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Late-onset Sepsis: Epidemiology, Evaluation, and Outcome

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Abstract

Late-onset neonatal sepsis is a common serious problem in preterm infants in neonatal intensive care units. Diagnosis can be difficult because clinical manifestations are not specific and none of the available laboratory tests can be considered an ideal marker. For this reason, a combination of markers has been proposed. Complete blood count and acute-phase reactants evaluated together help in diagnosis. C-reactive protein is a specific but late marker, and procalcitonin has proven accurate, although it is little studied in newborns. Blood, cerebrospinal fluid, and urine cultures always should be obtained when late-onset sepsis is suspected. Blood culture, the gold standard in diagnosis, is highly sensitive but needs up to 48 hours to detect microbial growth. Various cytokines have been investigated as early markers of infection, but results are not uniform. Other diagnostic tests that offer promise include: neutrophil surface markers, granulocyte colony-stimulating factor, toll-like receptors, and nuclear factor kappa B. The greatest hope for quick and accurate diagnosis lies in molecular biology, using real-time polymerase chain reaction combined with DNA microarray. Sepsis and meningitis may affect both the short- and long-term prognosis for newborns. Mortality in neonatal meningitis has been reduced in recent years, but short-term complications and later neurocognitive sequelae remain. Late-onset sepsis significantly increases preterm infant mortality and the risk of cerebral lesions and neurosensory sequelae, including developmental difficulties and cerebral palsy. Early diagnosis of late-onset sepsis contributes to improved neonatal prognosis, but the outcome remains far from satisfactory.

Objectives After completing this article, readers should be able to:

1. Understand the difficulties of diagnosing late-onset sepsis clinically and via laboratory tests and optimal use of available markers.
2. Describe new diagnostic perspectives.
3. Correlate mortality from sepsis with the infectious agent.
4. Identify the primary neurodevelopmental sequelae.

Abbreviations

CRP:	C-reactive protein
CSF:	cerebrospinal fluid
G-CSF:	granulocyte colony-stimulating factor
HRC:	heart rate characteristics
IL:	interleukin
LOS:	late-onset sepsis
NICHD:	National Institute of Child Health and Human Development
NICU:	neonatal intensive care unit
PCR:	polymerase chain reaction
PCT:	procalcitonin
TLR:	toll-like receptor

Definition

Neonatal sepsis is defined classically as a clinical syndrome characterized by systemic signs of infection frequently accompanied by bacteremia. Positive blood culture confirms sepsis, and when the blood culture is negative, the condition is considered as clinical sepsis. It is almost impossible to distinguish sepsis from meningitis in the neonate clinically. However, cerebrospinal fluid (CSF) that is positive for pathogenic bacteria indicates meningitis. In older medical literature, late-onset-sepsis (LOS) was considered to be disease that manifested beyond 1 week of age. More recently, most authors consider LOS as that which manifests more than 72 hours after birth. (1)

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Diagnosis

Early diagnosis of LOS is a major challenge for neonatologists because no ideal marker for infection has been identified to date. Almost all the diagnostic tests have been studied in septic patients during the first week after birth, but few studies have focused specifically on LOS. Difficulties in diagnosis may delay the initiation of treatment and make sepsis one of the most important causes of neonatal mortality. Also, LOS increases the length of hospital stay, as well as the social and economic costs, and compromises the long-term outcomes of newborns. (2)

An alarming fact in many neonatal intensive care units (NICUs) is that for each confirmed case of infection, between 11 and 23 uninfected newborns are treated. (3) Such inadvertent use or overuse of antimicrobials can produce changes in newborn infant flora and bacterial resistance mechanisms, favoring the emergence of multidrug-resistant bacteria responsible for high mortality rates. (4) A recent study showed that empiric antibiotic treatment resulted in a threefold increase in risk of infection from resistant bacteria for every day of ampicillin and gentamicin use and up to a 34-fold increase with cephalosporin use in neonates previously exposed to antibiotics. (5)

Strategies allowing for rapid diagnosis of sepsis are needed to reduce neonatal morbidity and mortality and to support the rational use of antimicrobials. (2)

Clinical Diagnosis

Early, precise diagnosis of neonatal sepsis is not easy because the clinical manifestations are not specific and often quickly evolve to more severe stages of the septic process. A clinical impression that the newborn is not well or has temperature instability, poor peripheral perfusion, and jaundice are among the frequent findings in neonatal sepsis. (6) The primary clinical findings in a multicenter study of 2,416 very low-birthweight infants were: apnea (55%); feeding intolerance, abdominal distension, or guaiac-positive stools (43%); increased respiratory support (29%); and lethargy and hypotonia (23%). (7)

A new technology related to heart rate characteristics (HRC) monitoring may be a promising tool in the early diagnosis of LOS. Before clinical suggestions of sepsis, neonates have reduced heart rate variability and transient decelerations. Abnormal HRC can be detected over the 24 hours before the diagnosis of proven and clinical sepsis. Although the mechanism by which sepsis leads to these abnormalities is not known, it is speculated that cytokines play a role. HRC monitoring adds independent information to laboratory tests and clinical signs in

the diagnosis of neonatal sepsis and can be used to identify infants at increased risk for developing sepsis. (8)(9)

Due to the poor accuracy of clinical diagnosis, suspicion of sepsis must be confirmed by fast, sensitive laboratory tests.

Ideal Infection Marker

Diagnostic tests in the neonatal period must be sufficiently sensitive for infected newborns not to remain untreated, specific enough to allow the rational use of antimicrobials, and have predictive negative value that allows safe withholding or discontinuation of antibiotics. The ideal laboratory method must use a small volume of specimen, be inexpensive and easy to perform, be rapid, and allow differentiation between etiologic agents as well as comparisons between laboratories. (10)

Laboratory Diagnosis

Blood Culture

Positive blood culture is considered the gold standard in sepsis diagnosis, although a positive blood culture may not be obtained for a number of reasons and, therefore, other tests must be used to help in diagnosis. Positive results from blood culture depend on the technique used, microorganism density, previous antibiotic treatment, and sample volume. (11) The automated method requires only 1.0 mL of blood and with the radiometric technique is very sensitive, with a high percentage of positive blood cultures, reaching 74% in our service.

Blood culture should be collected by peripheral venipuncture before beginning antibiotic treatment, and if positive, should be repeated during treatment to evaluate treatment effect. Patients who have central catheters can have blood obtained by this route, but another sample should be collected by peripheral access for better interpretation of results. A positive culture could result from simple colonization in the catheter, especially when coagulase-negative *Staphylococcus* is identified. Bacterial growth time, number of positive cultures, and evaluation of the clinical manifestations help differentiate true sepsis from catheter colonization.

Colonization is considered to be the presence of the microorganism and multiplication in the host without any clinical manifestation or immunologic response at the moment it is isolated. Infection is indicated by the damage caused by invasion, multiplication, and action of the infectious agent and from its toxic products in the host, with immunologic interaction. (12) The bacterial blood culture growth curve helps differentiate between contamination and infection. (Figure). In true infection,

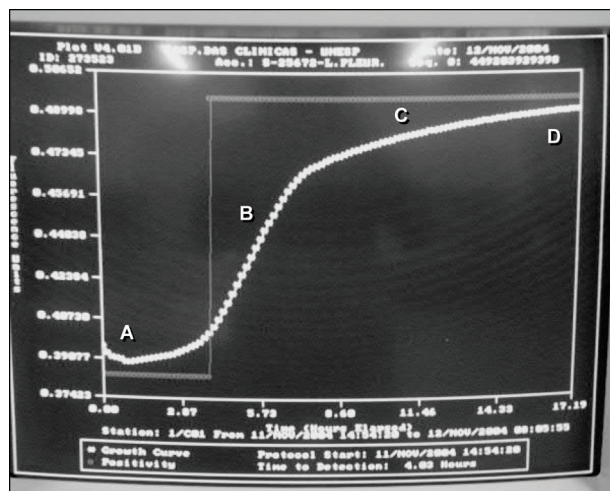


Figure. Bacterial blood culture growth curve: true infection (patient admitted NICU Botucatu – UNESP – Brazil). Phases: A: lag, B: log, C: stationary, D: bacterial death

the curve shows several phases: lag (metabolic adaptation of the bacteria to the new environment), log (fast bacterial growth), stationary (growth reduction by culture medium limitation), and bacterial death. (13)

Bacterial growth time is the other parameter used. In one investigation, this parameter was studied retrospectively on 451 positive blood cultures from 215 newborns in 2-year period. (14) An automated system was used, and blood was collected with appropriate technique. The positive blood cultures were classified according to the organism isolated and subdivided into three groups: definite pathogens, considered organisms known to cause disease in the newborn (group B *Streptococcus*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and other gram-negative bacteria); possible pathogens, considered organisms known to cause disease under special situations such as the presence of an indwelling catheter (coagulase-negative staphylococci); and contaminants, considered organisms that rarely cause disease in newborns (*Corynebacterium*, *Propionibacterium*). Complete information was obtained on 416 blood cultures. Twelve became positive after 72 hours and were classified as contaminants; of the 404 remaining cultures, 86% were positive at 36 hours, 96% at 48 hours, and 98.5% by 60 hours. Considering only definite pathogens, the time to positivity was: 90% by 36 hours, 93% by 48 hours, and 98.5% by 60 hours. Coagulase-negative staphylococci were isolated in 63.9% (266/416) of the cultures. Comparing the growth of this microorganism with definite pathogens, the median time to positivity was 24.6 hours versus 17.9 hours. The median time to

positivity of the fungal isolates was 32.6 (15.3 to 55.8) hours. The negative predictive value for bacteremia of a negative blood culture was 97.9% at 36 hours and 99.4% at 48 hours; and when definite bacterial pathogens only were considered, the negative predictive value at 36 and 48 hours was 99.7% and 99.8%, respectively. The study suggests that a 36-hour observation period is sufficient to rule out sepsis in the asymptomatic baby, and a 3-day incubation period is sufficient to detect all clinically important blood culture isolates using the automated system.

CSF Culture

In contrast to suspected early-onset infection, in which lumbar puncture is somewhat controversial, CSF collection for culture, cytologic, and biochemical evaluation is mandatory in suspected LOS. As many as 25% of newborns who have sepsis have meningitis, (15) and 15% to 55% of patients who have meningitis (positive CSF culture) have negative blood cultures. (15)(16) Lumbar puncture must be performed before treatment is started, but if there is hemodynamic instability, it can be performed after treatment has started. Even in these circumstances, lumbar puncture can identify the inflammatory process and frequently provides positive cultures with gram-negative organisms. Lumbar puncture is contraindicated in cases of thrombocytopenia and coagulation disorders. (17)

There are difficulties in diagnosing neonatal meningitis from the CSF findings alone, including a high frequency of traumatic lumbar puncture (39.5%) and the variability of normal cytologic and biochemical variables in the neonate. (18) Recently, a multicenter study evaluated the diagnostic utility of adjusting CSF white blood cell counts based on CSF and peripheral red blood cell counts in neonates who have traumatic lumbar puncture. Traumatic lumbar puncture was defined as CSF with at least 500 red blood cells/mm³. The CSF white blood cell count was adjusted using several methods: subtracting the number of white cells that can be accounted for by the number of red blood cells in CSF, according to the ratio of 500:1 and 1,000:1 red-to-white blood cells in CSF; subtracting the expected number of white blood cells calculated using the ratio of peripheral blood; and calculating the observed-to-predicted CSF white blood cells ratio. Of the 6,374 lumbar punctures included, 114 (1.8%) were positive for meningitis (positive culture or Gram stain), 39.5% (2,519) were traumatic, and 2.0% of the neonates who had traumatic lumbar puncture had meningitis. The median of white blood cell counts for traumatic and nontraumatic lumbar puncture was 13

Table 1. Accuracy of Diagnostic Tests in Late-onset Sepsis

Test	S (%)	SP (%)	References
Gram-specific PCR for gram-negative	86	99	20,21
Gram-specific PCR for gram-positive	74	98.5	
Tumor necrosis factor-alpha	73 to 82	80 to 94	22,23
IL-6 + CRP or PCT	100	96	24,25
IL-8 + CRP	80	87	26
IL-8 urine	92	94	27
CD64 + IL-6 or CRP	100	88	10

CRP=C-reactive protein, IL=interleukin, S=sensitivity, SP=specificity, PCR=polymerase chain reaction, PCT=procalcitonin

(4 to 53) and 4 (2 to 9), respectively, and the median of red blood cell counts was 4,625 (1,365 to 20,000) for traumatic and 17 (3 to 99) for nontraumatic lumbar puncture. The area under the receiver operating characteristic curve for white blood cell count unadjusted (0.77) and adjusted by all methods (0.78 to 0.81) was similar. Adjusting CSF white blood cell counts to account for increased red blood cells did not improve the diagnosing of meningitis and resulted in decreased sensitivity at various cut offs (unadjusted 86%; adjusted 75% to 82%). (18)

Urine Culture

Culture of urine collected by suprapubic bladder puncture should be performed if LOS is suspected, but the positivity is low, reaching only 7% in our service. If suprapubic bladder puncture is not possible, the option is vesical catheterization.

Molecular Biology

The new molecular biology techniques are very promising. Their advantages are rapid, precise etiologic diagnosis that allows rational use of antimicrobials. Current limitations include high costs and poor availability.

POLYMERASE CHAIN REACTION. Amplification by polymerase chain reaction (PCR) using DNA sequences from microorganisms is highly sensitive and allows fast identification of these agents. Although real-time PCR does not identify the profile of bacterial sensitivity, amplification of known resistance genes allows recognition of resistant bacteria and can reduce the unnecessary use of antimicrobials. The use of real-time PCR combined with DNA microarray should help in understanding antimicrobial susceptibility patterns. (19)

Rapid tests such as Gram-specific, probe-based, quan-

titative PCR can identify and differentiate gram-positive and gram-negative agents. The result is obtained in a few hours and without wrong classification. In pre-term infants, this test is highly accurate for gram-negative infections (Table 1). (20)(21) A new real-time PCR technique combining the real-time PCR of the 16S-rRNA gene with specific probes and sequencing was evaluated prospectively in 288 newborns who had suspected sepsis. (28) First, the authors applied the universal Taq-

man probe to indicate the presence of bacterial DNA. If blood culture was positive or PCR indicated bacterial DNA, the samples were investigated with four specific probes to detect gram-negative bacteria, *S aureus*, *S epidermidis*, or any other coagulase-negative staphylococci. A total of 295 blood cultures were obtained and 50 were positive. The universal PCR had a sensitivity of 42%, specificity of 95%, positive predictive value of 64%, and negative predictive value of 89%. This method to detect bacteremia had high specificity but showed low sensitivity. New research should be encouraged to improve the diagnostic accuracy.

CYTOKINES. Cytokines are important chemical mediators in progenitor cell maturation in bone marrow, inflammatory cascade regulation, and innate and adaptive immunity. Increased cytokine concentrations in blood can precede clinical and laboratory evidence of infection.

Tumor necrosis factor-alpha is the initiator of the inflammatory response, stimulates interleukin (IL)-6 production, increases early, and remains high in cases of shock. The accuracy of tumor necrosis factor-alpha in helping to diagnose LOS varies (Table 1), and its use combined with IL-6 has produced controversial results in relation to their sensitivity. (22)(23)

IL-6 increases early and induces production of acute-phase reactants, but its half-life is short and its sensitivity decreases after 12 to 24 hours of infection, inducing false-negative results. The association of IL-6 with C-reactive protein (CRP) or procalcitonin (PCT) can improve diagnostic accuracy (Table 1). (24) The rapid test for determining IL-6 by paper chromatography gives a result in about 20 minutes and is promising, with specificity and positive predictive value reported to be 100% when associated with CRP. (25)

IL-8 amplifies the inflammatory response, with similar chemotactic and kinetic activity to IL-6, but with a longer half-life, and it can be measured in other body fluids. IL-8 serum values combined with CRP or PCT can reduce the unnecessary use of antibiotics in NICUs. (6)(25) In a randomized, multicenter study, IL-8 values greater than 70 pg/mL associated with CRP values greater than 10 mg/L provided good accuracy (Table 1) and significantly reduced antibiotic use from 49% to 36%. (29) IL-8 is also being studied in urine from preterm infants who have LOS, and preliminary results are promising, with higher accuracy than serum IL-8 in diagnosing sepsis and with the advantage of being a noninvasive method (Table 1). (29)

IL-10 is an anti-inflammatory IL responsible for downregulation of the inflammatory process and maintaining homeostasis in vital organs, but the excessive anti-inflammatory response can result in immune function suppression. (10) High IL-10 concentrations in preterm infants who have sepsis can indicate poor prognosis related to higher mortality. (30)

IL-1-alpha, IL-1-beta, and receptor antagonist IL-1ra have not been shown to be useful in diagnosing neonatal sepsis. (10)(19)

The interaction between pro- and anti-inflammatory cytokines may have an important role in the outcome of sepsis and requires further study. Small sample sizes and methodology differences in studies are contributory factors to nonuniform cytokine results in neonatal sepsis. More studies are needed, using meta-analysis to determine the impact of these markers in the early diagnosis of neonatal sepsis. Circulating cytokine concentrations may not reflect their biologic activity.

SURFACE MARKERS. Evaluation of cellular response to cytokine action could better identify the immunologic response to infection in the newborn. CD11 and CD64 neutrophils are promising infection markers in newborns that are involved in phagocyte processes and pathogen death. (10)(19) In preterm very low-birthweight infants who have suspected LOS, lymphocyte surface markers (CD25 and CD45RO) do not appear to be useful, although CD64 from neutrophils may be highly accurate, alone or in association with IL-6 or CRP (Table 1). (10)

GRANULOCYTE COLONY-STIMULATING FACTOR. Granulocyte colony-stimulating factor (G-CSF), a mediator produced by bone marrow that facilitates neutrophil proliferation and differentiation, has been investigated as a marker of neonatal infection. Initial studies show high sensitivity (95%) and a predictive negative value of 99%.

(19) A pilot study showed high accuracy (0.88) for G-CSF combined with IL-8, and a clinical trial in a pediatric ICU and NICU in Switzerland is in progress to evaluate the accuracy of the combination in predicting infection. (31)

TOLL-LIKE RECEPTORS. Toll-like receptors (TLRs) are responsible for recognizing bacterial lipopolysaccharide bound to CD14 protein, which is the prerequisite of the innate immune response. (32) Currently, 11 TLRs have been described. An interesting aspect, with few studies in the neonatal period, is that polymorphisms of some of these receptors are associated with susceptibility to infection. (32) TLR expression patterns possibly could be used in diagnosis and treatment of neonatal sepsis. Compared with adults, healthy neonates have a mild deficiency in TLR2 expression without a difference in TLR4 expression, while infants who have sepsis already present TLR2 upregulation at the onset of sepsis, making this a potential early marker of infection in the neonatal period. (33)

NUCLEAR FACTOR KAPPA-B. Nuclear factor kappa-B can be found in nearly all cell types and plays a fundamental role regulating immune response to infection. Activation of nuclear factor kappa-B is related to more severe sepsis in children (34) and seems promising in both diagnosis and treatment. However, to date, no studies have been performed in newborns.

OTHER. Other markers such as IL-2, gamma-interferon, adhesion molecules (ICAM-1, VCam-1, E selectin, L selectin), and complement activation factor products (C3a-desArg, CebBbP, sC5b-9) all have been described as useful in diagnosing sepsis but require better evaluation in the neonate. (10)

Hematologic Tests Used in Daily Practice

Complete blood cell count and acute-phase reactants such as CRP are used commonly to diagnose neonatal infection. Serial measurements and a combination of hematologic tests can help to improve infection diagnosis, although the hematologic tests are most useful in excluding infection through their high predictive negative value. Screening scores for sepsis are proposed to improve the accuracy of these diagnostic tests, which evaluate complete blood cell count parameters either associated or not associated with acute-phase reactants. (35)(36)

The most commonly used hematologic scoring system is the Rodwell score, which gives one point to each

alteration found in seven findings: leukocytosis or leukopenia, neutrophilia or neutropenia, elevated immature neutrophil count, elevated immature-to-total neutrophil ratio, immature-to-mature neutrophil ratio of at least 0.3, degenerative changes in neutrophils, and low platelet count. A score of 3 or more has 96% sensitivity and 78% specificity, and a score less than 3 has a predictive negative value of 99%. (36)

Acute-phase Reactants

Acute-phase reactants are primarily proteins produced by the liver as part of the inflammatory response to infection or tissue lesions. The most commonly used is CRP. It is important to know that CRP values are influenced by mode of delivery, gestational age, type of organism causing sepsis, surgery, and granulocytopenia. (37) At the beginning of sepsis, CRP concentrations are increased (>1 mg/dL) in only 16% of cases. After 24 hours, positivity increases to 92%, reaching its highest level in 2 to 3 days and decreasing from the fourth day, when infection is under control. In cases of neonatal bacterial meningitis, CRP concentrations usually are very high and can reach 7 to 10 mg/dL. It has been suggested that if CRP values do not fall after 48 hours of antibiotic therapy, antimicrobial resistance or poor clinical course should be considered. (38) CRP is measured best by a quantitative method (nephelometry or turbidimetry), although a semiquantitative method using latex reagent might be an alternative in less-developed countries if the equipment needed for quantitative determinations is not available. (39) CRP sensitivity at the time of sepsis evaluation is 60%. An alternative to improve CRP accuracy at the onset of sepsis is to associate it with IL-6, which can achieve 100% sensitivity. (24) Serial measurements at 24 and 48 hours after the onset of infection improve the sensitivity to 82% to 84%, respectively. CRP is a specific but late marker of infection, useful in excluding sepsis and for evaluating infection control. (10) Serial CRP determinations showing persistently normal values (<1 mg/dL) in more than 90% of the cases suggest infants who are not infected with high specificity and may help to minimize exposure of neonates to antibiotics and decrease the likelihood of resistant organisms emerging. (40)

Another acute-phase marker is PCT, the precursor of calcitonin, which usually is synthesized in thyroid C cells. In infection, increased PCT seems to be associated with production in other cells and organs, consequently providing evidence of a systemic inflammatory response. It has chemotactic activity and increases cyclic AMP. Increased PCT in early-onset sepsis and LOS has a sensitiv-

ity and specificity that varies between 87% and 100%, especially in sepsis confirmed by blood culture. The increase is less in infections caused by coagulase-negative staphylococci. It can be useful for diagnosis and for documenting infection control. Serum concentrations increase in the first 4 hours after exposure to bacterial endotoxin, peaking at 6 to 8 hours and remaining high for at least 24 hours. The half-life is 25 to 30 hours, and concentrations do not seem to be affected by gestational age. (10)(19) In very low-birthweight infants who have confirmed LOS, PCT, with a cut off of 0.5 ng/mL, was more sensitive than CRP (97% versus 72%), and PCT values reduced more quickly with treatment than CRP values (24 to 48 hours versus 5 days). (41) Another study involving preterm infants in the first 12 hours of sepsis showed that PCT, using a cut off of 0.99 ng/mL, had better sensitivity (97.5%) and predictive negative value (88.9%) than CRP and immature-to-total neutrophil ratio. (42)

Results are still inconclusive for the role of serum amyloid A as a marker of neonatal infection. (43) Other acute-phase reactants such as alpha-1-antitrypsin, fibronectin, haptoglobin, lactoferrin, neopterin, and orosomucoid, increase in infected newborns, but they have poor accuracy and are not used routinely. (10)

Prognosis

The World Health Organization estimates that 4 million neonatal deaths occur each year, of which more than one third are related to serious infections and one quarter of those are attributed to neonatal sepsis syndrome/pneumonia. (44) In developing countries, neonatal mortality is responsible for 60% of infant mortality, with sepsis being one of the primary causes of death in newborns.

The percentage of deaths attributed to infection increases with postnatal age from 4% in the first 3 days after birth to 14.6% between 4 and 7 days, reaching 36% between 8 and 14 days and 52% between 15 and 28 days. (45)

Data from the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network of a cohort of 6,215 very low-birthweight infants who survived beyond 3 days show large variation in mortality from LOS as a function of the infectious agent. (45) In this study, mortality from sepsis was 18%. The death rate among infants who had gram-positive infections was 11% (coagulase-negative staphylococci, 9% and group B *Streptococcus*, 22%). Infants who had gram-negative and fungal infections had higher risks for death (36% and 32%, respectively). Of note, 71% of

Table 2. Short-term Prognosis for Late-onset Sepsis According to Etiologic Agent

Etiologic Agent	Septic Shock	Mortality
Gram-positive bacteria	8.5%	7% to 11%
Gram-negative bacteria	45%	20% to 74%
Fungus	45%	32% to 50%

the deaths by gram-negative agents occurred within 72 hours of the blood culture.

In the NICU at Botucatu School of Medicine University Hospital – UNESP, mortality from confirmed LOS varied from 10% to 44% between 1999 and 2003. Shock was more frequent with gram-negative and fungal organisms (45%) compared with gram-positive pathogens (8.5%). The highest mortality occurred in fungal sepsis (50%), followed by gram-negative (20%) and only 7% for gram-positive (data not published). Data from the Brazilian Network of Neonatal Research between 2006 and 2008 showed a 24% incidence of confirmed LOS and 21% of clinical sepsis in very low-birthweight infants, with mortalities of 26.5% and 36%, respectively. (46)

The NICHD multicenter study with more than 6,000 preterm infants weighing less than 1,000 g evaluated the impact of neonatal infection by gram-positive, gram-negative, and fungal agents on neurologic prognosis to 18 to 22 months corrected age and found no significant differences between the agents. However, the high mortality in sepsis from gram-negative and fungal agents could have contributed to this result. (47) The short-term prognosis for LOS according to etiologic agent is shown in Table 2.

The prognosis for fungal sepsis is poor, with a higher mortality rate compared with bacterial sepsis (32% versus 17%, $P < 0.005$), higher incidence of cerebral palsy (14% versus 6%, $P < 0.05$), and poor neurodevelopment at 18 months corrected age. (48)

Neonatal Infection and Neurodevelopment

Experimental studies indicate that proinflammatory cytokines can be neurotoxic and increase blood-brain barrier permeability in the preterm infant. (49) Also, infected neonates frequently present with hypotension, respiratory insufficiency, and hypoxemia that may compromise cerebral blood flow, thereby increasing the risk of cerebral lesions and adverse neurodevelopmental outcome. (47)(50)

A recent single-center study of preterm babies born at less than 30 weeks gestational age evaluated by the Bayley Scales of Infant Development II Scores at 1 year of corrected age showed that LOS is an independent predictor of poor prognosis. It increases by 2.9 times the chance of delayed motor and mental development (Table 3). (51)

A multicenter cohort study of 6,093 extremely low-birthweight preterm infants evaluated the impact of neonatal infection on neurodevelopment and growth prognosis at 18 to 22 months corrected age. (47) The infected infants (3,932) had a worse prognosis for neurodevelopment, including cerebral palsy, low Bayley Scales of Infant Development II Scores (< 70) on the mental development index and psychomotor development index, and vision impairment. Approximately 40% of the patients were below the 10th percentile for weight, height, and head circumference. However, the infected children were more immature, had lower birthweights, and had greater exposure to postnatal corticosteroids and comorbidities that influenced prognosis.

In extremely low-birthweight preterm infants who participated in the Indomethacin Prophylaxis Trial in Preterm Infants and survived up to 36 weeks postconceptional age, neonatal infection increased the risk of later death and neurosensory sequelae but was a weaker predictor of poor development than bronchopulmonary dysplasia, cerebral lesions, and severe retinopathy of prematurity. (52)

Mortality from meningitis has decreased from 50% in the 1950s to numbers around 6% in the current decade.

Table 3. Long-term Prognosis for Late-onset Sepsis and Meningitis

Late-onset Sepsis

- Delayed motor and mental development
- Cerebral palsy
- MDI and PDI < 70

Meningitis

- Risk of worse prognosis if cerebrospinal culture positive
- Hearing and vision impairment
- Convulsions
- Neurodevelopmental impairment
- Behavioral problems

MDI=mental development index, PDI=psychomotor development index

(53) In national cohorts from England and Wales, comparison between two periods of 1985 to 1987 and 1996 to 1997 showed a significant reduction in deaths from confirmed cases of meningitis from 29% to 10%.

(54) However, the disease remains devastating, with high frequencies (20% to 50%) of short-term complications that include hydrocephalus, abscesses, convulsions, and ventriculitis, primarily in gram-negative meningitis.

(53)

Neonates who have meningitis have a 1.6 to 2.2 increased risk of neurocognitive impairment. The highest risk of adverse prognosis is found for those in comas, experiencing convulsions, or needing inotropic support. (2)

Although long-term prognosis data are scarce, sequelae have not decreased, especially in newborns who have positive CSF cultures. Sequelae include: intellectual disability; convulsions; cerebral palsy; visual, hearing, and language deficits; and behavioral problems. (53)(54)

Conclusion

The improved survival of preterm infants of decreasing birthweight and gestational age has resulted in a cohort of patients at high risk of LOS and death. Early recognition of the signs and symptoms of sepsis, in conjunction with the use of nonspecific but sensitive markers and identification of the etiologic agent, the gold standard in diagnosis, are fundamental for instituting adequate treatment. Strategies based on better practices designed to reduce the incidence of LOS and diagnose the infection earlier as well as investment in treatment resources that modulate the inflammatory response and block the progress of infection are required for improving prognosis. Follow-up of infants who had neonatal sepsis is fundamental in attempting to reduce the risk of adverse outcome and in improving the quality of life for these patients.

American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications

- Know the clinical manifestations, laboratory features, and differential diagnosis of neonatal sepsis.
- Know the infectious agents that cause neonatal sepsis.



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NeoReviews Quiz

7. Late-onset sepsis is typically defined as neonatal sepsis that manifests more than 72 hours after birth. Of the following, the *most* common clinical feature of late-onset sepsis in the newborn, as reported by Fanaroff and associates, is:
- A. Abdominal distension.
 - B. Apnea.
 - C. Hypotonia.
 - D. Lethargy.
 - E. Respiratory distress.
8. Time to positivity of neonatal blood cultures has been studied by Kumar and associates using an automated colorimetric microbial detection system. Of the following, the period of observation *most* sufficient to detect all clinically important blood culture isolates is:
- A. 24 hours.
 - B. 36 hours.
 - C. 48 hours.
 - D. 72 hours.
 - E. 96 hours.
9. Acute-phase reactants, proteins produced by the liver as part of an inflammatory response to infection, are often used for diagnosing neonatal sepsis. Of the following, the *most* commonly used acute-phase reactant for the diagnosis of neonatal sepsis is:
- A. Alpha-1-antitrypsin.
 - B. C-reactive protein.
 - C. Fibronectin.
 - D. Lactoferrin.
 - E. Procalcitonin.
10. The ideal laboratory test for the diagnosis of neonatal sepsis is one that uses a small volume of blood or other body fluid, is inexpensive and easy to perform, is rapid, and is accurate with high sensitivity and specificity. Of the following, the diagnostic test with the *highest* sensitivity and specificity for the diagnosis of neonatal sepsis is:
- A. Hematologic score plus C-reactive protein.
 - B. Interleukin-6 plus C-reactive protein or procalcitonin.
 - C. Interleukin-8 plus C-reactive protein.
 - D. Interleukin-8 in the urine.
 - E. Tumor necrosis factor-alpha.
11. Meningitis is an important issue in late-onset sepsis. A true statement about cerebrospinal fluid analysis in meningitis is that:
- A. The rate of positive culture for gram-positive agents is high, even after the beginning of treatment.
 - B. Adjusting white blood cell count in traumatic lumbar puncture increases the diagnostic accuracy.
 - C. Lumbar puncture always is required in late-onset sepsis.
 - D. Traumatic lumbar puncture is an uncommon complication in neonates but limits cerebrospinal fluid analysis.
 - E. Cerebrospinal fluid analysis has prognostic value, with a high rate of neurodevelopmental sequelae in culture-proven meningitis.

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