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Culture Negative Sepsis and Systemic Inflammatory Response Syndrome in Neonates

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Educational Gaps

1. The definition of systemic inflammatory response syndrome in neonates has limited clinical utility.
2. There are a number of other causes of the clinical picture commonly treated as culture negative sepsis in premature infants.

Abstract

Sepsis is a common and potentially devastating occurrence in NICUs. Sepsis is defined as the constellation of findings making up the systemic inflammatory response syndrome plus an infection. Newer studies now suggest that treatment of infants who have nonspecific signs of illness with prolonged antibiotics can lead to serious complications. The complexities of practicing medicine in the NICU sometimes limit our ability to secure a diagnosis of culture proven sepsis. The administration of antibiotics until bacterial infection can be reasonably ruled out should occur concurrently with evaluations of other plausible noninfectious diagnoses.

Objectives

After completing this article, readers should understand that:

1. Many infants with systemic inflammatory response syndrome do not have positive bacterial cultures.
2. The most important step to ensure detection of bacteremia in ill-appearing infants is to send an adequate quantity of blood to the laboratory for culture.
3. Continued antimicrobial therapy in the face of negative cultures may be associated with increased infant mortality.
4. Many noninfectious clinical syndromes can cause a sepsislike clinical picture.
5. Continued antimicrobial therapy for presumed occult bacterial infection may reflect an incorrect assessment of the cause of the infant's systemic inflammatory response syndrome symptoms.

Abbreviations

CMV: cytomegalovirus
CNS: central nervous system
CSF: cerebrospinal fluid
EEG: electroencephalogram
ELBW: extremely low birth weight
HR: heart rate
HSV: herpes simplex virus
Ig: immunoglobulin
LOS: late-onset sepsis
NEC: necrotizing enterocolitis
PCR: polymerase chain reaction
PDA: patent ductus arteriosus
SIRS: systemic inflammatory response syndrome
VLBW: very low birthweight

Cases

Infant J is an 8-week-old male who was born at 27 weeks' gestation. He required intubation at delivery and remained on a ventilator for 2 weeks. He was on continuous positive airway pressure for 9 more days, followed by high flow nasal cannula. Over a 2-week period, he was evaluated twice for recurrent episodes of apnea, hypertension, and desaturation.

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Complete blood count with differential and C-reactive protein were normal each time, blood cultures remained negative, and chest and abdominal radiographs did not reveal a cause. He was kept on antibiotics the second time due to other alterations in his behavior, including decreased spontaneous movements. An electroencephalogram (EEG) was obtained that revealed seizure activity. In total he received 9 days of antibiotics before improving after antiseizure therapy was started.

Infant M is a former 26-week gestation twin. For several weeks after birth, he was critically ill with shock and respiratory failure. He required maximal intensive care efforts including vasopressors, inhaled nitric oxide, and high frequency ventilation. He was treated with broad spectrum antibiotics for 14 days after birth and again for 10 days for presumed sepsis and pneumonia, after an acute change in his ventilator and oxygen requirements. Blood cultures were sterile, but endotracheal culture grew *Citrobacter freundii*. Chorioretinitis was noted on his first ophthalmological examination to screen for retinopathy of prematurity at 32 weeks' corrected gestational age. Evaluation for congenital infection revealed positive immunoglobulin (Ig) G and IgM for *Toxoplasma gondii*.

Introduction

The purpose of this article is to characterize the concept of culture-negative sepsis in the premature infant. Our goal is to aid clinicians in both detecting suspected bacterial infection and in evaluating critically ill infants for other possible causes of a sepsislike picture.

Sepsis is a major cause of neonatal morbidity and mortality worldwide, with an estimated 245,000 to over 3 million cases of neonatal sepsis occurring annually in the developing world alone. (1) In the developed world, the majority of neonates admitted to NICUs will be treated for suspected bacterial infection at least once. Perhaps because the mortality rate for severe infections in very low birth weight (VLBW; those born <1,500 g) infants ranges between 20% and 40%, (2) the rates of clinical diagnosis of sepsis, with attendant antibiotic therapy exceed the rates of culture-proven bacterial infection. In the National Institute for Child Health and Human Development Neonatal Research Network, although 50% of VLBW infants were treated with 5 or more days of antibiotics, only 1.9% of VLBW infants had culture-proven infection. (3) Extremely low birth weight (ELBW; those born <1,000 g) infants are at the highest risk for infection. Sixty-five percent experience one or more infections during their NICU stay. However, 39% of these infections are diagnosed based on clinical grounds alone in absence of any positive cultures. (4) Clearly, many infants described as "septic" in the NICU have a clinical syndrome not associated with positive blood cultures.

Definitions of Systemic Inflammatory Response Syndrome, Sepsis, and Septic Shock and Discussion of the Limitations

Before we discuss this clinical problem and the differential diagnosis, the limitations of the definition of sepsis in this population will be addressed. The definitions of systemic inflammatory response syndrome (SIRS), sepsis, and septic shock have been articulated by a multidisciplinary consensus panel of adult specialists, and validated in adult patients. These definitions were modified for pediatric patients, including neonates, by the International Pediatric Sepsis Consensus Conference and were published in 2005 (Table 1). (5) The application and clinical use of these definitions in premature infants has been problematic, due in large part to the tremendous age-dependent variation in vital sign norms, as well as to a multitude of other physiologic differences between adults, children, and neonates. (6)

SIRS is a state of physiologic dysregulation represented by deviations in vital signs and laboratory values. Table 1 details the specific definition used by the consensus panel. This definition of SIRS requires the use of age-based vital sign norms. Unfortunately, in the most premature neonates, establishing normative values for vital signs has been problematic. (7) The definition of SIRS also relies heavily on temperature deviations. Not only are fevers rare in premature neonates, infant's core temperatures are regulated artificially by warmers and incubators. Delving deeper into this issue is beyond the scope of this article. Therefore, the remainder of our discussion on culture negative sepsis will treat the concept of SIRS as a state of physiologic dysregulation represented by deviations in vital signs and laboratory values, as detailed in Table 1. Further, we accept that practicing pediatricians and neonatologists are able to detect tachycardia, bradycardia, tachypnea, and low or high leukocyte counts of concern. Whether a respiratory rate is exactly two SDs outside the norm is less important than the detection of a concerning clinical constellation of abnormal vital signs and laboratory or imaging finding or what is considered a clinically significant change from baseline.

Although definitions of SIRS and sepsis as outlined by the consensus conference offer specific guidelines as to the degree of deviation in vital signs or laboratory results that are considered significant, the concept of infection is vague. Sepsis is SIRS caused by an infection. In neonatology

Table 1. **Definitions of SIRS, Infection and Sepsis Modified for Pediatric Patients Including Neonates**

Systemic inflammatory response syndrome (SIRS): The presence of the findings listed under at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count.
Temperature
• Core temperature of >38.5°C or <36°C
HR
• Tachycardia, defined as a mean HR >2 SD above normal for age
– in the absence of external stimulus, chronic drugs, or painful stimuli
• Otherwise unexplained persistent elevation over a 0.5- to 4-h time period
• Bradycardia, defined as a mean HR <10th percentile for age
– in the absence of external vagal stimulus, β-blocker drugs, or congenital heart disease
• Otherwise unexplained persistent depression over a 0.5-h time period
Respiratory rate
• Mean respiratory rate >2 SD above normal for age
• Mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia
Leukocyte count
• Leukocyte count elevated or depressed for age
• >10% immature neutrophils
Infection: A suspected or proven (by positive culture, tissue stain, or PCR test) infection caused by any pathogen or a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical examination, imaging, or laboratory tests (eg, white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans).
Sepsis: SIRS in the presence of or as a result of suspected or proven infection.

HR=heart rate; PCR=polymerase chain reaction; SIRS=systemic inflammatory response syndrome.

literature and in clinical practice, the evidence used to diagnose infection is varied and inconsistent. As a consequence, almost all episodes of SIRS are presumed to be infectious in etiology. The results of this frequently erroneous presumption are two: antibiotics are used inappropriately and unnecessarily, and a correct diagnosis for the infant's illness is not pursued adequately.

Clinical Concept of Culture Negative Sepsis in the NICU

Given the potentially dire sequelae of infection in premature neonates, the variations in the presentation of neonatal sepsis, and the limitations of blood culture sensitivity, the phenomenon of culture negative sepsis has long been accepted as a diagnosis in the NICU. For the purposes of discussion, the term culture negative sepsis will be applied to situations where an infant has signs and symptoms of SIRS ascribed to a bacterial etiology, but in whom an organism has not been isolated in properly collected cultures of blood, cerebrospinal fluid (CSF), or urine.

The diagnosis of culture negative sepsis has persisted due, in part, to the acceptance in NICU culture of the idea that a clinician can recognize septic patients and somehow distinguish them from the nonseptic ill premature infant. If we were adept at identifying symptomatic sepsis, it should be the case that among symptomatic infants, the rates of true infection versus the rates of antibiotic treatment would be more similar than in asymptomatic patients. In one series, the rate of infection in asymptomatic infants was 0.9%, whereas the rate of treatment was 15.6%. (8) Similarly, a review of observational studies of neonatal sepsis revealed that among symptomatic infants 2.3% were infected and 38.2% were treated, and for critically ill infants only 10.4% were infected, whereas 78.4% were treated. (8) This study illustrates that the clinical presentation can only be minimally relied upon to bolster our convictions of sepsis if we are using positive blood culture as the gold standard in our sepsis diagnosis.

The outcomes for infants who fit this syndrome of culture negative sepsis have been compared with infants who experienced confirmed bacterial sepsis and infants without sepsis, and the findings suggest that infants treated for sepsis without an identified source go on to have adverse outcomes similar to the patients who have confirmed sepsis.

It has been shown in a number of studies that infants who experience sepsis go on to have higher rates of neurodevelopmental impairment. (4)(9)(10)(11) When infants who have confirmed bacterial sepsis are compared with infants who have no sepsis and infants who have culture negative sepsis, the infants who have culture negative sepsis have outcomes similar to culture proven sepsis; they have statistically significantly higher rates of impairment as evaluated with the Bayley Scales of Infant Development, cerebral palsy, and hearing and vision impairment than uninfected infants at 18 to 22 months' corrected age. (4) Why might it be that infants who have

negative bacterial cultures, who were evaluated for infection in the same way as their counterparts who have positive cultures, go on to have similar outcomes? Culture negative sepsis patients have outcomes more similar to proven infection patients than to those patients who had no infection. Wynn et al (12) showed that infants evaluated for very late onset sepsis (at >120 days after birth) had approximately five times the risk of death compared with infants still hospitalized at that age who had no very late sepsis evaluation. One possibility is that the clinical instabilities and morbidities that put an infant at risk for infection (intubation, central lines, immune dysfunction such as neutropenia, and intolerance of enteral feedings) also make an infant manifest physiologic instability that mimics SIRS and sepsis. It is perhaps the case that regardless of the acquisition of infection, due to multifactorial complications, these infants would have gone on to be more likely to die or be impaired. It is also possible that nonbacterial causes of SIRS still generate a cytokine storm, which places the infant at increased risk for mortality and adverse outcomes.

Sensitivity of Bacterial Blood Cultures

Although blood culture systems have improved in recent years, their sensitivity for diagnosis of bloodstream infection is still dependent upon the volume of blood used to inoculate the culture medium. (13)(14)(15)(16) Clinicians have relied on the belief that neonates and young children, when bacteremic, have higher bacterial loads. These high bacterial loads in bacteremic infants and children are cited to justify the use of smaller blood volumes for inoculation of blood culture bottles. However, this noting that infants and children have consistently higher levels of bacteremia is not consistently supported when studied. Inoculum volumes of less than 0.5 mL do not reliably detect bacteremia at levels below 4 colony forming units per mL. (14) Low level bacteremia is possible in the NICU where infants are often exposed to multiple courses of antibiotics, including in utero antibiotics. Antibiotic treatment within 4 days of a bacteremic episode has been associated with false-negative blood cultures and low level bacteremia. (17) Depending on gestational age and body weight, an ELBW or VLBW infant can be expected to have circulating blood volumes of as little as 60 mL, and certainly less than 200 mL, making the collection of serial high volume blood cultures impractical. However, it is possible to improve upon current practice where the average volume of blood submitted for aerobic culture from neonatal patients is less than 1 mL. (18)(19) There is general consensus that at least a single blood culture of 1 mL should be collected if bloodstream infection is suspected and has a sensitivity for detection of bacteremia of approximately 90%. (20) An adequate blood culture sample is twice as likely to yield a noncontaminant positive result. (18) Given the low likelihood of anaerobic infections (except in specific clinical scenarios), many experts recommend deferring routine anaerobic culture in favor of using a larger aliquot of blood to inoculate a single aerobic culture bottle. Inoculating the full milliliter into a single aerobic bottle will have a higher yield for most patients. (21)

Risks and Benefits of Antibiotic Therapy

If there were no adverse effects of antibiotic therapy, eliminating the practice of treating culture negative sepsis with prolonged empiric antibiotics would be of little consequence. In fact, antimicrobials lend themselves to prolonged use with little scrutiny, in part, because they do have so few immediately apparent adverse effects. Unfortunately, the consequences of unnecessary antibiotic therapy can be severe and delayed in their presentation. Infection with resistant organisms, fungal infections, necrotizing enterocolitis (NEC), late-onset sepsis (LOS), and death have all been linked to prolonged empiric antibiotic administration. The intestinal microbiome is increasingly being recognized as an important contributor to health and disease states in neonates and children. Alteration of the intestinal microbiome, including reduced microbial diversity and selection for antibiotic resistant strains has been identified within days of the initiation of antibiotic therapy. (22) Greater than 5 days of initial empiric antibiotic administration in VLBW infants has been independently associated with LOS and death, and with the composite outcome of LOS, death, or NEC, with a number needed to harm of only 3. (23) Among ELBW infants, similar findings have been reported, with the odds of death, NEC, and death or NEC being increased in infants who received greater than 5 days of early antibiotics with sterile cultures. (24) Both groups revealed that each day of antibiotics increased the odds of bad outcomes. These are retrospective reports, but the repeated finding of the independent association between prolonged antibiotic use and serious complications is concerning.

Although fungal infections are a potential complication of antibiotic therapy in all patient populations, among premature neonates, the evidence for antibiotic associated candidiasis is strong and has potentially dire consequences. Previous antibiotic use, especially third generation cephalosporin exposure, is among the risk

factors for invasive candidiasis in VLBW infants. (25) (26) Increasing numbers of antibiotics and antibiotic days have been found to correlate with the risk of candidemia. (27) The incidence of late onset candidemia in VLBW infants varies, and has been found to be as high as 20% in ELBW infants. In the National Institute of Child Health and Development Neonatal Research Network, *Candida* was the third most common organism isolated in cases of LOS. (3) The mortality rate for infections with *Candida albicans* among VLBW infants is approximately 30%. (3)(26)(27)(28) Importantly, the neurodevelopmental outcome of infants who have survived invasive candidiasis is consistently worse than otherwise similar former premature infants. (29)(30)(31) There is substantial evidence that prolonged antibiotic exposure increases an infant's risk for future *Candida* infections, and invasive candidiasis is associated with poor long-term outcomes. Even a small decrease in the rate of unnecessary antibiotic exposure could have a substantial impact on the rate of late infectious complications in NICUs. We should aim to minimize the adverse effects of unnecessary antibiotic use in the same way that we evaluate the need for central lines and urinary catheters to prevent central line infection and urinary tract infections.

Causes of Culture-Negative SIRS or a Septic Appearance in the Premature Newborn

The potential causes of culture-negative SIRS in the newborn are myriad. Removing the unknowable (but probably small) percentage of infants who may truly have a bacterial infection that cannot be successfully detected by adequate culture techniques, and accepting that a certain number of infants have a clinically detectable

Table 2. Infectious Causes of Culture Negative SIRS in Premature Infants

Suspected Diagnosis	Clinical Associations	Recommended Diagnostic Tests
Bacterial infection with fastidious or anaerobic organism	Recent surgical procedure or invasive radiologic study	Anaerobic blood cultures
Enterovirus infection	Summer, contacts with gastrointestinal symptoms	Enterovirus PCR from nasopharynx, CSF, and blood. Viral culture from nasopharynx
Herpes simplex virus infection	Vesicular rash, encephalopathy, seizures, and transaminitis	HSV PCR from CSF (for CNS disease) and blood (for disseminated disease). HSV culture from eyes, mouth, perirectal area, and any lesions
CMV infection	Intrauterine growth restriction, rash, thrombocytopenia, fever, and transaminitis	CMV PCR from blood and urine; CMV culture from urine
Influenza	Respiratory symptoms, fall and winter	Influenza virus PCR or culture from nasopharynx
Adenovirus	Fever, rash	Adenovirus PCR or culture from nasopharynx
Parainfluenza	Respiratory symptoms, fall and winter	Parainfluenza virus PCR or culture from nasopharynx
Toxoplasmosis	Retinitis	IgG, IgM, IgE, and IgA testing of serum and cerebral spinal fluid by a reference laboratory, retinal examination, and brain imaging
Fungemia	Sepsis, shock, hyperglycemia, and thrombocytopenia	Multiple blood cultures, including cultures from central line if present
Syphilis	Rhinitis, hepatomegaly, rash, lymphadenopathy, and placental pathology	Review maternal RPR, infant RPR (infant should be fourfold higher compared with maternal RPR)
Meningitis	Lethargy, encephalopathy, apnea, seizures, and shock	Lumbar puncture for bacterial culture, cell count with differential, protein, glucose. Consider HSV and enterovirus PCR

CMV=cytomegalovirus; CNS=central nervous system; CSF=cerebrospinal fluid; HSV=herpes simplex virus; Ig=immunoglobulin; PCR=polymerase chain reaction; RPR=rapid plasma reagin; SIRS=systemic inflammatory response syndrome.

aberration in vital signs or behavior attributable to pathology when none exists, we are left with patients who have a potentially diagnosable condition other than bacterial sepsis. Tables 2–5 outline some of these potential diagnoses and recommendations for their diagnosis.

Selected Differential Diagnoses of Sepsis

The differential diagnosis for SIRS is vast and the evaluation for each patient will be dictated by individual clinical presentation. Here, we discuss the presentation and basic investigation for a small subset of the diagnoses that are relatively common, possible to definitively diagnose, and often have indistinct clinical presentations. Refer to Tables 2–5 for information about diagnoses not discussed here.

Seasonal Viral Infections

Despite improved infection control programs in most hospitals, the transmission of viral pathogens from visitors or hospital staff to hospitalized neonates remains common. Outbreaks of norovirus, adenovirus, influenza, respiratory syncytial virus, and other viruses in NICUs have been reported. Rapid polymerase chain reaction (PCR)-based tests for many viruses are now widely available and should be sent from an ill infant without an identified source of infection. Many hospitals now perform respiratory viral panels that should be performed for ventilated infants who have respiratory compromise. Enteroviral infections should be considered, particularly in late summer and early fall months.

Neonatal Herpes Simplex Virus Infection

The majority of cases of neonatal herpes simplex virus (HSV) infection are acquired perinatally from a mother with active, although often asymptomatic, genital infection. Neonatal HSV has three possible manifestations (skin, eye, mouth disease, central nervous system [CNS] disease, and disseminated disease) with CNS and disseminated disease being the most serious and likely to be confused with culture negative sepsis. Disseminated disease usually presents in the first week after birth with severe illness, including fever, progressive pneumonitis, meningoencephalitis, liver failure, thrombocytopenia, and neutropenia. CNS disease may present at any time in the first 6 weeks after birth and may have any of the symptoms associated with meningoencephalitis (seizures, lethargy, apnea, irritability, or poor feeding). Distinguishing findings in HSV CNS disease include CSF mononuclear pleocytosis and an abnormal EEG. Empiric treatment with acyclovir is warranted for any neonate who has severe early sepsis or aseptic meningitis or signs and symptoms of meningoencephalitis without an identified bacterial cause until HSV testing is negative (Table 2).

Cytomegalovirus

The rate of congenital cytomegalovirus (CMV) infection is approximately 1%, and the majority of congenital infections are asymptomatic in the neonatal period. The classic syndrome associated with congenital CMV, including blueberry muffin rash, hepatosplenomegaly, thrombocytopenia, growth restriction, periventricular calcifications, and retinitis is distinct and recognizable. However, premature infants may present with symptoms similar to bacterial sepsis, including apnea, bradycardia,

Table 3. Cardiopulmonary Causes of Culture Negative SIRS in Premature Infants

Suspected Diagnosis	Clinical Associations	Recommended Diagnostic Tests
Structural cardiac disease	Cyanosis, acidosis, and shock	Cardiology consultation, echocardiogram
PDA	Widened pulse pressure, desaturations, and acidosis	Echocardiogram
Pulmonary hypertension	Cyanosis, right to left shunting at PDA	Echocardiogram
Pulmonary hypoplasia	Respiratory failure, history of oligohydramnios, premature prolonged rupture of membranes	No definitive test
Surfactant protein deficiency	Severe and prolonged symptoms similar to RDS	Genetic testing, lung biopsy
BPD	Desaturations, increased oxygen requirement, and increased ventilatory requirement	No definitive test. Chest radiograph with chronic changes consistent with BPD and possibly superimposed variable atelectasis

BPD=bronchopulmonary dysplasia; PDA=patent ductus arteriosus; RDS=respiratory distress syndrome; SIRS=systemic inflammatory response syndrome.

Table 4. Neurologic and Gastrointestinal Causes of Culture Negative SIRS in Premature Infants

Suspected Diagnosis	Clinical Associations	Recommended Diagnostic Tests
Neurologic		
Intraventricular hemorrhage	Apnea, lethargy, acidosis, and hyperglycemia	Cranial ultrasound, acute drop in hematocrit
Seizures	Subtle or other abnormal (eg, clonic) movements, vital sign variability, and encephalopathy	EEG, neurology consultation
Subgaleal hemorrhage	Signs of hypovolemia, boggy expanding scalp	Head CT scan, acute drop in hematocrit
Intracranial hemorrhage	Seizures, apnea, abnormal tone, and abnormal neurologic examination	Cranial ultrasound, head CT scan
Opiate withdrawal	Jitters, seizures, inconsolability, tachypnea, fever, diarrhea. Maternal history of drug exposure, or history of at least 3 d of continuous sedation for older infant	No definitive test. Urine drug screen if infant has not voided more than once, meconium or umbilical cord drug screen
Gastrointestinal		
Necrotizing enterocolitis	Abdominal distention, discoloration, tenderness, hematochezia, shock, thrombocytopenia, and acidosis	Abdominal imaging, exploratory laparotomy
Malrotation	Bilious emesis, poor feeding, abdominal distention. Shock and acidosis if with volvulus	Abdominal radiograph may have normal or abnormal gas pattern. Upper GI to make diagnosis
Bowel obstruction (meconium plug syndrome, meconium ileus, Hirschsprung disease)	Abdominal distention, poor feeding, bilious emesis, and delayed passage of stool	Contrast enema, rectal biopsy for Hirschsprung disease; sweat test with meconium ileus

CT=computed tomography; EEG=electroencephalogram; GI=gastrointestinal; SIRS=systemic inflammatory response syndrome.

abdominal distention, hypotonia, and lethargy. CMV is diagnosed by identification of virus in body fluids, commonly urine or pharyngeal secretions. After 3 weeks after birth, it is difficult to determine if CMV isolated is due to congenital infection or postnatal acquisition. CMV infection acquired in the postnatal period can cause illness in premature infants, with a range of signs and symptoms including neutropenia, thrombocytopenia, lymphocytosis, hepatosplenomegaly, hepatitis, pneumonitis, colitis, and even fulminant sepsis. (32)(33)(34)

Other Congenital Infections

Many congenital infections are either asymptomatic or create a constellation of findings that are not commonly confused with bacterial sepsis. There are a few exceptions. Early congenital syphilis can present at age 1 to 2 months with snuffles, hepatomegaly, rash, lymphadenopathy, thrombocytopenia, anemia, meningitis, and pneumonia alba. Hepatitis B is usually asymptomatic in the neonatal period but may present with rash, hepatomegaly, or transaminitis. Toxoplasmosis has classic intracranial and ophthalmologic findings but may also have jaundice, seizures, hepatosplenomegaly, anemia, and lymphadenopathy. It may be worthwhile to consider further investigation for congenital infection in neonates, like infant M from case 2, if they have some of these findings that are not classically seen in bacterial sepsis, especially hepatomegaly, anemia, lymphadenopathy, and if calcifications are found on routine cranial ultrasound screening.

Patent Ductus Arteriosus

The ductus arteriosus is a physiologic shunt that causes symptoms in premature infants when it fails to close resulting in persistent pulmonary overcirculation due to left to right shunting. One third of VLBW infants and half of ELBW infants can be expected to have a patent ductus arteriosus (PDA) that is symptomatic. (35) Symptoms of a PDA can be similar to sepsis both early and late in the infant's stay. A PDA with significant or labile shunting can lead to perturbations in oxygen saturation, respiratory rate, and blood pressure. This can often lead to an infant having "spells" that can mimic the apnea and bradycardia that are sometimes a harbinger of sepsis. The physical examination is an unreliable screen for the

Table 5. Metabolic and Autoinflammatory Causes of Culture Negative SIRS in Premature Infants

Suspected Diagnosis	Clinical Associations	Recommended Diagnostic Tests
Metabolic		
Galactosemia	Jaundice, vomiting, irritability, lethargy, hepatomegaly. Associated with *E coli* urinary tract infections and urosepsis	Newborn screen, urinalysis for evidence of infection and reducing substances. RBC galactose-1-phosphate uridyl transferase activity in conjunction with consultation with metabolic specialist
Organic acidemias	Toxic encephalopathy, seizures, abnormal tone, poor feeding, vomiting, coma, acidosis, elevated liver function tests, neutropenia, and hyperammonemia	Urine organic acids, plasma amino acids, and blood ammonia level
Urea cycle disorders	Irritability, poor feeding, vomiting, seizures, hypotonia, respiratory distress, and coma	Plasma amino acids, blood ammonia level, and urine orotic acid
Congenital adrenal hyperplasia	Hyponatremia, hyperkalemia, failure to thrive, adrenal crisis with hypoglycemia and shock	Newborn screening, 17-hydroxyprogesterone level
Other inborn errors of metabolism	Lethargy, poor appetite, abdominal pain, vomiting, failure to thrive, jaundice, seizures, encephalopathy, acidosis, and hyperammonemia	Newborn screening, metabolic disease specialist consultation
Hypoglycemia	Jitters, seizures, and lethargy	Serum glucose
Autoinflammatory diseases (39)		
Disorders of IL-1-β activation, cytokine signaling disorders, NF-κ B activation, macrophage activation	Periodic or episodic fevers in conjunction with varied findings, commonly urticarialike rash, arthralgias, arthritis, pleuritis, lymphadenopathy. Some syndromes have characteristic physical features	Consultation with a rheumatologist, immunologist, or other specialist

IL=interleukin; RBC=red blood cell; SIRS=systemic inflammatory response syndrome.

presence of a significant PDA, and any infant who has symptoms compatible with PDA should be screened with an echocardiogram.

Seizures

Seizures are more common in premature neonates than the general population and are more likely to have a nonclassical presentation. The infant in our case has a very common story among premature neonates diagnosed with seizures. In one series of EEGs from a tertiary care NICU, epileptiform activity was identified in 3.9% of preterm infants. Subtle clinical findings were the most common presentation, as opposed to the observation of overt tonic or clonic movements. (36)(37) When EEGs are performed prospectively on premature infants, epileptiform activity is identified less frequently; in only 2 of 333 patients in one series. (38) It is reasonable to consider seizures in the differential diagnosis of any former preterm infant who has subtle signs of illness, especially including changes in heart rate (HR), blood pressure, and apnea. An EEG is a relatively quick and noninvasive test at most tertiary care centers.

Metabolic Disorders

The incidence of metabolic diseases as a group has been estimated to be approximately 1 in 1,000 neonates. (36) Inborn errors of metabolism that present in the newborn period often have nonspecific features. In general, the majority of metabolic disorders that present in the newborn period will have as part of their constellation of symptoms one or more of the following: increased anion gap metabolic acidosis, hypoglycemia, and hyperammonemia.

Lactic acidosis may be a part of metabolic conditions but may also result from other illnesses that result in compromised perfusion. In such cases, the lactic acidosis quickly resolves once perfusion is restored. If the anion gap remains elevated despite correcting for lactic acidosis, other sources of anions such as organic acids and ketones and their causative metabolic disorder may be the etiology of the acidosis. Findings such as ketones or reducing substances on urinalysis may also point to a metabolic condition.

Conclusions

Although SIRS is a common and serious illness among VLBW and ELBW infants, most infants who have SIRS have negative blood cultures. A clinical evaluation, including properly collected blood cultures of adequate volume, is highly sensitive for detection of bacteremia. Certainly, the prompt initiation of empiric antimicrobial therapy to an ill appearing neonate is entirely reasonable. If the bacterial cultures demonstrate no growth after 48 hours, then the antibiotics should be stopped. However, the facility with which we have become accustomed to treating culture negative sepsis with prolonged antibiotics poses real dangers to our patients. Furthermore, the immediate presumption that patients who have a SIRS-like clinical syndrome have bacterial sepsis may preclude timely and accurate diagnosis of other treatable causes of SIRS.

Premature infants potentially have a multitude of reasons for physiologic instability during their NICU course, which should be fully investigated in any infant ill enough to warrant the initiation of antibiotics, especially when there is no clinical improvement after 48 hours of empiric antibiotic therapy. Finally, although the decision to discontinue empiric antibiotics for patients who have negative blood cultures is difficult for all practitioners, new data indicate that excessive antibiotic therapy carries significant immediate and long-term costs. As a consequence, the need to obtain and then trust well-collected blood cultures is high, as is the need to identify nonbacterial causes of SIRS in infants.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical manifestations, laboratory features, and differential diagnosis of neonatal sepsis.
- For antibiotics used commonly in the neonate, know indications for their use, clinical effects, pharmacokinetics, adverse effects, and toxicity.

References

1. Darmstadt GL, Zaidi AKM, Stoll BJ. Neonatal infections: a global perspective. In: Remington JS, Klein JO, Wilson CB, Nizet V, Maldonado YA, eds. *Infectious Diseases of the Fetus and Newborn Infant*. 7th ed. Philadelphia, PA: Elsevier; 2011:24–51
2. Haque K. Definitions of bloodstream infection in the newborn. *Pediatr Crit Care Med*. 2005;6(suppl 3):S45–S49
3. Stoll BJ, Hansen NI. Infections in VLBW infants: studies from the NICHD Neonatal Research Network. *Semin Perinatol*. 2003; 27(4):293–301
4. Stoll BJ, Hansen NI, Adams-Chapman I, et al; National Institute of Child Health and Human Development Neonatal Research Network. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. *JAMA*. 2004;292(19):2357–2365
5. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):2–8
6. Hofer N, Müller W, Resch B. Systemic inflammatory response syndrome (SIRS) definition and correlation with early-onset bacterial infection of the newborn. *Arch Dis Child Fetal Neonatal Ed*. 2010;95(2):F151
7. Kent AL, Meskell S, Falk MC, Shadbolt B. Normative blood pressure data in non-ventilated premature neonates from 28-36 weeks gestation. *Pediatr Nephrol*. 2009;24(1):141–146
8. Escobar GJ. What have we learned from observational studies on neonatal sepsis? *Pediatr Crit Care Med*. 2005;6(suppl 3): S138–S145
9. Schlapbach LJ, Aebischer M, Adams M, et al; Swiss Neonatal Network and Follow-Up Group. Impact of sepsis on neurodevelopmental outcome in a Swiss National Cohort of extremely premature infants. *Pediatrics*. 2011;128(2):e348–e357
10. van der Ree M, Tanis JC, Van Braeckel KN, Bos AF, Roze E. Functional impairments at school age of preterm born children with late-onset sepsis. *Early Hum Dev*. 2011;87(12):821–826
11. Vohr BR, Wright LL, Poole WK, McDonald SA. Neurodevelopmental outcomes of extremely low birth weight infants <32 weeks' gestation between 1993 and 1998. *Pediatrics*. 2005;116(3):635–643
12. Wynn JL, Benjamin DK Jr, Benjamin DK, Cohen-Wolkowiez M, Clark RH, Smith PB. Very late onset infections in the neonatal intensive care unit. *Early Hum Dev*. 2012;88(4):217–225
13. Buttery JP. Blood cultures in newborns and children: optimising an everyday test. *Arch Dis Child Fetal Neonatal Ed*. 2002;87 (1):F25–F28
14. Schelonka RL, Chai MK, Yoder BA, Hensley D, Brockett RM, Ascher DP. Volume of blood required to detect common neonatal pathogens. *J Pediatr*. 1996;129(2):275–278
15. Chu A, Hageman JR, Schreiber MD, Alexander K. Antimicrobial therapy and late onset sepsis. *NeoReviews*. 2012;13(2):e94–e102
16. Bhatti M, Chu A, Hageman JR, Schreiber M, Alexander K. Future directions in the evaluation and management of neonatal sepsis. *NeoReviews*. 2012;13(2):e103–e110
17. Kellogg JA, Ferrentino FL, Goodstein MH, Liss J, Shapiro SL, Bankert DA. Frequency of low level bacteremia in infants from birth to two months of age. *Pediatr Infect Dis J*. 1997;16(4):381–385
18. Connell TG, Rele M, Cowley D, Buttery JP, Curtis N. How reliable is a negative blood culture result? Volume of blood submitted for culture in routine practice in a children's hospital. *Pediatrics*. 2007;119(5):891–896

19. Neal PR, Kleiman MB, Reynolds JK, Allen SD, Lemons JA, Yu PL. Volume of blood submitted for culture from neonates. *J Clin Microbiol.* 1986;24(3):353–356
20. Nizet V, Klein JO. Bacterial sepsis and meningitis. In: Remington JS, Klein JO, Wilson CB, Nizet V, Maldonado YA, eds. *Infectious Diseases of the Fetus and Newborn Infant.* 7th ed. Philadelphia, PA: Elsevier; 2011:222–275
21. Zaidi AK, Knaut AL, Mirrett S, Reller LB. Value of routine anaerobic blood cultures for pediatric patients. *J Pediatr.* 1995;127(2):263–268
22. Johnson CL, Versalovic J. The human microbiome and its potential importance to pediatrics. *Pediatrics.* 2012;129(5):950–960
23. Kuppala VS, Meinzen-Derr J, Morrow AL, Schibler KR. Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. *J Pediatr.* 2011;159(5):720–725
24. Cotten CM, Taylor S, Stoll BJ, et al; NICHD Neonatal Research Network. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. *Pediatrics.* 2009;123(1):58–66
25. Weese-Mayer DE, Fondriest DW, Brouillette RT, Shulman ST. Risk factors associated with candidemia in the neonatal intensive care unit: a case-control study. *Pediatr Infect Dis J.* 1987;6(2):190–196
26. Bendel CM. Candidiasis. In: Remington JS, Klein JO, Wilson CB, Nizet V, Maldonado YA, eds. *Infectious Diseases of the Fetus and Newborn Infant.* 7th ed. Philadelphia, PA: Elsevier; 2011:1055–1078
27. Saiman L, Ludington E, Pfaller M, et al; for The National Epidemiology of Mycosis Survey Study Group. Risk factors for candidemia in Neonatal Intensive Care Unit patients. The National Epidemiology of Mycosis Survey study group. *Pediatr Infect Dis J.* 2000;19(4):319–324
28. Spiliopoulou A, Dimitriou G, Jelastopulu E, Giannakopoulos I, Anastassiou ED, Christofidou M. Neonatal intensive care unit candidemia: epidemiology, risk factors, outcome, and critical review of published case series. *Mycopathologia.* 2012;173(4):219–228
29. Benjamin DK Jr, Stoll BJ, Fanaroff AA, et al; National Institute of Child Health and Human Development Neonatal Research Network. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. *Pediatrics.* 2006;117(1):84–92
30. Friedman S, Richardson SE, Jacobs SE, O'Brien K. Systemic Candida infection in extremely low birth weight infants: short term morbidity and long term neurodevelopmental outcome. *Pediatr Infect Dis J.* 2000;19(6):499–504
31. Lee BE, Cheung PY, Robinson JL, Evanochko C, Robertson CM. Comparative study of mortality and morbidity in premature infants (birth weight, < 1,250 g) with candidemia or candidal meningitis. *Clin Infect Dis.* 1998;27(3):559–565
32. Simpson JH, Lynch R, Grant J, Alroomi L. Reducing medication errors in the neonatal intensive care unit. *Arch Dis Child Fetal Neonatal Ed.* 2004;89(6):F480–F482
33. Stavroudis TA, Miller MR, Lehmann CU. Medication errors in neonates. *Clin Perinatol.* 2008;35(1):141–161
34. Fischer C, Meylan P, Bickle Graz M, et al. Severe postnatally acquired cytomegalovirus infection presenting with colitis, pneumonitis and sepsis-like syndrome in an extremely low birthweight infant. *Neonatology.* 2010;97(4):339–345
35. Hamrick SEG, Hansmann G. Patent ductus arteriosus of the preterm infant. *Pediatrics.* 2010;125(5):1020–1030
36. Enns GM, Packman S. Diagnosing inborn errors of metabolism in the newborn: laboratory investigations. *NeoReviews.* 2001;2(8):e192–e200
37. Scher MS, Aso K, Beggarly ME, Hamid MY, Steppe DA, Painter MJ. Electrographic seizures in preterm and full-term neonates: clinical correlates, associated brain lesions, and risk for neurologic sequelae. *Pediatrics.* 1993;91(1):128–134
38. Hayashi-Kurahashi N, Kidokoro H, Kubota T, et al. EEG for predicting early neurodevelopment in preterm infants: an observational cohort study. *Pediatrics.* 2012;130(4):e891–e897
39. Lionetti G, Lapidus S, Goldbach-Mansky R, Frankovich J. Autoinflammatory diseases in the neonate: mimickers of neonatal infections. *NeoReviews.* 2010;11(10):e566–e577

NeoReviews Quiz
New minimum performance level requirements

Per the 2010 revision of the American Medical Association (AMA) Physician's Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for *AMA PRA Category 1 Credit*™. In order to successfully complete 2013 *NeoReviews* articles for *AMA PRA Category 1 Credit*™, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

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1. A term infant has been receiving treatment for meconium aspiration and persistent pulmonary hypertension. He is now 8 days old and had been showing some signs of improvement but has had clinical deterioration over the past several hours. Which of the following sets of characteristics would lead to the specific diagnosis of systemic inflammatory response syndrome (SIRS)?
   A. The patient has temperature of 38.0°C, otherwise unexplained tachycardia, and white blood count in normal range but showing 7% immature neutrophils. The respiratory rate is normal.
   B. The temperature is 40°C, the heart rate and respiratory rates are normal, and there is an elevated leukocyte count with 25% immature neutrophils.
   C. The patient was recently extubated but is now requiring re-intubation and packed red blood cell transfusion. Heart rate has been elevated for the past 4 hours. Temperature and leukocyte count are normal.
   D. The temperature is 36.2 °C, the leukocyte count is normal, the mean heart rate and respiratory rate are both >2 SD above normal for age.
   E. The patient's blood culture is positive for Gram negative rods. The patient is requiring dopamine for hypotension. Heart rate and respiratory rate are elevated. Temperature and leukocyte count are normal.

2. A 3-week-old, 28-weeks'-gestational-age male has had increasing apnea and bradycardia. He requires re-intubation and placement on mechanical ventilation. He is hypotensive and has elevated white blood cell count. A blood culture is obtained and he is started on antibiotics. Three days later, his blood culture shows no growth. Which of the following is true regarding blood cultures?
   A. As blood cultures are so often negative in the setting of neonatal sepsis, their utility is questionable and sepsis should be treated on the basis of clinical judgment, without reliance on culture.
   B. As neonatal sepsis is likely to have a high bacterial load compared with adults and young children, cultures are invariably positive even with collection of small amounts of blood <0.5 mL.
   C. When there is limited blood obtained from a patient in an evaluation for bacterial sepsis such as in this patient's case, there should be priority for obtaining an anaerobic culture, as aerobic culture is unlikely to yield a useful finding.
   D. A general rule is that 0.5 mL of blood sent for culture will result in a sensitivity of bacterial detection of 95%.
   E. If this patient had received antibiotic treatment within the past several days prior to obtaining the culture, there may be reduced levels of bacteremia, leading to a false-negative culture.

3. The parents of a 30-weeks'-gestational-age female have been reading about the dangers of infection in premature infants and request that their infant receive antibiotics continuously for the first month of age regardless of any testing or clinical symptoms. Which of the following statements about potential benefits or adverse effects of antibiotic therapy in premature infants is true?
   A. Although there may be short-term effects of antibiotics, their use is unlikely to have any long-term adverse effects if used for less than 2 weeks' duration.
   B. More antibiotic therapy is associated with reduced length of stay.
   C. There may be benefit of routine antibiotic therapy in promoting "good" bacterial growth in the intestines.
   D. Antibiotic use is associated with fungal infections, particularly candidiasis.
   E. There is no real short- or long-term adverse effect of such antibiotic use, although there may be cost considerations.

4. A 28-weeks'-gestational-age female has thrombocytopenia, anemia, and hepatomegaly. Which of the following is true regarding congenital infections that may present with sepsislike symptoms in premature infants?
   A. As antibiotics are the mainstay of treatment for congenital infections, the distinction between bacterial versus other congenital infections is mainly for prognostic purposes.
   B. Congenital syphilis may present at 1–2 months with these symptoms, and also with pneumonia or meningitis.
   C. The majority of cases of neonatal herpes simplex virus infection occur from health care worker associated contact with patients.
   D. In virtually all cases, herpes simplex virus infection manifests in the first 5 days after birth.
   E. Cytomegalovirus infection in neonates is only a problem for congenital infections as an infection acquired postnatally is always asymptomatic.

5. An 8-week-old, 28-weeks'-gestational-age male is noted to have increased apnea and desaturation events, and episodes of hypertension. Complete blood cell count and C-reactive protein are normal. A blood culture obtained the previous day shows no growth. An electroencephalogram (EEG) is performed. Which of the following is true regarding seizures in premature infants?
   A. As EEGs are unreliable in premature infants, and as this patient's symptoms are suspicious for sepsis, the patient should receive at least 7 days of antibiotic therapy regardless of culture results.
   B. The most common findings in seizures in premature infants are likely to be subtle clinical findings, and not overt tonic or clonic movements.
   C. Seizures are very commonly found on EEG in premature infants at rates of 30%–50% for very low birth weight infants.
   D. Seizures are more rare in premature infants than the general population but tend to have a classic presentation of tonic-clonic activity.
   E. Treating this patient for sepsis with antibiotics will likely lead to reduced seizure activity.

Culture Negative Sepsis and Systemic Inflammatory Response Syndrome in Neonates

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