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Diagnosis and management of bacterial infections in the neonate

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Evaluation and treatment of a neonate for possible bacterial infection is one of the most common clinical practices in the newborn nurseries. More than half of neonates admitted to neonatal intensive care units (NICUs) carry a discharge diagnosis of "rule out sepsis," and these infants account for up to 25% of NICU days in some units [1]. Optimal diagnosis and treatment strategies are difficult to define: the signs and symptoms of neonatal sepsis are protean and nonspecific; the disease is rare (1 to 5 cases/1000 live births) [1–3], but carries a high risk of mortality (5%–15%); the neonate's immune system is underdeveloped; and the infections are caused by a group of organisms that are unique to the perinatal period. There is also a "fear factor" in that clinicians know that to delay treatment raises the risk of mortality, but also that presumptive treatment with antibiotics based on subtle laboratory or clinical findings results in overtreatment. For instance, historically, between 11 and 23 noninfected newborns were treated with antibiotics for every one with proven sepsis [4,5]. Further, definitive culture tests are not rapid or particularly sensitive, and screening tests such as white blood cell (WBC) count and acute phase reactants have at best a positive predictive value of only 40% [6]. Finally, there is a wide variation of practice, with ranges of length of stay for term infants with sepsis evaluations but negative cultures ranging from 2 to 3 days (29%), to 7 or more days (28%) (M. Musci, personal communication, 2002).

These factors have resulted in a conservative clinical approach, in which evaluation and antibiotic treatment are initiated in a number of babies who have minimal clinical or laboratory findings. Current methods may not permit a substantial reduction in the number of infants in whom treatment is initiated, but they do allow us to shorten duration of antibiotic therapy to reduce risks such as

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alterations in normal flora [7], medication errors, intravenous infiltrates, and financial and emotional costs to the parents.

The goals of this article are to provide a systematic but clinically realistic approach to the diagnosis of neonatal sepsis that will (1) miss no cases, which will lead to some overtreatment of noninfected neonates; (2) minimize duration of therapy for those infants who prove to be uninfected; (3) provide a safe observation protocol for at-risk infants who are not treated; and (4) review modalities of antibiotic and supportive therapies. The discussion is limited to early-onset, perinatally acquired bacterial infections in the first 3 to 5 days of life.

Early diagnosis of neonatal sepsis

Symptomatic or asymptomatic?

Perinatally acquired bacterial sepsis occurs both in infants with signs and symptoms of sepsis and in those who have not yet developed symptoms but who are at significant risk for the disease based on perinatal risk factors. The relevant signs and symptoms are often nonspecific, and may end up being attributed to other causes; however, because of the rapidity of deterioration in neonates with true sepsis and the probable success of treatments if instituted early in the course, clinicians faced with a symptomatic infant must move promptly through the diagnostic tests and start appropriate antimicrobial and supportive therapy. Signs and symptoms of sepsis include respiratory distress or grunting, lethargy or irritability, fever or hypothermia, hypo- or hyperglycemia, acidosis, hypotonia, vomiting, poor feeding activity, apnea, cyanotic spells, seizures, persistent pulmonary hypertension, poor perfusion or shock, petechiae or purpura, unexplained jaundice, or most important, ‘‘not looking well’’ [6].

The spectrum and severity of symptoms required to embark upon diagnostic and therapeutic course for sepsis is a matter for clinical judgment and cannot be dictated by a written protocol; however, specific data for some of these symptoms and signs are available to aid in decision-making. Respiratory distress in the term infant may be due to delayed transition or retained fetal lung fluid, but sepsis and pneumonia are a relatively common cause of respiratory distress. Infants with meconium aspiration syndrome should be considered infected until proven otherwise; antibiotic treatment is indicated in that bacteria may have been aspirated with the meconium, and sepsis may have been the inciting cause of fetal distress and meconium passage. Ten percent of full-term neonates with fever ($\geq$37.8°C) not due to environmental causes may have bacterial sepsis [8]. In contrast, hypothermia is a nonspecific finding in the first 2 days of life, because many neonates have some transitional difficulty with temperature control. An unexplained elevation of serum bilirubin concentration, especially of the direct fraction, may be associated with sepsis or urinary tract infection [9].

The incidence of neonatal sepsis or bacteremia in asymptomatic infants is low, but not negligible. Over 90% of neonates with sepsis have at least one symptom,

Table 1
Risk factors for neonatal sepsis

Conditions	Incidence of proven sepsis
PROM >18 hours	1%
Maternal + GBS (preprophylaxis era)	0.5%–1%
Maternal + GBS (in prophylaxis era)	0.2%–0.4%
Maternal + GBS and PROM, fever or preterm	4%–7%
Chorioamnionitis	3%–8%
+GBS and chorioamnionitis	6%–20%
PROM + preterm	4%–6%
PROM + low Apgar score	3%–4%

and the majority have three or more symptoms. Further, over 90% of septic neonates present with symptoms in the first 24 hours of life, with the remainder presenting before 48 hours [10,11]; therefore, careful observation for symptoms in the first 48 hours of life is a key factor in a diagnostic strategy for neonatal sepsis.

As noted above, the decision to evaluate and treat a neonate for possible sepsis based on signs and symptoms is a matter of clinical judgment. Certainly, most newborn infants with significant respiratory distress not clearly due to delayed transition, shock, or fever should be treated pending culture results. Beyond that recommendation, the clinician must rely on careful history, physical examination, assessment of the course and severity of the symptoms, and laboratory investigations.

Risk factors for neonatal sepsis

It is incumbent upon the clinician to pay careful attention to the perinatal history to assess the risk of sepsis in every newborn infant. Asymptomatic infants at low risk may receive routine newborn care; medium-risk infants should be carefully observed under a specific protocol; and in some cases, asymptomatic infants at highest risk should receive empiric antibiotic treatment pending culture results and clinical course. The major perinatal risk factors for neonatal sepsis are listed in Table 1. The table lists the incidence of proven sepsis given the presence of the risk factors; in most studies, the risk of highly suspected but culture-negative sepsis is twice the rate of proven disease. Also, note that risk factors are additive; prolonged rupture of membranes (PROM) plus two other risk factors raises the risk of sepsis 25 fold [6]. Risk factors include

- PROM. Once the membranes have been ruptured for >18 hours, the risk of sepsis in the neonate increases approximately 10 fold over baseline, to a rate of 1% for proven and 2% for suspected sepsis [12,13]. The risk of proven sepsis with PROM in the preterm infant (PPROM) increases to 4%–6%. A 5-minute Apgar score <6 also raises the sepsis risk to 3%–4% [12].
- Chorioamnionitis/maternal fever. The problem with chorioamnionitis is one of diagnostic definition in day-to-day clinical practice, with wide variability and interpretation among clinicians. The generally accepted definition is

presence of maternal fever >100.4°F with two or more of the following findings: fetal tachycardia, uterine tenderness, foul vaginal discharge, or maternal leukocytosis. The reported range of neonatal sepsis when chorioamnionitis is present is 3%–20%, with an odds ratio of 6:42 (2.32–17.8) [14]. Maternal fever without signs of chorioamnionitis also raises the risk of sepsis, but may be confounded by noninfectious causes of maternal fever such as dehydration or epidural anesthesia.

- Maternal colonization with group B *Streptococcus* (GBS). Maternal colonization with GBS without clinical complications and without antibiotic prophylaxis carries a neonatal sepsis risk of 1% [15]; the risk rises to a best estimate of 4%–7% in the presence of clinical complications such as PROM, maternal fever, or prematurity [16]; and as high as 20% in the presence of chorioamnionitis [14]. GBS bacteruria and having a twin with GBS disease also raises the neonatal risk. Although specific data are lacking, there is anecdotal evidence that the risk of GBS sepsis is also higher in pregnancies subsequent to one in which the neonate developed GBS sepsis. Further, there is an additive risk in the presence of multiple risk factors (Tables 2, 3).
- Prematurity. The focus of this article is on sepsis in the term neonate; however, many near-term preterm infants are cared for in well-baby nurseries, and these infants are at increased risk for sepsis. For example, as noted in Table 2, the odds ratio of developing GBS sepsis in infants <37 weeks' gestation is 4.8 relative to the incidence in full-term infants. The risk of sepsis from any cause also starts to rise at 35–36 weeks' gestation as compared with >37 weeks' gestation [8].
- Maternal urinary tract infection (UTI). As noted, GBS bacteruria is a risk factor for sepsis. Likewise, UTI of any cause raises the risk of sepsis in the neonate, in part due to raising the risk of prematurity and chorioamnionitis [21].
- Other risk factors. Perinatal asphyxia in the presence of PROM and not readily explained by an obstetric cause such as placental abruption raises the risk of neonatal sepsis [13]. Male gender has also been implicated as a risk factor [13]; the reasons for this finding are unknown. Another commonly accepted risk factor is the presence of foul smell to the amniotic fluid, or "smelly baby." It is thought that this sign may be due to the presence of anaerobic bacteria, but there is no evidence that this finding constitutes an independent risk factor for sepsis.

Intrapartum chemoprophylaxis of GBS-colonized mothers with penicillin or ampicillin dramatically decreases the risk of GBS sepsis in the neonate. The attack rate of GBS sepsis in colonized mothers has been reduced up to 70% through implementation of consensus guidelines for intrapartum prophylaxis [17–19]. The reduction in GBS disease may be as high as 90% in pregnancies with GBS colonization but no other risk factors [19]. The national overall attack rate for GBS has declined from 1.5/1000 live births to 0.5/1000 live births since

Table 2
Maternal colonization with GBS: additive risk factors

Condition	Odds ratio for proven early-onset GBS sepsis
Maternal + GBS at 36 weeks	26.7
Maternal + GBS and <37 weeks	4.8
Maternal + GBS and <28 weeks	21.7
Maternal + GBS and maternal fever or PROM	11.5

Data from Benitz WE, Gould JB, Druzin ML. Risk factors for early-onset group B streptococcal sepsis: estimation of odds ratios by critical literature review. Pediatrics 1999;103(6):e77.

the institution of these guidelines [20]. The Centers for Disease Control (CDC), American College of Obstetrics and Gynecology (ACOG), and American Academy of Pediatrics (AAP) have recently further refined the guidelines to drop the risk-factor strategy for maternal management, and to recommend that all pregnant women be screened for GBS by culture and that antibiotic prophylaxis be offered during labor [20].

The problem for day-to-day clinical management is that the prevention strategy, although very effective, does not eliminate the risk of GBS disease. Many of the failures of prophylaxis occur in the presence of chorioamnionitis, in which sepsis may be underway in the fetus, too late for antibiotic prevention of the disease [14]. There are other opportunities for failure, including timing of prophylaxis: antibiotics must be administered approximately 4 hours before delivery to be effective [20]. Further, a number of women have known or suspected penicillin allergy, and there are no data to show that alternative antibiotics (erythromycin, clindamycin, or vancomycin) are effective. Thus, although chemoprophylaxis has been remarkably effective, this strategy is not complete enough to allow the clinician to ignore the possibility of GBS sepsis in the neonate. In fact, one could argue that vigilance must be even higher than in the preprophylaxis era, because clinicians may have a lower index of suspicion for a disease with lower incidence in the population.

The sepsis work-up

A two-pronged approach is used for the evaluation of neonates with possible sepsis. Nonspecific sepsis screen tests are used to evaluate the likelihood of

Table 3
Summary of very high risk for early-onset GBS sepsis

Maternal GBS colonization plus:	Attack rate
PPROM (preterm)	35%–50%
Chorioamnionitis	6%–20%
Maternal GBS bacteruria	8%
Twin with GBS disease	40%
Previous sibling with GBS	Anecdotal increase in risk

Data from Benitz WE, Gould JB, Druzin ML. Risk factors for early-onset group B streptococcal sepsis: estimation of odds ratios by critical literature review. Pediatrics 1999;103(6):e77.

infection, and specific diagnostic tests are performed to confirm the presence of a specific pathogen in body fluids. Ideally, screening tests for neonatal sepsis would exhibit both high positive and negative predictive accuracy for the presence or absence of disease. Unfortunately, this ideal situation does not yet exist, with most screening tests having poor positive predictive accuracy; however, as noted below, strategies have been developed that offer a high negative predictive value, thereby providing some utility in ruling out sepsis. Isolation of bacteria from a central body fluid is the standard and most specific method to diagnose sepsis; however, the most useful specific diagnostic test, the blood culture, is also fraught with inaccuracy, with too many false-negative results to qualify as a gold-standard test for making the diagnosis. Therefore, at the end of the day, the clinician is often faced with a judgment call, taking into consideration the constellation of signs, symptoms (or lack thereof), screening tests, and specific diagnostic tests, before the diagnosis of neonatal sepsis can be made or excluded.

Definitive, specific diagnostic laboratory tests

Blood culture

Sterile acquisition by venipuncture or arterial puncture of 0.5 mL to 1.0 mL of blood, placed in a standard tryptic soy broth culture bottle, is a standard microbiologic technique available in all hospital laboratories. Acquiring the sample from a fresh umbilical artery catheter is also acceptable with a low contamination rate, although samples from an indwelling umbilical venous catheter appear to be unreliable [22]. The culture is incubated for up to 5 days, although the modern culture systems will identify almost all early-onset neonatal pathogens within 48 hours.

The problem with the blood culture in neonates is that the sensitivity for identifying sepsis is only 50% to 80% at best. Data from the era before widespread prophylactic antibiotic use in laboring mothers show that even in neonates sick enough to die, only 80% of autopsy proven sepsis was diagnosed by premortem blood cultures [23,24]. Likewise, only 50% of neonates with bacterial pneumonia diagnosed clinically and by tracheal aspirate cultures had positive blood cultures [25]. Currently, the increased use of maternal antibiotics has further reduced the rate of positive blood cultures in early-onset sepsis; as few as 2.7% of neonates with clinical sepsis may have positive blood cultures [10]. In addition to the partial treatment from maternal antibiotics, bacteremia may be transient in the early stages of disease, and the small blood volume typically taken from infants for culture may be insufficient to detect low bacterial-density sepsis in infants [26]. In summary, a positive blood culture with a pathogenic organism is diagnostic of neonatal sepsis; however, a negative blood culture in no way rules out the disease.

Lumbar puncture

To lumbar puncture (LP) or not to LP? That is the question, and there is no easy answer. Early-onset meningitis is a rare event, occurring in no more than

0.25/1000 live births in the era before maternal GBS prophylaxis. Meningitis can be missed if cerebrospinal fluid (CSF) is examined only in patients with positive blood cultures, because up to 28% of meningitis patients have a negative blood culture, and up to 37% of meningitis cases may be missed if an LP is not routinely performed as part of the sepsis work-up [27]. On the other hand, the rate of meningitis in infants without symptoms of meningitis may be 0%, or less than 1% in the worst-case scenario [28,29]. In similar manner, asymptomatic infants receiving a sepsis work-up because of routine causes of respiratory distress have meningitis in fewer than 1% of cases [30,31]. An unpublished meta-analysis by Gerdes of these studies found that one would need to perform between 1000 and 2000 lumbar punctures to find one case of meningitis in neonates without symptoms of meningitis and with a negative blood culture. Rather than apply an all-or-nothing approach, a reasonable recommendation is to perform a lumbar puncture in neonates with symptoms of meningitis (lethargy, hypo- or hypertonia, seizures, apnea, excessive irritability, bulging fontanelle, or septic shock), in symptomatic babies in whom sepsis is the leading diagnosis (eg, may exclude those with simple meconium aspiration or respiratory distress syndrome [RDS]), or in babies with a positive blood culture.

Once the CSF is obtained, bacterial cultures are very reliable in the absence of pretreatment, because CSF infection tends to have high bacterial density and there are fewer interfering proteins than are found in blood. On the other hand, the interpretation of CSF cell counts and chemical analyses is difficult. The upper limit of the mean ±2 standard deviations CSF cell count in term neonates is 25 cells/mm^3, but white blood cell counts up to 32/mm^3 may be found in uninfected neonates. At the low end, however, up to 30% of neonates with GBS meningitis may have normal CSF counts below this upper limit. Further, glucose and protein concentrations are rarely useful, due to wide normal ranges (24 to 119 mg/dL for glucose, and 20 to 170 mg/dL for protein) [32].

Urine culture

Urine cultures from bag specimens are notoriously unreliable and open to contamination, so it follows that they should not be obtained as part of an initial sepsis work-up. Sterilely acquired bladder tap or catheterized specimens minimize false-positive cultures, but they are difficult to obtain in the low-urine state of the newborn infant, and there is a very low yield in the first 72 hours of life [33]; therefore, a urine culture is not suggested as part of the work-up for early-onset disease.

Tracheal aspirate cultures

Although differentiation of colonization from infection can be problematic when assessing endotracheal tube cultures in the chronically ventilated patient, tracheal aspirate cultures have proven useful when obtained within the first 12 hours of life. A positive tracheal aspirate culture may be found in 44% of infants with clinical pneumonia and negative blood cultures [25], and identification of bacteria on tracheal aspirate gram stain correlates well with clinical or

pathological pneumonia and with bacteremia [34]. Therefore, tracheal aspirate cultures and gram stains will increase diagnostic accuracy when obtained from neonates with suspected sepsis who require intubation and ventilation for presumed pneumonia or respiratory failure.

Detection of bacterial antigens

Early studies showed promising data on the utility of bacterial antigen testing in early onset sepsis, in particular the urine latex particle agglutination (LPA) test for GBS. Further study, however, showed that the test had a sensitivity as low as 67% and a positive predictive value of only 56%, thus falling short of the criteria expected for a definitive diagnostic test [35]. Although this test could be considered as a screening test, there are other easier, less expensive screening tests available, so there does not appear to be a place for urine bacterial antigen tests in the routine evaluation of potentially septic infants. The LPA test for GBS may be useful, however, in CSF from patients with partially treated meningitis.

Adjunctive, nonspecific diagnostic and screening tests

The difficulties in identifying the septic neonate have prompted evaluation of many adjunctive tests that may indicate the possibility of infection, but do not identify the inciting organism. Because neonatal sepsis is a low-incidence, high-severity disease, it is most important for these adjunctive tests to miss no cases (high sensitivity), and to convincingly rule out sepsis when the disease is not present (high negative predictive accuracy.) Because negative predictive accuracy and positive predictive accuracy are inversely related, tests with a high negative predictive value will typically have a low positive predictive value. Therefore, the goals of adjunctive tests are to serve as a part of the total evaluation of the patient in deciding whether to initiate antibiotic therapy, and more important, to discontinue antibiotic treatment quickly in those in whom infection is unlikely to be present.

Many acute phase reactants and cytokines have been shown to correlate with the diagnosis of neonatal sepsis. Many of these tests have reasonable sensitivity, but very few have a high specificity, and very few have a positive predictive value of more than 40% [6,36]. Some tests have performed well in a research setting, but require special handling or are not readily available in hospital laboratories. Because of these limitations, discussion will focus on two readily available tests: the WBC and differential counts, and C-reactive protein (CRP). Adjunctive tests for diagnosing neonatal sepsis are listed in Box 1.

White blood cell count and related indices

The most frequently determined adjunctive test is the WBC and differential count, and related indices such as the absolute neutrophil count (ANC), immature/total ratio (I/T), total WBC, and immature leukocyte count. The normal ranges of these indices are very broad, and are also very dependent on the timing of the sample. Manroe et al demonstrated that in their population, the lower limit

Box 1. Adjunctive tests for diagnosing neonatal sepsis

White blood cell (WBC) and differential counts
C-reactive protein (CRP)
Mini-ESR (Erythrocyte sedimentation rate)
Endotoxin
Haptoglobin
Acridine orange stain
Fibronectin
Nitro blue tetrazolium (NBT) test
Orosomucoid
Soluble interleukin (SIL)-2 receptor
Elastase alpha-1-proteinase inhibitor complex
Interleukin 6
C3d
Neutrophil CD11b
Granulocyte-colony stimulating factor (CSF)
Procalcitonin
Bacterial polymerase chain factor (PCR)
Inter-alpha-inhibitor proteins
Interleukin 8
Tumor necrosis factor α

for ANC, for example, was 1800/mm^3 at birth, rose to 7200/mm^3 at 12 hours of age, and then declined to 1800/mm^3 by 72 hours of age [37]. Shelonka et al, with a larger number of healthy infants studied at 4 hours of age, found the ANC 10% to 90% range to be 9500/mm^3 to 21,500/mm^3 [38]. Escobar and colleagues, in a relatively low-risk population, found the lower 10% limit of ANC to be 5580/mm^3 [11].

Another commonly used WBC index is the immature-to-total neutrophil ratio (I/T), defined as band forms plus any earlier cells such as metamyelocytes divided by the total neutrophil count (early forms plus polymorphuclear cells). Manroe et al [37] defined the upper limit of normal I/T at 0.16 in the first 3 days of life, and found a high sensitivity but weak specificity for diagnosis of sepsis using this cutoff; however, subsequent work has shown a higher limit for normal values for I/T in healthy neonates, up to 0.27 [38]. Further population-based studies showed only moderate sensitivity and specificity for sepsis, using an upper limit of 0.25 to 0.30 [11].

A low total leukocyte count <5,000 to 7500/mm^3 has also been correlated with the diagnosis of neonatal sepsis, although many septic infants have higher counts, giving this test a low sensitivity of 29%, but a reasonable specificity of 91% [6]. Further, although many suggested sepsis screening protocols use an upper limit of normal of 30,000 to 40,000/mm^3, there is little evidence in the

Table 4
Normal ranges for WBC indices at 4 hours of age

	Mean	±SD	10%–90% range
Total WBC (×10 9/L)	24.06	6.11	16.20–31.50
ANC (×10 9/L)	15.62	4.69	9.50–21.50
I/T ratio	0.16	0.10	0.05–0.27

From Schelonka RL, Bradley YA, desJardins SE, Hall RB, Butler J. Peripheral leukocyte count and leukocyte indexes in healthy newborn term infants. J Pediatr 1994;125:603–6; with permission.

literature that an elevated total WBC in the first 3 days of life is useful in the diagnosis of sepsis.

Table 4 lists the most recent information on normal ranges of WBC indices, and Table 5 lists statistical outcomes for ANC and I/T ratio in a population-based study. Although these provide useful information in the evaluation of neonates for sepsis, the wide range of reported normal values and predictive values must be kept in mind. There are a number of factors that contribute to the encountered variability. The studies of neonates with sepsis suffer from lack of diagnostic definition. A positive blood culture makes the diagnosis of proven sepsis, but the studies also use different criteria for the diagnosis of suspected sepsis, making inter-study comparison difficult. Study population differences may lead to variation due to clinical factors other than infection that may alter WBC indices. For example, maternal hypertension and perinatal asphyxia may cause neutropenia [37]. Although maternal hypertension does not alter I/T ratio, other nonspecific stresses such as asphyxia [38], maternal fever, or stressful labor may elevate the I/T ratio [39,40]. Total WBC can be higher in capillary than in arterial or venous specimens [41]. There is also significant inter-observer variability in the subjective differentiation of immature from mature neutrophil forms [42]. Timing is also important, as noted above, and the WBC indices in the septic infant may be normal at the time of initial evaluation but abnormal 4 to 12 hours later [43–45].

Table 5
Predictive values of adjunctive diagnostic tests

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
ANC $\leq$ 1750/mm [36]	38–96	61–92	20–77	96–99
ANC $\leq$ 10% (<5580/mm^3) [11]	48	73	4	98
I/T $\geq$ 0.2 [6]	90–100	30–78	11–51	99–100
I/T $\geq$ 0.25 [11]	45	84	6	98
I/T $\geq$ 0.3 [11]	35	89	7	98
CRP > 1.0 mg/dL	70–93	78–94	7–43	97–99.5
WBC $\leq$ 5000/mm^3 I/T $\geq$ 0.2, and CRP > 1.0 mg/dL [45] (screen + if 2/3 are abnormal)	100	83	27	100

In summary, the WBC, ANC, and I/T ratio are far from perfect adjunctive tests for diagnosing neonatal sepsis; however, the information obtained from these tests, particularly the high negative predictive value of normal tests, may be useful in developing strategies for diagnosis and treatment.

C-reactive protein

CRP is an acute-phase reactant protein synthesized by the liver in response to, and as part of, the inflammatory response. Interleukin-6 is the major stimulus to production of CRP, along with interleukin-1 and tumor necrosis factor α. CRP is released 4 to 6 hours after the onset of the stimulus, peaks at 24 to 48 hours, and then diminishes over time as the inflammation resolves [46,47]. Once in the circulation, CRP participates in the immune response as it forms CRP-ligand complexes with damaged cell wall, which then activate complement and bind to phagocytic cells and amplify the immune response [48].

Although a number of inflammatory conditions elevate serum CRP, in the neonate the number one cause of inflammation is infection. Further, CRP is an inexpensive, readily available, automated laboratory test. For these reasons, CRP has been well-studied as an adjunctive test for the diagnosis of neonatal sepsis. An upper limit of normal of 1.0 mg/dL was suggested in a number of studies [45,49,50] and confirmed by Benitz et al [51], who constructed receive-operator characteristic curves from data on 1186 infants. As suggested by the time lag in CRP response, elevated CRP has been most useful for indicating neonatal infection when determined serially, with at least two measurements 12 to 24 hours apart [45,49–52]. With the proviso of the need for CRP determination 12 to 24 hours after the onset of suspected infection, the range of reported statistical outcomes is as follows: sensitivity 70% to 93%; specificity 41% to 98%; positive predictive accuracy 6% to 83%; and negative predictive accuracy 97% to 99% (see Table 5) [45,49–51,53–56]. Among the reasons for relatively poor specificity of CRP are the number of perinatal conditions that may cause an inflammatory response without having proven infection, such as maternal fever, prolonged rupture of membranes, fetal distress or stressful delivery, perinatal asphyxia, intraventricular hemorrhage, and meconium aspiration [49,50,57].

These data show that using the upper limit of normal of 1.0 mg/dL has limited utility in predicting the existence of infection, but the high negative predictive value may be quite useful in ruling out the presence of sepsis. Benitz and colleagues [51] did find, however, that if the CRP was >5.0 mg/dL, incidence of proven sepsis was 10%, making this cutoff level more useful in predicting disease. Further, normalization of CRP may be a good indicator of resolution of infection with treatment, and several authors have suggested that normalization of CRP can be used to determine duration of antibiotic therapy [58,59].

Sepsis screens

As noted above, none of the adjunctive tests have sufficient predictive accuracies to rule in or rule out sepsis in every clinical situation. To improve the

diagnostic capability of adjunctive diagnostic test, a number of authors have combined some of these tests into sepsis screens. Initial sepsis screen strategies used four or five tests [5,45,60], and others have used the more complicated cytokine assays [54,61]; however, none of the studies improved positive predictive accuracy sufficient to recommend the use of screens for proving sepsis. The ability to rule out sepsis with 100% negative predictive accuracy has been achieved with several of these sepsis screen strategies, however. For routine clinical use, this 100% ability to rule out sepsis can be achieved with the use of sepsis screens in infants at risk for infection, obtained at least 12 to 24 hours after birth, and using the combination of the simple laboratory investigations of WBC and CRP has been as useful as screens using more complicated tests [45,52]. A similar sepsis screen using WBC indices and CRP has been in use for over 10 years at University of Pennsylvania Health System hospitals, and has been useful in screening for sepsis, and most important, aiding in discontinuing antibiotics when sepsis is unlikely (Table 6). Timing of the sepsis screens should be taken into consideration, given the known time frame of response of WBC and CRP. Our initial 10-year experience at Pennsylvania Hospital showed that obtaining a sepsis screen at birth in asymptomatic neonates is not useful, so an initial screen in an asymptomatic patient is obtained at 12 to 24 hours of age. A commonly observed pattern in a noninfected infant born from a stressful labor and delivery shows an elevation of WBC or I/T at 12 hours of age with a normal CRP, and an increase in CRP at 24 to 48 hours of age but with normalizing WBC indices. This scenario is most often benign, in that most infants with sepsis have progressively abnormal WBC indices and CRP.

Approach to the diagnosis and management of the neonate with suspected sepsis

The clinical research data and published recommendations for management of neonates with possible infection continue to be confusing. Although most neonates with sepsis are symptomatic within the first 48 hours of life, the variability in symptomatic presentation of sepsis, the short length of stay for normal newborns, and the rapidity of deterioration of the septic infant make simple ob-

Table 6
Sepsis screen (screen positive if ≥2 points)

Test	Point value
Absolute neutrophil count <1750/mm^3	1 point
Total white blood count <7500/mm^3 or >40,000/mm^3	1 point
Immature/total neutrophil ratio ≥0.20	1 point
Immature/total neutrophil ratio ≥0.40	2 points
CRP + (≥1 mg/dL)	1 point
CRP + (≥5 mg/dL)	2 points

servation and early discharge home uncomfortable for most clinicians. The GBS prevention strategies that have reduced the incidence of GBS sepsis are a good thing, but they have not eliminated GBS or other types of neonatal sepsis. Therefore, clinicians cannot allow this current lower incidence of disease to lull them into complacency, and if anything, a higher degree of vigilance is necessary in situations in which the index condition is rare. The CDC recommendations for monitoring infants exposed to GBS are useful, but they do not account for the approximately 50% of septic neonates with organisms other than GBS. Further, the CDC recommendations are not all data-driven. For example, the recommendation for obtaining a blood culture as a screening tool for GBS-exposed neonates whose mothers did not receive adequate prophylaxis seems unnecessarily invasive, and recent data indicate that such blood cultures do not aid in the diagnosis of GBS sepsis [10]. To further complicate the issue, neither the "definitive" tests such as blood culture nor the adjunctive screening tests are sufficiently reliable to use in isolation.

The following approach for symptomatic and asymptomatic at-risk infants is a multi-pronged synthesis of data and published recommendations, which attempts to use the best of clinical assessment, laboratory data, and experience. The approach is deliberately simple, without the need for complicated decision-analysis tools. The primary goals of this strategy are to identify and treat all septic neonates, and to limit the duration of treatment for babies who are quickly determined not to be infected.

The symptomatic neonate

The clinician must promptly evaluate the newborn infant with signs and symptoms of possible sepsis. Clinical judgment of the constellation of signs and symptoms and review of the patient's perinatal history are used to determine which babies to start immediately on antibiotic therapy for symptomatic sepsis, and which babies to continue to observe and monitor with a sepsis screen. The clinician must remember that the burden of proof is on the clinician to show there is not an infection causing the symptoms, not on the baby to prove that he or she is ill. Further, risk factors are not proof factors, so the absence of risk factors should not dissuade one from treating a symptomatic neonate. Once treatment is indicated, a blood culture should be performed before treatment. A chest radiograph should be ordered if there is respiratory distress. A lumbar puncture should be performed if there are symptoms referable to meningitis, or if symptomatic sepsis is the leading diagnosis. Serial sepsis screens using WBC, I/T, and CRP are recommended, not necessarily to decide on initiation of treatment, but as aids to discontinuing treatment if the screens are negative. Although initial symptoms are a matter of clinical judgment, the clinician may change the patient's designation to "asymptomatic" if the initial symptoms resolve by 12 to 24 hours or the initial symptoms are consistent with a firm diagnosis of a noninfectious condition, such as transient tachypnea of the newborn or congenital heart disease, for example (Fig. 1).

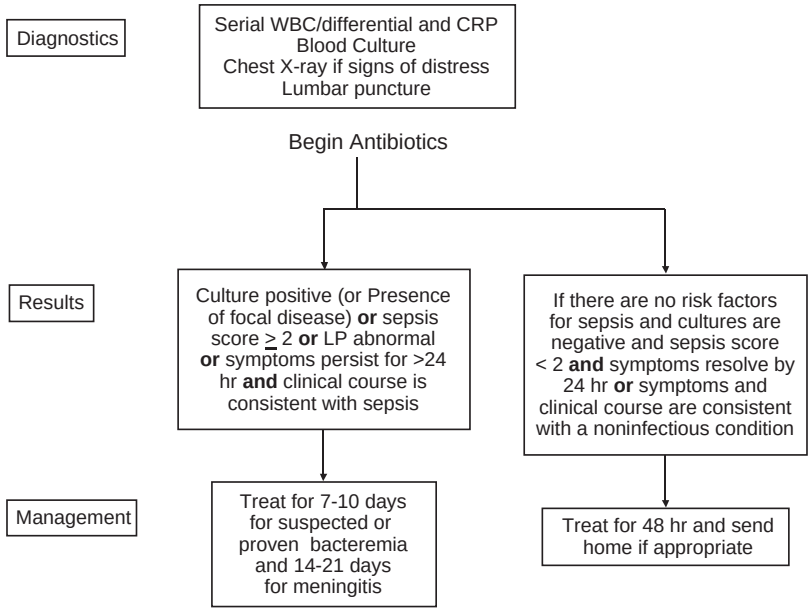

Fig. 1. Infants with symptoms of sepsis and infants of mothers with chorioamnionitis.

The asymptomatic neonate with one or more risk factors

Recommended management for the asymptomatic term and near-term (≥35 weeks gestation) neonate with one or more sepsis risk factors is detailed in Fig. 2. The vast majority of asymptomatic infants with risk factors are safely observed with an observation protocol and sepsis screening on the well-baby nursery. The exceptions are asymptomatic but very high-risk infants who have multiple risk factors, most notably infants with maternal GBS colonization and chorioamnionitis, who should be treated on the symptomatic neonate protocol [20]. A sepsis screen (WBC and CRP) should be obtained at 12 to 24 hours of life. One strategy for use of sepsis screen data is in Table 6. The definition of an abnormal sepsis screen is based on the synthesis of the available data, with a simple point system to score the WBC indices and CRP. Babies who remain asymptomatic and have a normal sepsis screen may be discharged home around 48 hours of age. The exception permitting earlier (24-hour) discharge is the asymptomatic infant ≥38 weeks' gestation with the single risk factor of GBS exposure who received adequate prophylaxis, defined as ≥4 hours of penicillin, ampicillin, or cefazolin [20]. The exception for entering a patient on the asymptomatic neonate protocol is the baby whose mother had GBS exposure, but had an elective cesarean section without labor or rupture of membranes; whose sepsis risk is extremely low; and who may receive routine care.

As noted above, a positive sepsis screen has low positive predictive value and cannot be used as a sole predictor of sepsis, but a positive screen does raise a red

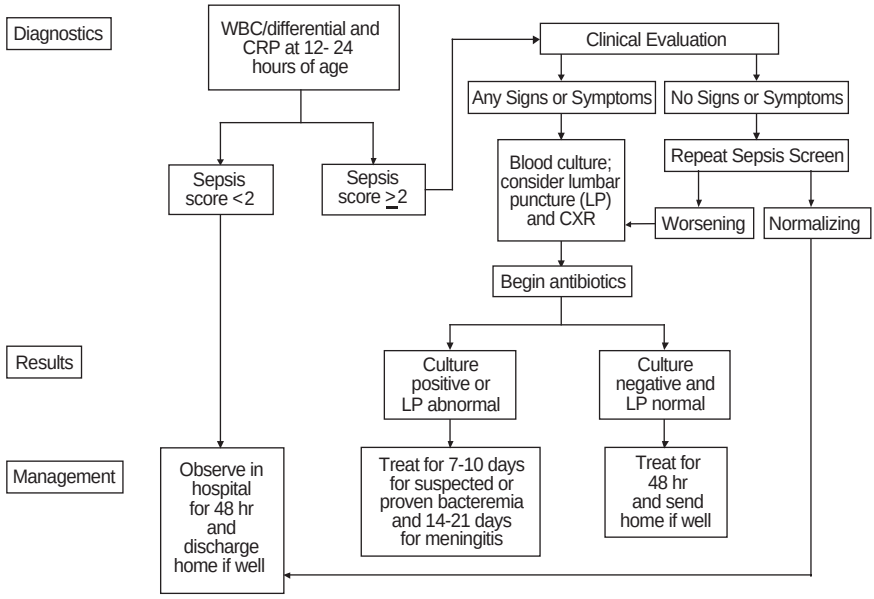

Fig. 2. Asymptomatic infants of at least 35 weeks' gestation with one or more sepsis risk factors.

flag for the infant who should receive further evaluation. Therefore, asymptomatic infants with risk factors who have a positive sepsis screen at 12 to 24 hours of age should be evaluated for signs and symptoms that may be subtle or evolving. If the baby is deemed well and the perinatal history is relatively uncomplicated, continued observation and a repeat sepsis screen in 8 to 12 hours is reasonable, with treatment started if a second sepsis screen is deteriorating. If the initial screen is positive and there are any clinical or historical concerns, the baby should be started on the symptomatic neonate protocol at that time. The point is that an at-risk neonate, even if asymptomatic, should not be discharged home with a positive sepsis screen that is not normalizing. Using sepsis screening with this approach does not place undue emphasis on a positive screen that has low positive predictive value; however, it does respect the high negative predictive value of a negative screen, and thus provides a safe approach for the asymptomatic neonate. For the same reasons, the protocol suggests discontinuing antibiotics after 48 hours in asymptomatic infants with positive sepsis screens but negative cultures.

Treatment of neonatal sepsis

The issues discussed above concerning diagnosis of neonatal sepsis are complicated. On the other hand, once the decision is made to initiate treatment for neonatal infection, the clinical decisions are actually more straightforward. The

microbiology of neonatal sepsis drives the choice of antimicrobial agents, the duration of therapy is driven by type and location of the infection, and supportive care is dictated by the physiologic condition of the patient and modern neonatal intensive-care techniques.

Microbiology of neonatal sepsis

The microbiology of infections during the neonatal period comprises a unique spectrum of microorganisms that occur because of perinatal exposure to recto-vaginal maternal flora during labor and delivery (ascending infection), occasional transplacental passage of bacteria from maternal bacteremia, and the interaction of bacteria with the immature neonatal immune system. Perinatally acquired sepsis in the first 3 to 5 days of life is most often caused by group B *Streptococci* (approximately 50%), followed in frequency by *Escherichia coli* (20%), coagulase negative or positive *Staphylococcus* (17%), other enteric gram negative organisms (7%), other *Streptococci* (3%), and various anaerobes (3%) [62]. *Hemophilus influenza* has also been reported. These infections are acquired, for the most part, through the ascending infection route. *Listeria monocytogenes* due to contaminated food products is isolated sporadically and occasionally in point-source epidemic form. *Listeria* causes a septic or flulike syndrome in the mother, and is passed transplacentally to the fetus. Concern for a possible increase in non-GBS neonatal infections in full-term infants in the current era of maternal prophylaxis for GBS has not been borne out in recent surveys of etiologies of early-onset disease, although there is some concern in this regard in the preterm population [62,63].

Choice of antibiotics

Treatment of neonates with suspected sepsis or meningitis should commence as soon as appropriate cultures and intravenous access can be obtained. The initial choice of drugs for empirical treatment is dependent on knowledge of the probable pathogens based on the perinatal history, including any maternal symptoms, cultures, or instrumentation. For instance, if a mother was known to have a gentamicin-resistant gram-negative UTI, one would choose an antibiotic appropriate to that organism. Likewise, if a mother had a history of recent instrumentation such as amniocentesis, one would consider the possibility of coagulase-negative *Staphylococcus*. If there are no mitigating issues in the history, then the septic neonate is likely to have one of the common pathogens listed above. Fortunately, ampicillin plus an aminoglycoside such as gentamicin is a traditional, highly effective combination that treats virtually all common perinatal pathogens [64]. An added advantage is the synergy seen with these two drugs against GBS and *Listeria.* The third-generation cephalosporin cefotaxime may be considered for *H influenza* or for gram-negative meningitis, in view of the superior CSF penetration of cefotaxime over gentamicin. If *Staphylococcus* is suspected, vancomycin should be started until culture results are available.

Table 7
Dose recommendations for treatment of neonatal sepsis in the first week of life

Drug	Post-conceptional age (weeks)	Dose (mg/kg/dose)	Interval (hours)
Ampicillin	All	100	12
Pencillin G	All	100,000 units/kg/dose	12
Gentamicin	≤29	5	48
	30–33	4.5	48
	34–37	4	36
	≥38	4	24
Cefotaxime	All	50	12
Vancomycin	≤29	10–15	18
	30–36	10–15	12
	≥37	10–15	12

Recommended doses for term and near-term neonates of these commonly used antibiotics are listed in Table 7 [65]. These guidelines should be further individualized in the event of renal or hepatic failure. Once an organism is identified and sensitivities are determined, therapy should be changed to the most specific, safest, and least expensive drug or drugs to which the organism is sensitive. Monitoring of serum levels is required for infants receiving full courses of aminoglycosides or vancomycin. Specific drugs of choice and durations of therapy for every bacteria and clinical condition are beyond the scope of this article.

Important microbiologic factors raise specific caveats concerning the treatment of GBS infections and of neonatal meningitis. A small percentage of GBS isolates demonstrate tolerance to penicillins, and infants infected with a tolerant strain have a risk of recurrence after apparently effective treatment [66,67]. Further, GBS strains typically have mean inhibitory capacities (MICs) 4 to 10 times greater than group A strains [68]. Therefore, the dose of ampicillin in neonates with suspected sepsis should be 200 mg/kg/d, or 200,000 units/kg/d of penicillin G. Although other gram-positive bacteria are sensitive to lower doses, GBS is the most common etiology of neonatal sepsis, and therefore all infants with suspected sepsis should be initially covered with this higher dose. Some experts recommend higher doses for treatment of GBS meningitis, up to 300 to 400 mg/kg/d of ampicillin or up to 400,000 units/kg/d of penicillin G. Synergy against GBS between penicillins and aminoglycosides has been demonstrated both in vivo and in vitro [69], so the recommendation is to treat with both a penicillin and an aminoglysoside until the infection is under control, and then continue with a penicillin for 10 days in the case of sepsis, and at least 14 days for GBS meningitis. Recurrent infections, osteomyelitis, or endocarditis require a longer duration of treatment. Patients with bacterial meningitis should have repeat lumbar punctures performed until the CSF is sterile. Gram-negative meningitis requires a 3-week duration of therapy. Gram-negative meningitis may be treated with ampicillin and gentamicin, or with ampicillin and cefotaxime. Although cefotaxime has superior CSF penetration and is preferred by many clinicians, clinical studies have shown equivalent results with either regimen [70].

As for duration of therapy for suspected sepsis unproven by positive cultures, there are few data to support any specific practice. Most clinicians treat suspected sepsis or culture-negative pneumonia for 7 days, although some studies have indicated that a shorter duration of treatment may not carry a risk of recurrent or partially treated infection.

Supportive care and monitoring

Success in diagnosis and treatment of neonatal sepsis is only partially due to the use of appropriate antibiotics. Clinical monitoring of asymptomatic, at-risk infants is paramount in the well-baby nursery so that the early signs and symptoms of sepsis can be recognized and action taken. Once symptomatic, neonates with sepsis should be treated in an intensive-care nursery, with full cardiopulmonary monitoring and availability of ventilatory support. Cardiac output and perfusion are maintained with volume infusions and pressor agents, as needed. Anemia, thrombocytopenia, and disseminated intravascular coagulation are treated with appropriate transfusions. Aggressive nutritional support is needed to combat the catabolic state associated with sepsis.

The role of immunotherapy in augmenting the immature immune system has been extensively studied, but no definitive standards of care have been derived from these studies. WBC transfusions, intravenous immunoglobulin infusions, and treatment with colony-stimulating factors such as granulocyte and granuloctye-macrophage colony-stimulating factor have not been shown to definitely improve outcome in neonates with sepsis.

Monitoring the effectiveness of therapy is primarily a clinical enterprise, and most septic infants improve symptomatically within 24 to 48 hours. With most infections, positive culture sites should be recultured after 48 hours of treatment. The WBC count and I/T ratio may increase dramatically as the infant responds to treatment, and should begin to normalize by 72 hours. CRP is a useful adjunct to monitor the effectiveness of treatment; neonates whose CRP concentrations do not gradually decrease after 48 to 72 hours of therapy may not be responding properly. Infants who do not respond well may have infection with a resistant organism, a focal or metastatic focus infection, a viral illness, or a noninfectious process. The goal of treatment should be to have an asymptomatic infant with negative repeat cultures and normal WBC counts and CRP, all occurring with at least 3 days of antibiotic treatment remaining. Finally, when the infant is discharged from care, appropriate follow-up arrangements should be made to ensure continued progress [64].

Summary

Perinatally acquired bacterial neonatal sepsis is a low-incidence but high-risk disease. Although the incidence of the most common etiology, group B *Streptococcus*, has been reduced by prophylactic strategies, neonatal sepsis is by

no means eradicated, and therefore vigilance must remain high for making the diagnosis. Accurate diagnosis is difficult because the signs and symptoms are difficult to distinguish from other causes of neonatal distress, and definitive diagnostic tests are not available for this disease. In the analysis of each individual patient, the clinician must make a judgment call, taking into consideration the perinatal history, the constellation of signs and symptoms, and the results of both adjunctive and specific diagnostic tests before the diagnosis of neonatal sepsis can be made or excluded. Once that decision is made, knowledge of the specific disease states and clinical algorithms for management aid in formulating a plan of treatment with antimicrobial agents and supportive care.

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