Laboratory Evaluation of Neonatal Sepsis

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Bacterial infections can be a devastating complication in the newborn and continue to be a significant cause of mortality and long-term morbidity of hospitalized newborns and premature infants. The diagnosis of neonatal sepsis is difficult to establish and remains a challenge for neonatal health care providers. Early signs and symptoms of neonatal sepsis are often nonspecific and easily confused with conditions that are expected in this population. Neonatal care providers have evaluated numerous tests searching for one that would be helpful in the diagnosis of neonatal sepsis, one that quickly confirms the diagnosis, and one that conclusively rules it out. This article examines the tests in current use and some of the more recent diagnostic markers used alone or in combination to improve sensitivity and specificity for early detection of sepsis.

Keywords: Neonatal sepsis; Laboratory tests; Bacterial infections

Bacterial infections can be a devastating complication in the newborn and continue to be a significant cause of mortality and long-term morbidity of hospitalized newborns and premature infants.[1] In the United States, the estimated annual incidence of severe sepsis in newborns is 0.3 per 100 live births.[2] The estimated mortality for neonates with severe sepsis is 10.3%, with most deaths occurring within the first 48 hours of infection.[3,4] Mortality rates vary by causative organisms. Data from the National Institute of Child Health and Human Development Neonatal Research Network reported mortality rates with gram-negative infections at 36% and 32% with fungal infections. Infected infants had significantly longer hospital stays, ongoing neurodevelopmental impairment, and higher mortality rates than very low birth weight infants who did not have late-onset sepsis.[1,3,5] The diagnosis of neonatal sepsis is difficult to establish and remains a challenge for neonatal health care providers. Early signs and symptoms of neonatal sepsis are often nonspecific and easily confused with conditions that are expected in this population. The fear of missing a case of neonatal infection with its serious outcomes has led to overuse of antibiotics in the neonatal intensive care environment and the emergence of resistant organisms.

Neonatal care providers have evaluated numerous tests searching for one that would be helpful in the diagnosis of neonatal sepsis, one that quickly confirms the diagnosis, and one that conclusively rules it out. Despite extensive investigation over the past several decades, there is still no single test that meets the criteria that would make it the ideal marker for the early diagnosis of sepsis in the newborn.[6,7] This article examines the tests in current use and some of the more recent diagnostic markers used alone or in combination to improve sensitivity and specificity for early detection of sepsis.

Historical Review

In lieu of rapid definitive diagnosis, alternative screening methods have been and some still used over the decades in neonatal care. Although none is comparable in predictive value with the blood culture, many have been promoted and utilized clinically for their presumed presumptive value. Infecting pathogens vary geographically, and each neonatal intensive care unit, institution, community, and region will have pathogen profiles, monitored by their infectious disease personnel and departments. These profiles determine the first-line antimicrobial agents recommended for treatment of patients, with clinical signs of infection, before culture-specific information is available. This source of nonspecific information has prevailed and is probably beneficial from a public health and population-specific basis but, for those in clinical practice, has never replaced the patient-specific culture results.

In the early years of neonatal intensive care, surface cultures were promoted as providing presumptive identification of infectious organisms. Cultures of staff and nursery structures have been promoted to identify potential organisms but ultimately found to have low-cost benefit. Gram stains of various surfaces and body compartments in the newborn were previously recommended including umbilical cord swabs, nasal swabs, and gastric aspirate specimens but either lack reliable sensitivity or specificity to define treatment.[8] Latex particle agglutination for antigen to group B streptococcus in urine was considered a useful test for early diagnosis of group B streptococcus from 1979 into the 1990s. However, careful studies found the specificity of the test to be 99.5% to 100%; the sensitivity of the test was variable and often as low as 27% to

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54% and as high as 88%, making it inadequate to withhold treatment with clinical suspicion.[9,10] The predictive value of any of these surface cultures has not withstood the scrutiny of time nor cost considerations, unless clinical sepsis is identified in the presence of negative blood cultures as with maternal antibiotic prophylaxis.[11]

Diagnostic Characteristics of Laboratory Tests

The ideal laboratory test should have maximum sensitivity and maximum negative predictive accuracy to ultimately determine the usefulness of it as a clinical test. The method used to evaluate the efficacy of each test is comparing the specificity and sensitivity of the test result to an accepted reference standard confirming the disorder, disease, or abnormality. For the neonatal care provider faced with the decision to administer antibiotics or withhold them based on a test result, the predictive value of that test is of great importance. In neonatal sepsis, the terms used to describe accuracy and reliability of a test can be defined as follows:

Sensitivity: the ability of a test to correctly identify those infants who truly are infected; the percentage of patients with infection (based on a reference standard) who have an abnormal test

Specificity: the ability of a test to correctly identify those infants who do not have infections; the percentage of patients without infections (based on a reference standard) who have a normal test

Positive predictive value (PPV): the percentage of positive tests that are true-positive (ie, the infant has an infection); if the test is abnormal (positive), the percentage of infants with infection

Negative predictive value (NPV): the percentage of negative tests that are true-negative (ie, the infant does not have sepsis); if the test is normal, the percentage of infants with no infection

In an attempt to identify those infants with a serious infection, diagnostic tests with maximal (100%) sensitivity and NPV are the most desirable because all genuinely infected infants would be identified, treated, and potentially cured. The test should also have an acceptable specificity and PPVs (>80%–85%) so that unnecessary use of antibiotics would be kept to a minimum.[12] The clinical value of a test is related to its sensitivity and its specificity in the patient population being tested. These test parameters do not change with different populations of sick and healthy patients. However, the predictive value of a test may vary with the age, sex, and geographical location of the patient population.[13] Specificity, sensitivity, and predictive value are related, and the relationship of these concepts is illustrated in Fig 1.

Sepsis Workup

Documentation in the newborn record often refers to the "sepsis work-up" as if there was a panel of tests that were included in this diagnostic evaluation. Escobar[14] reported in 1999 that the discharge diagnosis of nearly 50% of all special care nursery admissions was "rule out sepsis." It is important to differentiate between early neonatal sepsis, likely due to perinatal exposure, from late neonatal sepsis, usually due to nosocomial exposure, when deciding the patient-specific evaluation for diagnosis. Actually, the reference to a sepsis workup is no more standard today than it was over the decades, although early in neonatal care, it was common to reference complete blood count (CBC), blood culture, urine culture (obtained by suprapubic bladder tap), and a lumbar puncture as the battery of tests used to "rule out sepsis." Suprapubic bladder taps or catheter specimens are seldom used routinely in the

		Condition as determined by "Gold standard"		
		Positive	***Negative***	
Test Outcome	***Positive***	**True Positive**	**False Positive** (Type I error, P-value)	**→ Positive predictive value**
	Negative	**False Negative** (Type II error)	**True Negative**	**→ Negative predictive value**
		↓ Sensitivity	**↓ Specificity**	

Fig 1. Specificity, sensitivity, predictive value, and the relationship of these concepts. The following mnemonic device was adapted from http://en.wikipedia.org/wiki/Positive_predictive_value.

newborn for early-onset sepsis evaluation to obtain routine urine cultures but are clinically indicated in late-onset urinary tract or sepsis evaluation. Lumbar punctures to evaluate cerebral spinal fluid for meningitis in asymptomatic newborns have a low yield and are often deferred in the absence of positive blood cultures or neurologic symptoms.[11,15]

Cultures

The criterion standard for diagnosing sepsis is the positive organism-specific blood culture, at least in the absence of maternal intrapartum antibiotic prophylaxis. The standard practice to treat mothers with antibiotics is presumed to reduce the NPV of neonatal blood cultures and renders negative blood culture results useless for antibiotic choice and course treatment decisions.[16-18] Without antibiotic exposure, the time required for obtaining results from cultures, particularly organism-specific results from positive blood cultures, can be 48 to 72 hours, often exceeding that necessary to institute definitive life-saving antimicrobial treatment.[19] Identification of the infecting organism for timely initiation of the ideal antimicrobial agent could prevent rapid dissemination of lethal organisms in the immune-compromised newborn.

Common practice is to treat newborns with broad spectrum antimicrobials when sepsis is suspected. Determining safe timing to discontinue antibiotic therapy before final negative blood culture results has historically been dependent on retrospective studies.[16] More recent data have provided clinicians with stronger assurance of likely growth time intervals and presumptive sepsis in the newborn allows for discontinuation of antibiotic after 48 hours of negative cultures rather than extending treatment for a minimum of 72 hours.[20,21] One study found that cultures had 100% specificity, 70.3% sensitivity, and 93.3% NPV by 36 hours, reporting 91.8% positive bacterial culture results in a large retrospective review.[22] The findings of Kumar et al[23] were similar, reporting positive cultures 89% at 36 hours and 97% at 48 hours with NPVs of 99.7% at 36 hours and 99.8% at 48 hours. These improvements in blood culture systems not only reduce the time for unnecessary antimicrobial exposure but also reduce the time in special care decreasing the cost of often under-reimbursed care.[24]

Blood culture sensitivity in the newborn has long been considered problematic with early reports of sensitivity for identifying sepsis only 50% to 80%.[25,26] The reliability of blood culture specimens in the newborn are optimized if 0.5 to 1.0 mL of blood is obtained and recommended aseptic technique is used to obtain more than 1 specimen from different percutaneous sites following recommended skin preparation to reduce contamination. Blood culture systems used in neonatal require inoculation in small volume solid culture medium and most are closed computer-based systems that assess evidence of growth every 10 to 15 minutes.[27] Only one aerobic blood culture medium bottle is commonly used in the newborn, given the low prevalence of anaerobic sepsis, unless

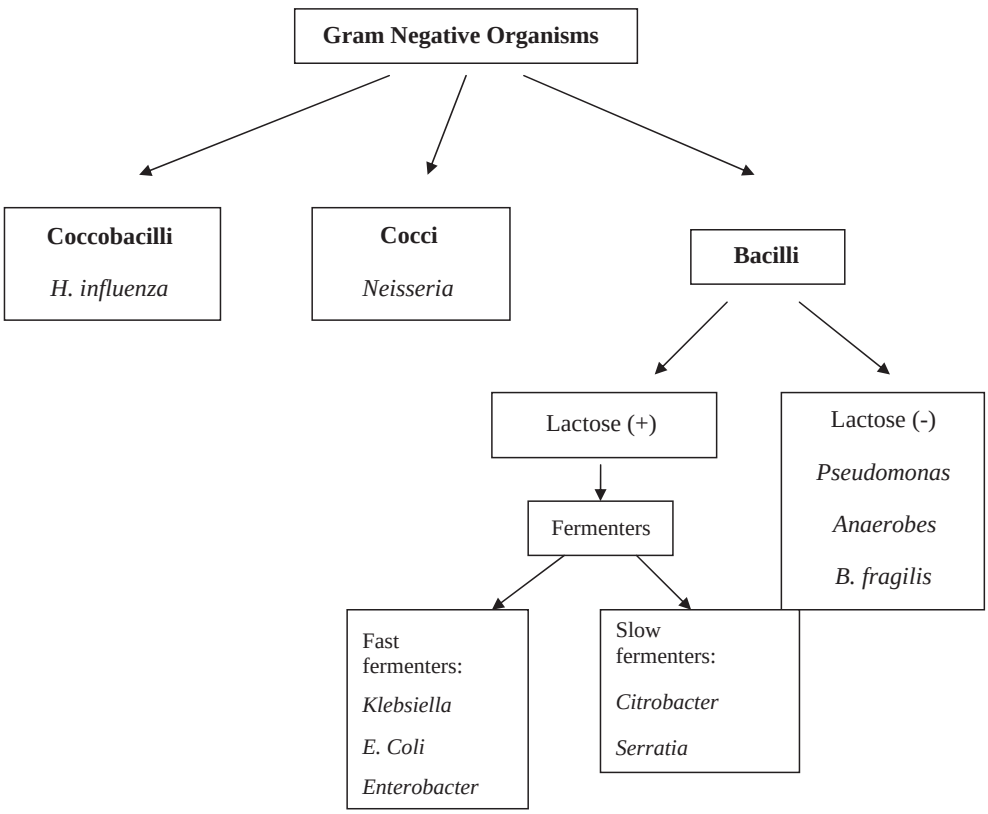

Fig 2. Gram-negative organisms.

there is high clinical suspicion. The widespread practice of obtaining a culture from a newly inserted umbilical arterial line is adequate, but specimens obtained from indwelling central lines are more likely to be contaminated especially with coagulase negative staphylococcus.[27] A pathogen-positive blood culture is considered diagnostic of neonatal sepsis, but despite careful technique, a negative culture does not confirm the absence of sepsis in the newborn.[15]

Gram Stain and Cell Morphology

Before obtaining the organism-specific culture results, when the bacterial growth appears, a gram stain is obtained to provide preliminary information about the growing organism. The gram stain identifies key features of the organism that often focuses the treatment choice of antimicrobial agents before the final culture results. Bacteria and yeast are identified by shape, stain absorption, arrangement, and response to biochemical tests oxidase, growth on chocolate or sheep blood agar, and lactose fermenting capability. Organisms are reported as gram positive (thick walled) or gram negative (think walled). It is reported by shape being cocci (spherical), bacilli (rod shaped), or coccobacillus (short rods). The bacterial arrangement is described as cocci in pairs, chains, or clusters. Furthermore, the organism is classified by reaction with certain medium including lactose fermenting or nonlactose fermenting, catalase positive or negative, and coagulase negative or positive. Laboratories report gram stain findings within hours of receiving a specimen that can be stained. Blood cultures are gram stained once an organism grows on the medium and is isolated for staining. See Figs 2 and 3 for identifying descriptions of common gram-negative and gram-positive pathogenic organisms in the newborn. In addition to the bacteria identified, gram stains can identify the presence of budding yeast usually *Candida albicans*, although other species of *Candida* are responsible for candidemia in the newborn.

White Blood Cell and Differential Count Evaluation

Over the years, neonatal care providers have made a science of interpreting the CBC and differential. Unlike in the healthy adult, the white blood cell (WBC) is less predictive of an inflammatory response in the newborn with wide intraindividual variations. Therefore, newborn practitioners have relied on the manual differential to render presumptive information about the presence or absence of infection. In the 1980s, the evidence seemed to indicate that mathematical ratios of immature and mature neutrophils provided independent predictive value.[28,29] Over the subsequent years, the value of the immature to total ratio alone has not retained its predictive status.[30] The WBC count does have value especially coupled with a significant left shift (increase in immature granulocyte count). Furthermore, if the absolute neutrophil count is severely depleted and/or the number of immature neutrophils exceeds

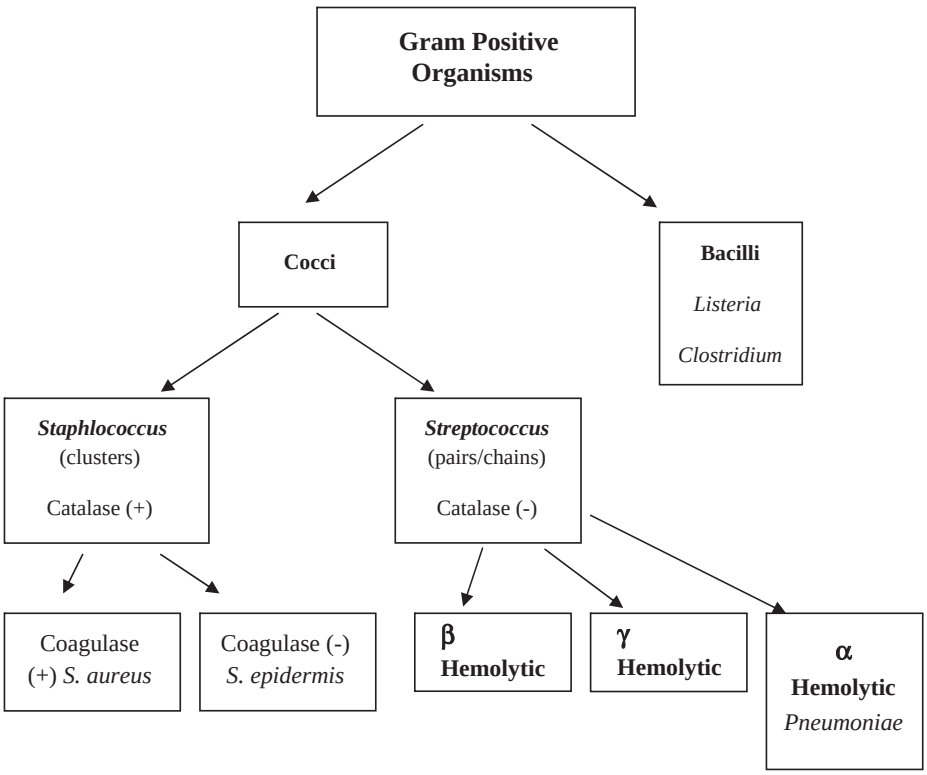

Fig 3. Gram-positive organisms.

the number of mature neutrophils, then the findings likely demonstrate evidence of a disseminated infection.

Obviously, this information is only supportive, as most affected newborns would have evidence of clinical deterioration despite the unknown infecting organism. The WBC count of less than 7500 and certainly less than 5000 remains suspicious of infection, with a specificity of 91% but a low sensitivity of 29%.[15] The WBC count of more than 40 000 is also indicative of an inflammatory response in the newborn often attributable to meningitis. Either of these abnormally high or low WBC counts coupled with a marked shift in the neutrophil count toward more immature forms (bands, metamyelocytes, myelocytes, promyelocytes, myeloblasts) than mature granulocyte forms (aka granulocyte neutrophils, polymorphonucleocyte, polymorphonuclear neutrophils), or increased left shift, may provide added suspicion to the likelihood of infection but without diagnostic specificity to determine organism-specific treatment. A decrease in the platelet count, usually less than 50 000, has a known association with infection often from classes of organisms but not a specific organism. In summary, the CBC only adds to the index of suspicion, and the use of discrete boundaries out of context remains artificial and subject to individual bias.[31]

Acute-Phase Reactants

Acute-phase reactants were first studied in the late 1980s and early 1990s, as it was recognized that WBC indices alone could not be used as decision criteria for the diagnosis of infection. Acute-phase reactants are diagnostic markers produced primarily by the liver as part of an immediate response to infection or tissue injury. This group of proteins has a wide range of activities that contribute to the host defense including neutralizing inflammatory agents, minimizing the local tissue damage, and participating in tissue repair, but their exact role in the inflammatory process is unknown.[32]

Several acute-phase reactants have been studied in relation to neonatal sepsis, with C-reactive protein (CRP) being the most widely used and investigated.[33,34] Because CRP is a nonspecific acute-phase response protein, numerous causes of inflammation and tissue damage can elevate CRP concentrations. The common causes of false-positive CRP values in neonates are surgery, immunizations, and severe viral infections such as herpes and rotavirus. Intraventricular hemorrhage and asphyxia have not consistently been shown to increase CRP values.[17]

C-reactive protein levels begin to rise within 4 to 6 hours, usually becoming abnormal within 24 hours of the onset of infection. C-reactive protein levels peak around 2 to 3 days after an infectious process and remain elevated until the inflammation begins to resolve.[7,32] C-reactive protein as a diagnostic marker in neonates has a higher sensitivity and specificity than total neutrophil counts and immature/total ratio.[12] The overall sensitivity of CRP at the onset of sepsis is about 60%, and the specificity between 60% and 90%. The PPV may be as low as 30% and NPV as high as 95%.[7,12] One needs to be cautious when measuring CRP in extremely premature infants. Studies have found that infants born extremely premature were less likely to show an appreciable increase in CRP response when compared with infants born at a later gestational. Maturational changes in the immune system and liver function are the most likely explanation for the increase in CRP with increasing gestational age.[17,35] C-reactive protein levels alone should not be used to diagnosis neonatal infection, and the sensitivity of a single CRP level is not sufficient to withhold antibiotics. Serial measurement of CRP levels seems to have some value in excluding serious infection and may provide an index for determining the effectiveness of antibiotics and the duration of therapy. Three consecutive values with CRP levels lower than 1 mg/dL (10 mg/L) obtained 24 hours apart, 8 to 48 hours after clinical symptoms present, indicate that sepsis is unlikely.[17,36] Serial CRP measurements yield diagnostic sensitivity of 75% to 98%, specificity of 90%, and a NPV of 99%. C-reactive protein can be considered as a "specific" but "late" marker of neonatal infection.[7,12,32] Recent studies, using CRP values of 1.2 to 6 mg/dL to diagnose sepsis and determine duration of therapy, showed specificity between 84% and 96% and NPV of 93% to 99%. The clinical practice of using higher CRP values led to fewer days of antibiotics without evidence of recurring infection.[33,34] Another recent study looking at infants with gram-negative sepsis using a CRP value of more than 4 mg/dL yielded 95.7% sensitivity, 88.9% specificity, and 98% NPV. In this study, the sensitivity of IgM as a single test at a value of 10 mg/dL or greater was 91.3%. The combination of IgM ($\geq$20 mg/dL) and a CRP (>4 mg/dL) yielded the best results, with a 100% sensitivity and 100% NPV.[37]

Because of the limitations of CRP as an early sepsis marker, multiple other diagnostic tests have been evaluated. These include procalcitonin (PCT), various cytokines, neutrophil expression of cell surface molecules, and polymerase chain reaction (PCR) assays.

The most extensively studied acute-phase reactant, other than CRP, is PCT. Procalcitonin is an acute-phase reactant produced by monocytes and hepatocytes. It starts to rise 4 hours after exposure to a bacterial endotoxin, with peak concentrations reaching at 6 to 8 hours. One limitation of PCT as an early marker for early-onset sepsis is that normal PCT concentrations continue to rise during the first 48 hours after birth, with a peak concentration at 18 to 30 hours.[38-40] Elevated concentrations are also found in neonates with respiratory distress syndrome or who have unstable blood pressures.[17] Previous reports of PCT concentrations in neonatal sepsis have been conflicting. In one study, PCT sensitivity was 81.4% and specificity was 80.6% at the time sepsis was first suspected.[41] In another, where the study group had positive blood cultures and clinical signs of sepsis, the sensitivity for PCT was 77% and the specificity was 91%.[42]

The diagnostic usefulness of using PCT for early-onset sepsis is limited by its rapid physiologic postnatal increase. It should not be the sole marker used to diagnosis late-onset sepsis but may be useful as part of an evaluation for sepsis in the neonate.[40,41] In a study by Vazzalwar and associates,[43] a PCT cutoff value of 0.5 ng/mL was found to be more sensitive than CRP in predicting late-onset sepsis in very low birth weight

infants. Procalcitonin level is elevated during early-onset and late-onset sepsis, and its overall value as a diagnostic test is comparable with CRP.

A number of other acute-phase proteins including fibronectin, granulocyte colony–stimulating factor, and α1-antitrypsin have been evaluated as diagnostic markers for neonatal sepsis. Although all could be used as markers for diagnosing sepsis, none has been routinely studied on a large scale or in the clinical setting. Except for CRP and PCT, acute-phase reactants are not commercially available for routine testing.

Cytokines

Cytokines are thought to be endogenous mediators of the immune response to bacterial infections and were extensively studied in the mid- and late-1990s. The rationale for investigating these markers was that leukocyte indices and acute-phase reactants are considered late markers and are not sensitive enough for diagnosing early-onset sepsis.

Attention in the research arena has been focused on proinflammatory cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor α (TNF-α). Proinflammatory cytokines are primarily responsible for initiating and effective defense against invasive pathogens. There is a normal phenomenon of elevation in cytokines after delivery that limits the use of these mediators as a diagnostic tool in the neonatal setting, especially in the immediate postpartum period. There are also several variables such as hypoxia, the severity of the infection, fetal distress, labor, prematurity, antenatal steroids, and other inflammatory conditions such as meconium aspiration that elevate cytokine levels and limit their use in diagnosing early-onset sepsis.[40]

Interleukin-6, the most studied of the cytokines in the neonatal population, is produced by phagocytes and endothelial cells in response to infection and inflammation. Interleukin-6 serum levels rise rapidly in the early stages of the inflammatory response, preceding the increase in CRP, and followed by a rapid decline.[12,44] The cutoff values for IL-6 to diagnose sepsis have ranged from 18 to 31 pg/mL.[44,45] Interleukin-6 sensitivity has been reported in the range of 76% to 100% and specificity of 70% to 96% indicating wide ranges between studies.[46] The concentration of IL-6 in preterm and term infants does not seem to be influenced by gestational age or maternal cytokine concentration.[17]

The characteristics and kinetic properties of IL-8 and TNF-α are very similar to those of IL-6. Both are proinflammatory cytokines produced in response to systemic infection or inflammation.[17,39] Interleukin-8 is considered to be an accurate marker, with sensitivities ranging from 80% to 91% and specificities from 76% to 100%.[47,48] In a recent study, IL-8 in the urine has proven to be a reliable and effective alternative method for detecting neonatal sepsis.[49] Although TNF-α has been shown to be an important mediator in septic shock, its usefulness as a diagnostic marker has not been found to be as good as that of IL-6 or IL-8.[44]

The very short half life of circulating cytokines increases the risk of false-negative results for early-onset sepsis. For this reason, cytokines combined with other more sustained markers of inflammation have been suggested as a better diagnostic tool.[39] The diagnostic accuracy of IL-8 is further enhanced by simultaneously measuring CRP, and the combination of the two tests has been suggested to be useful in restricting unnecessary antibiotic use.[47,48]

Most of the studies evaluating cytokines as a diagnostic tool have been conducted outside the United States, and many of the tests have not been approved by the US Food and Drug Administration as an approved test for neonatal sepsis. Despite that most cytokine markers have high NPV (good for ruling out sepsis), they have not been adopted for general use in the neonatal environment. The lack of automation for test results, the costs involved in manual immunoassays, and the large amounts of blood necessary for accurate results have hindered the acceptance of cytokines as a diagnostic marker for identifying neonatal sepsis.[45]

Cell Surface Markers

In the late 1990s and early 2000s, advances in flow cytometric technology led the way for easy detection of cell surface antigens on blood cells. Leukocyte surface antigens (adhesion proteins on the surface of the neutrophil) are known to increase within a few minutes after inflammatory cytokines are activated by bacteria and endotoxins.[6,45] The technological advances have made it possible to quantitate surface antigens rapidly, with precision and most importantly for neonates, with minimal blood volumes.[50] These characteristics make it a potential early warning marker for detecting bacterial infections. A variety of leukocyte surface markers, including CD11b and CD64, have been assessed as markers for neonatal sepsis.

The sensitivity and specificity of CD11b for diagnosing early-onset neonatal sepsis in two different studies was 96% to 100% and 100%, respectively.[48,50] Its accuracy in diagnosing late-onset sepsis in preterm infants was more varied. The discrepancy in the studies may have been related to the methodology of performing the test, different infant populations evaluated, and the timing of the tests determining the phase of infection when the specimen was drawn.[51]

CD64 is usually expressed in very low levels by unstimulated neutrophils and is activated by bacterial invasion. CD64 levels have been found to have high sensitivity (95%–97%) and NPV (97%–99%) for early- and late-onset sepsis in neonates of very low birth weight using cutoff values of 6136 and 4000 phycoerythrin molecules bound per cell, respectively.[51,52] Combining CD64 with IL-6 or CRP further enhances the ability to diagnose infections and improves the sensitivity and NPV to 100%.[51] Another study combined CD64 levels with the absolute neutrophil count and demonstrated 95% sensitivity. The study findings suggest that the CD64 index could replace the band count and the immature/total neutrophil count as a hematologic indicator of sepsis. The absolute neutrophil count/CD64 combination with a NPV of 93% suggests that it could be efficacious in guiding the clinician to withhold antibiotic therapy.[45]

Molecular Biomarkers

Nucleic acid amplification tests such as PCR have been used successfully to diagnose a wide variety of bacterial, viral, yeast, and protozoal infections in the neonate. The PCR uses the bacterial 16S ribosomal RNA gene to diagnose early- and late-onset sepsis. Shang et al[53] used bacterial 16S ribosomal RNA gene PCR analysis in 172 neonates with suspected sepsis and found a sensitivity of 100% and specificity of 97.8%. In another study, PCR in near-term infants with early-onset sepsis had specificity (97.5%) and NPV (99.2%) compared with blood cultures, but it failed to detect 59% of infants with positive blood cultures, making the sensitivity low at 41%.[54] The main advantage of PCR over blood cultures is that it is rapid (only 4–6 hours for results) and requires small amounts of blood to complete the test (0.2–0.3 mL). Results from one study showed that approximately eight antibiotic doses and 85 hours per neonate in the neonatal intensive care could be saved using negative PCR results. The high NPV of PCR results could influence clinical practice by reducing unnecessary antibiotic use and shortening the hospital length of stay.[55]

Summary

Accurate diagnosis of neonatal sepsis is difficult because of the imperfect diagnostic sensitivity of independent laboratory tests. All predisposing factors to infection such as prenatal history, clinical presentation of the newborn, and laboratory results must be considered to treat all those who have infections and yet minimize the use of antibiotics in those without infection.

A better understanding of the neonatal inflammatory response to infection has led to the identification of multiple diagnostic markers of sepsis. At present, there is no single test, marker, or panel of markers that is sufficiently reliable for the early detection of neonatal sepsis. Complicated analytical measurements are both time consuming and costly and are therefore not readily available for use in clinical practice. None of the current diagnostic markers are sensitive or specific enough to influence the decision to withhold antibiotic therapy but hold promise for the early discontinuation of antibiotic treatment with suspected sepsis. Further evidence from large multicenter trials is needed to evaluate the newer diagnostic markers prospectively for their incremental diagnostic value before they can be considered reliable for diagnosing early infections and be included as part of a routine sepsis evaluation for neonates. Therefore, the neonatal care provider remains dependent on a thorough history and physical assessment in combination with available laboratory tests to guide treatment for presumptive sepsis while awaiting culture results.

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