–1015.
4. Centers for Disease Control and Prevention (CDC). Group B Strep Infection in Newborns [webpage on the Internet]. Available at: http://www.cdc.gov/groupbstrep/about/newborns-pregnant.html.
5. Ohlsson A, Shah VS. Intrapartum antibiotics for known maternal Group B streptococcal colonization. Cochrane Database Syst Rev. 2014;6:CD007467.
6. Garcia-Prats JA, Cooper TR, Schneider VF, Stager CE, Hansen TN. Rapid detection of microorganisms in blood cultures of newborn infants utilizing an automated blood culture system. Pediatrics. 2000;105(3 Pt 1):523–527.
7. Stoll BJ, Hansen NI, Adams-Chapman I, et al. National Institute of Child Health and Human Development Neonatal Research Network. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA. 2004;292(19):2357–2365.
8. Ganatra HA, Stoll BJ, Zaidi AK. International perspective on early-onset neonatal sepsis. Clin Perinatol. 2010;37(2):501–523.
9. Pappas A, Kendrick DE, Shankaran S, et al. Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Chorioamnionitis and early childhood outcomes among extremely low-gestational-age neonates. JAMA Pediatr. 2014;168(2):137–147.
10. Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics. 2010;126(3):443–456.
11. Ng PC. Diagnostic markers of infection in neonates. Arch Dis Child Fetal Neonatal Ed. 2004;89(3):F229–F235.
12. Mehr S, Doyle LW. Cytokines as markers of bacterial sepsis in newborn infants: a review. Pediatr Infect Dis J. 2000;19(9):879–887.
13. Commins SP, Borish L, Steinke JW. Immunologic messenger molecules: cytokines, interferons, and chemokines. J Allergy Clin Immunol. 2010; 125(2 Suppl 2):S53–S72.
14. D'Alquen D, Kramer BW, Seidenspinner S, et al. Activation of umbilical cord endothelial cells and fetal inflammatory response in preterm infants with chorioamnionitis and funisitis. Pediatr Res. 2005;57(2):263–269.
15. Ng PC, Lam HS. Diagnostic markers for neonatal sepsis. Curr Opin Pediatr. 2006;18(2):125–131.
16. Lever A, Mackenzie I. Sepsis: definition, epidemiology, and diagnosis. BMJ. 2007;335(7625):879–883.
17. Buttery JP. Blood cultures in newborns and children: optimising an everyday test. Arch Dis Child Fetal Neonatal Ed. 2002;87(1):F25–F28.
18. Christensen RD, Baer VL, Gordon PV, et al. Reference ranges for lymphocyte counts of

neonates: associations between abnormal counts and outcomes. Pediatrics. 2012;129(5):e1165–e1172.
19. Chiesa C, Natale F, Pascone R, et al. C reactive protein and procalcitonin: reference intervals for preterm and term newborns during the early neonatal period. Clin Chim Acta. 2011;412(11–12):1053–1059.
20. Ng PC, Lam HS. Biomarkers for late-onset neonatal sepsis: cytokines and beyond. Clin Perinatol. 2010;37(3):599–610.
21. Lam HS, Ng PC. Biochemical markers of neonatal sepsis. Pathology. 2008;40(2):141–148.
22. van Dissel JT, van Langevelde P, Westendorp RG, Kwappenberg K, Frölich M. Anti-inflammatory cytokine profile and mortality in febrile patients. Lancet. 1998;351(9107):950–953.
23. Newman TB, Puopolo KM, Wi S, Draper D, Escobar GJ. Interpreting complete blood counts soon after birth in newborns at risk for sepsis. Pediatrics. 2010;126(5):903–909.
24. Griffin MP, Lake DE, Bissonette EA, Harrell FE, O'Shea TM, Moorman JR. Heart rate characteristics: novel physiomarkers to predict neonatal infection and death. Pediatrics. 2005;116(5):1070–1074.
25. Stoll BJ, Hansen NI, Bell EF, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993–2012. JAMA. 2015;314(10):1039–1051.
26. Lever A, Mackenzie I. Sepsis: definition, epidemiology, and diagnosis. BMJ. 2007;335(7625):879–883.
27. Benitz WE, Wynn JL, Polin RA. Reappraisal of guidelines for management of neonates with suspected early-onset sepsis. J Pediatr. 2015;166(4):1070–1074.
28. van Herk W, Stocker M, van Rossum AM. Recognising early onset neonatal sepsis: an essential step in appropriate antimicrobial use. J Infect. 2016;72(Suppl):S77–S82.
29. Polin RA, Watterberg K, Benitz W, Eichenwald E. The conundrum of early-onset sepsis. Pediatrics. 2014;133(6):1122–1123.
30. Bassler D, Stoll BJ, Schmidt B, et al. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: added role of neonatal infection. Pediatrics. 2009;123(1):313–318.
31. Haller S, Deindl P, Cassini A, et al. Neurological sequelae of healthcare-associated sepsis in very-low-birthweight infants: umbrella review and evidence-based outcome tree. Euro Surveill. 2016;21(8).
32. Neu J. Preterm infant nutrition, gut bacteria, and necrotizing enterocolitis. Curr Opin Clin Nutr Metab Care. 2015;18(3):285–288.
33. Greenberg RG, Benjamin DK. Neonatal candidiasis: diagnosis, prevention, and treatment. J Infect. 2014;69(Suppl 1):S19–S22.
34. Mukhopadhyay S, Taylor JA, von Kohorn I, et al. Variation in sepsis evaluation across a national network of nurseries. Pediatrics. 2017;139(3):e20162845.
35. Ahmadizar F, Vijverberg SJ, Arets HG, et al. Early life antibiotic use and the risk of asthma and asthma exacerbations in children. Pediatr Allergy Immunol. 2017;28(5):430–437.
36. Yamamoto-Hanada K, Yang L, Narita M, Saito H, Ohya Y. Influence of antibiotic use in early childhood on asthma and allergic diseases at age 5. Ann Allergy, Asthma Immunol. 2017;119(1):54–58.
37. Bailey LC, Forrest CB, Zhang P, Richards TM, Livshits A, Derusso PA. Association of antibiotics in infancy with early childhood obesity. JAMA Pediatr. 2014;168(11):1063–1069.
38. Saari A, Virta LJ, Sankilampi U, Dunkel L, Saxen H. Antibiotic exposure in infancy and risk of being overweight in the first 24 months of life. Pediatrics. 2015;135(4):617–626.
39. Ajslev TA, Andersen CS, Gamborg M, Sørensen TI, Jess T. Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics. Int J Obes. 2011;35(4):522–529.
40. Bhandari V. Effective biomarkers for diagnosis of neonatal sepsis. J Pediatric Infect Dis Soc. 2014;3(3):234–245.
41. Schelonka RL, Chai MK, Yoder BA, Hensley D, Brockett RM, Ascher DP. Volume of blood required to detect common neonatal pathogens. J Pediatr. 1996;129(2):275–278.
42. Klingenberg C, Kornelisse RF, Buonocore G, Maier RF, Stocker M. Culture-negative early-onset neonatal sepsis — at the crossroad between efficient sepsis care and antimicrobial stewardship. Front. Pediatr. 2018;6:285.
43. dwards MS, Baker CJ. Sepsis in the newborn. Krugman's Infect Dis Child. 2004;11:545–561.
44. Enguix A, Rey C, Concha A, et al. Comparison of procalcitonin with C-reactive protein and serum amyloid for the early diagnosis of bacterial sepsis in critically ill neonates and children. Intensive Care Med. 2001;27(1):211–215.
45. Liu L, Johnson HL, Cousens S, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet. 2012;379(9832):2151–2161.
46. van Herk W, Stocker M, van Rossum AM. Recognising early onset neonatal sepsis: an

essential step in appropriate antimicrobial use. J Infect. 2016; 72(Suppl):S77–S82.
47. Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA. 2004;292(19):2357–2365.
48. Shehab El-Din EMR, El-Sokkary MMA, Bassiouny MR, et al. Epidemiology of neonatal sepsis and implicated pathogens: a study from Egypt. BioMed Res Int. 2015;2015:509484.
49. Vergnano S, Menson E, Kennea N, et al. Neonatal infections in England: the NeonIN surveillance network. Arch Dis Child Fetal Neonatal Ed. 2011;96(1):F9–FF14.
50. Stoll BJ, Hansen NI, Sanchez PJ, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics. 2011;127(5): 817–826.
51. Zea-Vera A, Ochoa TJ. Challenges in the diagnosis and management of neonatal sepsis. J Trop Pediatr. 2015;61(1):1–13
52. Camacho-Gonzalez A, Spearman PW, Stoll BJ. Neonatal infectious diseases: evaluation of neonatal sepsis. Pediatr Clin North Am. 2013;60(2):367–389.
53. Thaver D, Zaidi AK. Burden of neonatal infections in developing countries: a review of evidence from community-based studies. Pediatr Infect Dis J. 2009;28(1 Suppl):S3–S9.
54. Du J, Li L, Dou Y, et al. Diagnostic utility of neutrophil CD64 as a marker for early-onset sepsis in preterm neonates. PLoS One. 2014;9(7):e102647.
55. Bhandari V. Effective biomarkers for diagnosis of neonatal sepsis. J Pediatr Infect Dis Soc. 2014;3(3): 234–245.
56. Wynn, J. L. (2016). Defining neonatal sepsis. Current Opinion in Pediatrics, 28(2), 135–140. https://doi.org/10.1097/MOP.0000000000000315
57. Shane, A. L., & Stoll, B. J. (2014). Neonatal sepsis: Progress towards improved outcomes. Journal of Infection, 68(Suppl 1), S24. https://doi.org/10.1016/j.jinf.2013.09.011
58. Weston, E. J., Pondo, T., Lewis, M. M., Martell-Cleary, P., Morin, C.,mJewell, B., … Schrag, S. J. (2011). The burden of invasive earlyonset neonatal sepsis in the United States, 2005–2008.Pediatric Infectious Disease Journal, 30(11), 937–941. https://doi.org/10.1097/INF.0b013e318223bad2
59. Bailit, J. L., Gregory, K. D., Reddy, U. M., Gonzalez-Quintero, V. H., Hibbard, J. U., Ramirez, M. M., … Zhang, J. (2010). Maternal and neonatal outcomes by labor onset type and gestational age. American Journal of Obstetrics and Gynecology, 202(3),m245.e1–245.e12. https://doi.org/10.1016/j.ajog.2010.01.051
60. Cohen-Wolkowiez, M., Moran, C., Benjamin, D. K., Cotten, C. M., Clark, R. H., Benjamin, J. D. K., & Smith, P. B. (2009). Early and late onset sepsis in late preterm infants. Pediatric Infectious Disease Journal, 28(12), 1052. https://doi.org/10.1097/INF. 0b013e3181acf6bd
61. Stoll, B. J., Hansen, N., Fanaroff, A. A., Wright, L. L., Carlo, W. A., Ehrenkranz, R. A., … Poole, W. K. (2002). Late-onset sepsis in very low birth weight neonates: The experience of the NICHD Neonatal Research Network. Pediatrics, 110(2), 285–291. https://doi.org/10.1542/peds.110.2.285
62. Hornik, C. P., Fort, P., Clark, R. H., Watt, K., Benjamin, D. K., Jr., Smith,P. B., … Cohen-Wolkowiez, M. (2012). Early and late onset sepsis in very-low-birth-weight infants from a large group of neonatal intensive care units. Early Human Development, 88(Suppl 2), S69–S74. https://doi.org/10.1016/s0378-3782(12)70019-1
63. Polin, R. A. (2012). Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics, 129(5), 1006–1015.
64. Verani, J. R., McGee, L., & Schrag, S. J. (2010). Prevention of perinatal group B streptococcal disease: Revised guidelines from CDC, 2010. Morbidity and Mortality Weekly Report, 59(RR-10), 1–36. Retrieved from https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5910a1.htm
65. Ramsey, P. S., Lieman, J. M., Brumfield, C. G., & Carlo, W. (2005). Chorioamnionitis increases neonatal morbidity in pregnancies complicated by preterm premature rupture of membranes. American Journal of Obstetrics and Gynecology, 192(4), 1162–1166. https://doi.org/10.1016/j.ajog.2004.11.035
66. March of Dimes. (2016). March of Dimes premature birth report card. Retrieved from http://www.marchofdimes.org/materials/prematurebirth-report-card-united-states.pdf
67. Shah, B. A., & Padbury, J. F. (2014). Neonatal sepsis: An old problem with new insights. Virulence, 5(1), 163–171. https://doi.org/10.4161/viru.26906
68. Nizet, V., & Klein, J. (2010). Bacterial sepsis and meningitis. In J.
69. Remington (Ed.), Infectious disease of the fetus and newborn infant (7th ed.). Philadelphia, PA: Elsevier Saunders
70. Goldstein, B., Giroir, B., & Randolph, A. (2005). International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. Pediatric Critical Care Medicine, 6(1), 2–8. https://doi.org/10.1097/01.PCC.0000149131.72248.E6

71. Puopolo, K. M., Draper, D., Wi, S., Newman, T. B., Zupancic, J., Lieberman, E., … Escobar, G. J. (2011). Estimating the probability of neonatal early-onset infection on the basis of maternal risk factors. Pediatrics, 128(5), e1155–e1163. https://doi.org/10. 1542/peds.2010-3464
72. Rubarth, L. (2003). The lived experience of nurses caring for newborns withsepsis.JournalofObstetric,Gynecologic,&NeonatalNursing, 32(3), 348–356. https://doi.org/10.1177/0884217503253437
73. Hornik, C. P., Fort, P., Clark, R. H., Watt, K., Benjamin, D. K., Jr., Smith, P. B., … Cohen-Wolkowiez, M. (2012). Early and late onset sepsis in very-low-birth-weight infants from a large group of neonatal intensive care units. Early Human Development, 88(Suppl 2), S69–S74. https://doi.org/10.1016/s0378-3782(12) 70019-
74. Okascharoen, C., Hui, C., Cairnie, J., Morris, A. M., & Kirpalani, H. (2007). External validation of bedside prediction score for diagnosis of late-onset neonatal sepsis. Journal of Perinatology, 27(8), 496–501. https://doi.org/10.1038/sj.jp.7211767
75. Okascharoen, C., Sirinavin, S., Thakkinstian, A., Kitayaporn, D., & Supapanachart, S. (2005). A bedside prediction-scoring model for late-onset neonatal sepsis. Journal of Perinatology, 25(12), 778–783. https://doi.org/10.1038/sj.jp.7211404
76. Guyatt GH, Oxman AD, Vist Ge, et al. GRADe: an emergingnconsensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924-926.
77. Trzeciak S, Dellinger RP, Abate NL, et al. Translating research to clinical practice: a 1-year experience with implementing early goal-directed therapy for septic shock in the emergency department. Chest. 2006;129:225-232.
78. Schorr C. Performance improvement in the management of sepsis. Crit Care Clin. 2009;25:857-867.
79. Black MD, Schorr C, Levy MM. Knowledge translation and the multifaceted intervention in the intensive care unit. Crit Care Med. 2012;40:1324-1328.
80. Kleinpell, R., Aitken, L., & Schorr, C. A. (2013). Implications of the new international sepsis guidelines for nursing care. *American Journal of Critical Care*, *22*(3), 212-222.
81. Memar, M. Y., Alizadeh, N., Varshochi, M., & Kafil, H. S. (2019). Immunologic biomarkers for diagnostic of early-onset neonatal sepsis. *The Journal of Maternal-Fetal & Neonatal Medicine*, *32*(1), 143-153.