Published in final edited form as:

Pediatr Clin North Am. 2013 April ; 60(2): 367–389. doi:10.1016/j.pcl.2012.12.003.

Neonatal Infectious Diseases: Evaluation of Neonatal Sepsis

Andres Camacho-Gonzalez, MD, MSc.,

Assistant Professor of Pediatrics, Emory School of Medicine-Children's Healthcare of Atlanta, 2015 Uppergate Drive, Suite 500, Atlanta, GA 30322, P:404-727-5642, F:404-727-9223

Paul W. Spearman, MD, and

Nahmias-Schinazi Professor and Chief, Pediatric Infectious Diseases, Vice Chair for Research, Emory Department of Pediatrics, Emory University, Chief Research Officer, Children's Healthcare of Atlanta, Georgia, 2015 Uppergate Drive, Suite 500, Atlanta, GA 30322, P:404-727-5642, F: 404-727-9223

Barbara J. Stoll, MD

George W. Brumley, Jr. Professor and Chair of the Department of Pediatrics, Medical Director of Children's Healthcare of Atlanta at Egleston, President of the Emory-Children's Center, 2015 Uppergate Drive, Suite 200, Atlanta, GA 30322

Andres Camacho-Gonzalez: acamac2@emory.edu; Paul W. Spearman: paul.spearman@emory.edu; Barbara J. Stoll: Barbara.Stoll@oz.ped.emory.edu

Synopsis

Neonatal sepsis remains a feared cause of morbidity and mortality in the neonatal period. Maternal, neonatal and environmental factors are associated with risk of infection, and a combination of prevention strategies, judicious neonatal evaluation and early initiation of therapy are required to prevent adverse outcomes. The following chapter reviews recent trends in epidemiology, and provides an update on risk factors, diagnostic methods and management of neonatal sepsis.

Keywords

Neonatal sepsis; immature immunity; early and late onset disease; Biological markers; treatment

Epidemiology of neonatal sepsis

Neonatal sepsis remains a feared and serious complication, especially among very low birthweight (VLBW) preterm infants. Neonatal sepsis is divided into early- and late-onset sepsis, based on timing of infection and presumed mode of transmission. Early-onset sepsis (EOS) is defined by onset in the first week of life, with some studies limiting EOS to infections occurring in the first 72 hours due to maternal intrapartum transmission of invasive organisms. Late-onset sepsis is usually defined as infection occurring after 1 week and is attributed to pathogens acquired postnatally. Risk factors for neonatal sepsis include maternal factors, neonatal host factors, and virulence of infecting organism (Table 1).

In the United States, widespread acceptance of intrapartum antibiotic prophylaxis (IAP) to reduce vertical transmission of Group B Streptococcal (GBS) infections in high-risk women has resulted in a significant decline in rates of EOS GBS infection.¹ Overall, it is not believed that IAP has resulted in a change in pathogens associated with EOS. However, some studies among VLBW preterm infants have shown an increase in EOS due to *Escherichia coli*.² A recent study done by the Eunice Kennedy Schriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) estimated the overall incidence of EOS to be 0.98 cases per 1000 live births, with increasing rates in premature infants.³ Studies with stratification of disease burden by gestational age and race have shown that black preterm neonates have a significantly higher incidence of neonatal sepsis as compared to the rest of the population, accounting for 5.14 cases/1000 births with a case fatality rate of 24.4%.⁴

Despite efforts to detect GBS colonization during pregnancy and provide appropriate GBS prophylaxis to colonized mothers, not all cases of early-onset GBS are prevented and GBS continues to be the most common cause of EOS in term neonates. Sepsis due to *E. coli* has increased in recent years, mainly affecting preterm newborns weighing less than 2500 grams at birth, and is considered the most common cause of EOS in this weight group. *E.coli* is frequently associated with severe infections and meningitis and it has become the leading cause of sepsis-related mortality among VLBW infants (24.5%).⁴ Together GBS and *E. coli* account for about 70% of cases of EOS in the neonatal period.^{5,6}

Rates of LOS are most common in preterm low birthweight infants. Studies from the NICHD NRN report that ~21% of VLBW <1500 g, developed 1 or more episode of blood culture confirmed LOS, with rates inversely related to gestational age (58% at 22 weeks GA and 20% at 28 weeks GA).^{7,8} Intrapartum antibiotic prophylaxis has not had an impact on rates of late-onset sepsis (LOS).^{1,9} VLBW preterm infants are at particular risk for LOS in part because of prolonged hospitalization and prolonged use of indwelling catheters, endotracheal tubes, and other invasive procedures. Several studies have documented rates of LOS from 1.87–5.42, with decreasing rates as birth weight increases.^{6,7} Coagulase negative staphylococci (CoNS) have emerged as the most commonly isolated pathogens among VLBW infants with LOS.

Development of the Immune system and Increased Risk of Neonates to Infections

The development of the immune system entails a number of changes that occur during the first years of life. Neonates, especially preterm infants, are relatively immunocompromised because of immaturity of the immune system as well as decreased placental passage of maternal antibodies. Here we highlight some of the components of the neonatal immune system that are immature and contribute to increased susceptibility to serious bacterial, fungal, and viral infections.

Innate Immune System

The innate immune system produces an immediate immunologic response and is capable of doing this without previous exposure to a specific pathogen. Recognition of pathogens occurs by identification of conserved biological regions known as pathogen associated molecular patterns (PAMPs). Recognition receptors such as TOLL-like receptors, NOD-like receptors and RIG-like receptors identify and respond to PAMPs with the production of cytokines and pro-inflammatory responses which activate the adaptive immune system.¹⁰ Studies comparing neonatal and adult innate immune functions show that neonatal cells have a decreased ability to produce inflammatory cytokines, especially tumor necrosis factor and interleukin-6.¹¹ In addition, they induce interleukin-10 production, which in itself is capable of inhibiting synthesis of pro-inflammatory cytokines.¹² Neutrophil and dendritic cell functions are also reduced; neutrophils show a decreased expression of adhesion molecules as well as a decreased response to chemotactic factors,^{13,14} and dendritic cells have a decreased capacity of producing interleukin-12 and interferon (IFN) gamma. The overall reduction in cytokine production in neonates also results in decreased activation of natural killer cells.¹⁵ Impairment of the innate immune system leads to an increased susceptibility to bacterial and viral infection in this population.

Adaptive Immune System

The adaptive branch of the immune system is designed to eliminate specific pathogens. In newborns the adaptive immune system slowly increases its function towards an adult-like response, minimizing the otherwise overwhelming inflammatory response that would occur when infants transition from a sterile to a colonized environment.¹⁶ Decreased cytotoxic function (strong T-helper 2 polarization with decreased IFN-gamma production), lack of isotype switching, and overall immaturity and decreased memory (due to limited pathogen exposure at time of birth), reduce the neonate's ability to respond effectively to infections.^{17–20} For example, the reduction of cell-mediated immunity increases the risks of infections due to intracellular pathogens such as *Listeria*, *Salmonella*, Herpes Simplex virus (HSV), cytomegalovirus and enteroviruses.

Transplacental passage of maternal IgG is inversely related to gestational age and limits the functional ability of the neonate to respond to certain pathogens.^{21,22} Minimal IgG is transported to the fetus in the first trimester, while fetal IgG rises in the second trimester from approximately 10% at 17–22 weeks gestation to 50% at 28–32 weeks gestation.^{23,24} Thus, preterm infants lack adequate humoral protection against a number of infant pathogens, while term infants will often be protected against the majority of vaccine-preventable neonatal infections through transplacental passage from the mother's serum. Histological studies have also demonstrated that the marginal zone of the spleen is not fully developed until 2 years of age, increasing the infant's susceptibility to encapsulated bacterial infections (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*).²⁵ Finally, decreased transfer of IgA, IgG, cytokines and antibacterial peptides present in human milk may be compromised, especially in premature babies. The lack of secretory IgA decreases the ability of the neonate to respond to environmental pathogens.²⁶

Complement

Complement levels increase with increasing gestational age, but are only about 50% of adult levels at term. Reduced complement levels are associated with deficient opsonization and impaired bacterial killing. Although both pathways seem to be capable of being activated, there may be variations in their activation level. In addition, profound C9 deficiency has been observed in neonates reducing the ability to form bacteriolytic C5b-9 (m), which will increase the risk of acquiring severe invasive bacterial infections.^{27,28}

Etiologic Agents in Neonatal Sepsis

The etiologic agents associated with neonatal sepsis in the United States have changed over time.⁵ In this section we review current data on organisms associated with early- and late-onset neonatal sepsis (Table 2).

Early Onset Sepsis

Group B-streptococcus

Despite widespread use of IAP to prevent vertical transmission of invasive GBS disease, missed opportunities for prevention exist and GBS remains the most common organism associated with EOS in the US. According to the Centers for Disease Control and Prevention (CDC), rates of early-onset invasive GBS disease have declined by 80% since the CDC prevention guidelines were first published.⁹ GBS are Gram-positive encapsulated bacteria for which 10 different serotypes have been identified; with serotype III strains responsible for the majority of disease (54%).²⁹ GBS commonly colonize the GI and genital tract with rates up to 20% in the adult population.³⁰ Transmission occurs late in pregnancy or during labor and delivery, and the likelihood of disease as well as the severity has been associated with the density of recto-vaginal carriage.^{31,32} GBS possess different virulence factors that determine its ability to cause invasive disease: (1) capsular polysaccharide, which helps evade phagocytosis, (2) pili, that allows adherence of GBS to the host's epithelial cells as well as transepithelial migration and (3) C5a peptidase which inhibits human C5a, a neutrophil chemo-attractant produced during complement activation. Among infected newborns, clinical manifestations develop very early after delivery and most infants will have signs of respiratory distress and cardiovascular instability. Infants with early-onset GBS are at increased risk for meningitis. Rapid deterioration of the clinical status is expected unless prompt antibiotic management is started. Risk of death is inversely related to gestational age, with mortality of 20–30% among infected infants less than 33 weeks gestation, compared with a mortality of 2–3% in full term infants.^{1,33}

Escherichia coli

Escherichia coli, a Gram-negative rod that commonly colonizes the maternal urogenital and GI tracts, is considered the second most common cause of neonatal sepsis in term infants and the most common cause in VLBW neonates with rates of 5.09 per 1000 live births.^{3,34,35} The antigenic structure of *E.coli* is represented by multiple antigens (O), (K) and (H) which in combination account for the genetic diversity of the bacteria. Strains with the K1 antigen have been associated with the development of neonatal sepsis and meningitis

as well as with increased risk of mortality when compared with K1 negative strains³⁶. Some studies suggest a more aggressive presentation for infants infected with *E.coli*, with a higher risk of thrombocytopenia and death in the first days of life.³ Several US studies have shown high rates of ampicillin resistance in *E.coli* strains that infect newborns. Although some studies have shown an association between intrapartum antibiotic exposure and ampicillin resistant *E. coli*, ampicillin resistance has increased throughout the community and a direct link between intrapartum use of ampicillin and the higher likelihood of resistance has not been established.^{3,37–39}

Listeria monocytogenes

Listeria is a facultative anaerobic, Gram-positive bacterium found in soil, decaying vegetation, fecal flora and raw unprocessed food.⁴⁰ Multiple virulence factors allow *listeria* to escape the immune system, including listeriolysin that helps the organism avoid the oxidative stress of phagolysosomes, allowing intracellular replication. *Listeria* proteins ActA, phospholipase C, and lecithinase allow polymerization of actin and lysis of phagosomal membranes, enabling cell-to-cell transmission.^{41,42} Pregnant women have 17% higher risk of *listeria* infection than non-pregnant women, and infection has been associated with spontaneous abortions as well as stillbirths. Early neonatal infections have a similar clinical presentation as EO GBS infections, with respiratory distress, sepsis and meningitis. In severe cases patients may present with a granulomatous rash (small patches with erythematous base) known as granulomatosis infantisepticum. Most cases of neonatal *listeria* are due to serotype 1, 2 and 4, with the latter serotype responsible for almost all cases of meningitis.⁴³ Suspicion for listeria sepsis should be increased in ill infants of mothers who have consumed raw milk, unpasteurized cheeses, or other unprocessed food products that have been contaminated with the organism.^{44,45}

Other Bacterial Etiologic Agents Seen in Early Onset Sepsis

Other less common but important pathogens associated with EOS include other streptococci (*S. pyogenes*, viridans group streptococci, *S. pneumoniae*), enterococci, staphylococci and non-typable *Haemophilus influenzae*. *Streptococcus pyogenes* was once the predominant organism responsible for neonatal sepsis. Although overall incidence has decreased significantly, severe cases of EO GAS continue to be reported. A recent literature review identified 38 cases of GAS (24 with EOS). Patients were most likely to present with pneumonia and empyema (42%) or toxic shock syndrome (17%). 70% of the isolates were M1 serotype and they were all susceptible to penicillin. Mortality was estimated to be 38% among patients with EOS⁴⁶. Pneumococcus, groups C and G streptococci, as well as viridans streptococci clinical presentation is very similar to GBS infection and transmission seems to be secondary to bacterial colonization of the maternal genital tract.^{47–51} Enterococcal EOS is usually mild compared to LOS and it is characterized by either a mild respiratory illness or diarrhea without a focal infection. *Enterococcus faecalis* is more frequently isolated than *E. faecium* and most of the isolates remain ampicillin susceptible.⁵² Although non-typable *Haemophilus influenzae* frequently colonizes the maternal genital tract, neonatal infection is relatively rare, but with high mortality rates especially in preterm neonates.^{3,53} Herschckowitz reported a cluster of 9 cases with 3 deaths;⁵⁴ similar high mortality rates were reported in a series by Takala.⁵⁵

Late onset Sepsis (LOS)

The increased survival of preterm low birthweight infants, particularly those who are VLBW, with need for prolonged hospitalization and use of invasive procedures and devices, especially long-term intravascular catheters, results in on-going risk of infection. LOS is largely caused by organisms acquired from the environment after birth. The following section reviews the most common organisms associated with LOS (Table 2).

Coagulase Negative Staphylococci (CoNS) and *Staphylococcus aureus*

CoNS have emerged as the single most commonly isolated pathogen among VLBW infants with LOS and are associated with 22–55% of LOS infections among VLBW infants.^{56,57} *Staphylococcus aureus* is associated with 4–8%.^{7,58} *Staphylococcus* commonly colonizes the human skin and mucous membranes and is capable of adhering to plastic surfaces with the subsequent formation of biofilms. These biofilms protect the bacteria from antibiotic penetration and can produce substances that will help them evade the immune system. Although CoNS infections are usually secondary to *Staphylococcus epidermidis*, other strains such as *S. capitis*, *S. haemolyticus* and *S. hominis* have also been reported.⁵⁹ Methicillin resistant *Staphylococcus aureus* (MRSA) has been isolated in 28% of staphylococcal infections in preterm neonates with no significant differences between MRSA and methicillin susceptible organisms in terms of morbidity, mortality and length of hospital stay. Overall 25% of infants infected with MRSA die, with no significant difference in death rates between infants infected with MRSA or MSSA.⁵⁸

Gram-negative Organisms

Gram-negative organisms are associated with about one-third of cases of LOS, but 40–69% of deaths due to sepsis in this age group. Transmission occurs from the hands of health-care workers, colonization of the GI tract, contamination of total parenteral nutrition or formulas, and bladder catheterization devices.^{60,61} The most common Gram-negative organisms isolated include *E. Coli*, *Klebsiella*, *Pseudomonas*, *Enterobacter*, *Citrobacter* and *Serratia*.⁶² In some case series *Klebsiella* is recognized as the most common gram-negative agent associated with LOS, ranging from 20–31% of cases.^{63,64} Infections due to *Pseudomonas* have been associated with the highest mortality.⁶⁵ *Citrobacter* is uniquely associated with brain abscesses, but dissemination can occur to other organs. Its ability to survive intracellularly has been linked to the capacity of creating chronic CNS infections and abscesses.^{66,67}

Candida Infections

Infections due to *Candida* species are the third leading cause of LOS in premature infants. Risk factors of infection include low birth weight, use of broad-spectrum antibiotics, male gender and lack of enteral feedings.⁶⁸ *C. albicans* and *C. parapsilosis* are the species most commonly associated with disease in neonates.^{69,70} Poor outcomes, including higher mortality rates and neurodevelopmental impairment, have been associated with the ability of the organisms to express virulence traits such as adherence factors and cytotoxic substances.⁷¹ *Candida* easily grows in blood culture media, but its isolation may require larger volumes of blood than normally obtain in neonates and therefore multiple cultures

may be necessary to document infection and clearance. Among those with a positive CSF culture, as many as 50% will have a negative blood culture; the discordance of blood and CSF cultures underscores the need for an LP.⁶⁸ Prompt removal of contaminated catheters is also recommended based on the ability of *Candida* species to create biofilms as well as better survival rates and neurodevelopmental outcomes in patients who had early removal and clearance of the infection.⁶⁸

Herpes Simplex Virus (HSV)—HSV is a potentially devastating cause of late-onset neonatal infection. HSV should be included in the differential diagnosis and treatment strategy of newborns who presents with signs and symptoms of sepsis, especially after the first few days of life. For a detailed discussion on Neonatal Herpes Simplex Virus Infection refer to chapter 8 of this issue.

Clinical Manifestations

Both EO and LO sepsis have non-specific clinical manifestations (Table 3). The importance of a lumbar puncture in neonates with suspected sepsis and without specific CNS clinical manifestations is underscored by studies showing growth of cerebrospinal fluid cultures despite negative blood cultures, especially in VLBW infants⁷²

Diagnostic Methods

Early diagnosis of neonatal sepsis is challenging because clinical characteristics are non-specific and difficult to differentiate from those of non-infectious etiologies, and because the repertoire of ancillary laboratory tests is limited and not always reliable. Blood culture remains the gold standard for diagnosis of neonatal sepsis, but the rate of positivity is low, influenced by factors such as intrapartum antimicrobial administration and limitations in blood volume per culture that can be obtained in neonates.^{73,74} Here we review the standard evaluation of neonatal sepsis, followed by a discussion of recent data on inflammatory markers and diagnostic methods in neonatal sepsis.

General Evaluation of Neonatal Sepsis

A neonate with signs and symptoms of sepsis (Table 3) requires prompt evaluation and initiation of antibiotic therapy. Blood, CSF (as clinical condition allows) and urine cultures (only useful after the 3rd day of life) should be obtained.^{72,75,76} Chest x-ray is indicated in patients having respiratory symptoms. If disseminated herpes is suspected (herpetic skin lesions, elevated hepatic transaminases, maternal peripartum herpes infection), surface cultures from conjunctiva, mouth, skin and anus as well as Herpes DNA PCR from CSF and blood should also be ordered.^{77,78} Ancillary tests such as complete blood count (CBC) and C Reactive protein (CRP) should not preclude a sepsis evaluation in a neonate since they can be normal (See below).⁷⁹ However, if positive they can be useful in supporting the diagnosis and determining length of therapy. Careful maternal and exposure history targeted towards identifying potential risk factors (Table 1) as well as a complete physical examination including skin and catheter insertion sites should be obtained.

Complete Blood Cell Count

Contrary to older children and adults, the white blood cell count (WBC) does not accurately predict infection in neonates. A recent multicenter review of CBC counts and blood cultures in neonates admitted to 293 NICUs in the United States, showed that low WBC and absolute neutrophil counts, as well as high immature-to-total neutrophil ratio (I:T ratio) were associated with increasing odds of infection, (OR 5.38, 6.84 and 7.9, respectively); however, the test sensitivities for detection of sepsis were low.⁸⁰ Studies looking at serial values of WBC and I:T ratios have shown better outcomes. Murphy and colleagues, in a single center historical cohort study, showed that 2 serial normal I:T ratios and a negative blood culture in the first 24 hours of life had a negative predictive value of 100% (95% CI:99.905–100%), but the specificity and positive predictive value were 51% and 8.8% respectively.⁸¹ CBC values need to be interpreted cautiously and in conjunction with other clinical and laboratory parameters.

C Reactive Protein

CRP was first described in the 1930's and since then multiple studies have shown elevation of the CRP in several infectious and non-infectious etiologies that share a common background of inflammation or tissue injury.⁸² In neonates, serial measurements of the CRP in the first 24–48 hours of symptoms increases the sensitivity of the test, with suggestion that normal CRP values during this period of time have a 99% negative predicted value for determination of infection.^{83,84} In contrast, elevated levels of CRP may be more difficult to interpret, especially for diagnosis of EOS because factors such as PROM, maternal fever, pregnancy-induced hypertension, prenatal steroid use, and fetal distress may also cause elevation of the CRP.^{85,86} Additionally, studies have suggested a physiologic variation of the CRP during the first few days of life limiting the use of single values.⁸⁶ Gestational age influences CRP kinetics, with preterm infants having a lower and shorter CRP response compared to healthy term infants.^{87,88} Studies suggest that CRP is best used as part of a group of ancillary diagnostic tests to help determine if an infant has infection, rather than as a single test..

Procalcitonin

Tissue release of procalcitonin (PCT) increases with infection making it a potential marker for early detection of sepsis. PCT differs from CRP, in that PCT levels increase more rapidly and may be more useful for detection of EOS. Auriti and colleagues in a multicenter, prospective observational study of 762 neonates showed a significant increase in the median value of PCT level in neonates with sepsis compared with those without sepsis (3.58 vs 0.49 ng/ml; $P < 0.001$). In addition, a cut-off value of 2.4 ng/ml was suggested as the most accurate level for differentiation of sepsis in neonates regardless of gestational age, with a sensitivity of 62% and a specificity of 84%.⁸⁹ A meta-analysis of 16 studies (1959 neonates), showed that PCT had a pooled sensitivity and specificity of 81 and 79% respectively.⁹⁰ Although these are promising results, further studies are needed to clarify the use of PCT in clinical practice.

Mannose Binding Lectin

Mannose-binding lectin (MBL) is a plasma protein, primarily produced by the liver with an important role in the innate immune defense. MBL activates the lectin pathway of the complement system increasing opsonization and enhancing phagocytosis.⁹¹ Genetic polymorphisms in the MBL gene have been associated with an increased risk of sepsis. In a recent study in which MBL levels were measured in 93 neonates, development of sepsis was associated with lower levels of MBL and with the presence of BB genotype in exon 1 of the MBL gene. MBL remains a research tool with further studies needed to confirm diagnostic utility.⁹²

Cytokine profile

Multiple cytokines have been studied for diagnosis of neonatal sepsis including IL-6, IL-8, IL-10 and TNF alpha. IL-6 and IL-8 increase very rapidly with bacterial invasion but they promptly normalize in serum levels (within the first 24 hours), limiting their ability to be used as clinical markers. TNF alpha has not shown to have high sensitivity, but the ratio of IL-10 and TNF alpha has been used for diagnosis of LOS in VLBW neonates with some success.^{93,94} Evaluating a combination of cytokine profiles may increase likelihood of identifying infection than single measurements.

Neutrophil CD64 and Neutrophil/Monocyte CD11B

These specific markers are cell surface antigens whose production increases after activation of leukocytes by bacteria and therefore can potentially be used for diagnosis of neonatal sepsis. Their up-regulation precedes that of CRP suggesting potential use in EOS. A recent study by Genel showed that CD64 had a sensitivity and specificity to accurately identify neonatal sepsis of 81 and 77% respectively, with a negative predictive value (NPV) of 75%. Similarly, CD11b had a sensitivity and specificity of 66 and 71%. Cost and processing time may be barriers to use of these markers in clinical practice.⁹⁵

Molecular techniques for Early Detection of Neonatal Sepsis

Important advances have been made in molecular diagnostics, and studies of real time PCR (RT-PCR) and a broad range of conventional PCR assays suggest improved sensitivity and specificity for sepsis diagnosis. A meta-analysis done by Pammi found that sensitivity and specificity of RT-PCR was 0.96 (95% C.I for sensitivity: 0.65–1.0 and 95% C.I. for specificity: 0.92–0.98). Similarly, broad range PCR had a sensitivity of 0.95 (95% C.I 0.84–0.98) and specificity of 0.98 (0.95–1.0). However, neither test achieved the minimum limits of sensitivity or specificity set up by the study and results were insufficient to replace blood cultures for diagnosis of neonatal sepsis.⁹⁶ Currently these techniques should be seen as adjuvants in the diagnosis of neonatal sepsis, with limitations that include the inability to provide information about antibiotic susceptibility as well as significant cost of implementation in clinical practice. An exception to this is the use of HSV PCR for the diagnosis of HSV encephalitis, which is the gold standard test for this condition. The role of HSV PCR from the blood in diagnosing disseminated HSV infection is less clear.

Genomics and Proteomics

Exciting alternatives for detection of neonatal sepsis include the use of genomics and proteomics for identification of host response biomarkers. Genomics targets genes that are up regulated with infection and proteomics analyzes the structure, function and interactions of proteins produced by a particular gene. Early studies in neonates have suggested potential utility in these techniques for identification of sepsis and necrotizing enterocolitis. A score based on proapolipoprotein CII (Pro-apoC2) and a des-arginine variant of serum amyloid, was used to withhold antibiotics in 45% of patients with suspected infection and to discontinue antibiotics in 16%.^{93,97} Studies are needed for validation of this score as well as for detection of other potential biomarkers.

Treatment

Prevention and Infection Control Practices

Prevention of neonatal sepsis is the goal—through implementation of what is known and development of new prevention strategies. Maternal prenatal care continues to be important for prevention of early-onset GBS sepsis with identification of maternal carriage of GBS through universal screening for all pregnant women. Early recognition of chorioamnionitis, with appropriate antimicrobial therapy for the mother, decreases maternal fetal transmission. The recent CDC GBS prevention guidelines emphasize the need for universal maternal GBS screening at 35–37 weeks gestation and include chromogenic agar and nucleic amplification tests (NAATs) as newer diagnostic techniques that can be used to increase the yield of GBS identification. They also clarify the definition of adequate intrapartum prophylaxis as use of penicillin, ampicillin or cefazolin at least 4 hours prior to delivery (Table 4). Clindamycin and vancomycin, which can be used in penicillin allergic patients, are not considered effective prophylaxis therapy.⁹ Other potential prevention strategies include rapid GBS testing during labor and a safe and effective GBS vaccine. Diagnostic tests during labor will identify colonized women who either had a negative screen at 35–37 weeks or were not screened prior to labor. Further studies are needed to improve sensitivity and specificity of rapid tests.⁹⁸

Efforts to reduce hospital acquired late onset infections require much closer attention to appropriate hand washing, infection control, and proper techniques for placement and management of central catheters. Recently, the American Academy of Pediatrics published guidelines for the prevention of health care-associated infections in the NICU. These guidelines emphasize the need for 100% compliance with appropriate hand washing techniques and recommend use of alcohol-based products for hand hygiene. Catheter bundles that include guidelines for insertion and management of central-lines have been shown to reduce risk of central line associated bloodstream infection.^{99–102} The use of heparin for prevention of line infections has been successful in single center randomized studies, but has not been confirmed in larger multicenter studies; therefore, its routine use is not recommended.^{103,104} Daily check lists that document continued need for central lines to reduce duration of line use and a goal of zero central-line associated infections should be the responsibility of the whole healthcare team.⁹⁹

Prevention Strategies

A variety of interventions to decrease rates of neonatal sepsis have been studied, including postnatal use of lactoferrin, anti-staphylococcal monoclonal antibodies, intravenous immunoglobulin (IVIG), granulocyte-macrophage colony stimulating factors, probiotics, glutamine and fluconazole prophylaxis for invasive candida infection. (Table 5)

Intravenous Immunoglobulin

Delay in the synthesis of immunoglobulin and a decrease trans-placental antibody transfer in neonates, suggested that the use of IVIG could be a potential strategy for prevention of neonatal sepsis. In 1994, a randomized controlled trial in 2,416 infants failed to show a decrease incidence of nosocomial infections, morbidity/mortality and duration of hospital stay among VLBW infants.¹⁰⁵ A follow-up meta-analysis of 10 trials showed that mortality was reduced with the use of IVIG in suspected (RR, 0.58 95% CI, 0.38–0.89) and proven infection (RR, 0.55; 95% CI, 0.31–0.98), but authors caution about their conclusions based on concerns about individual study quality.¹⁰⁶ Recently, the International Neonatal Immunotherapy Study (INIS) randomized 3,493 infants with suspected or proven sepsis to receive either two doses of polyvalent IgG immune globulin or placebo 48 hours apart. Their primary outcome was rate of death or major disability at the age of 2 years. There was no difference in the primary outcome between the two groups (RR, 1.00; 95% confidence interval, 0.92–1.08).¹⁰⁷

Antistaphylococcal Monoclonal Antibodies

Due to the burden of staphylococcal infections in neonatal sepsis, different anti-staphylococcal monoclonal antibodies had been developed. These include antibodies against the capsular polysaccharide antigen, antibodies against microbial surface components that recognize adhesive matrix molecules, antibodies to clumping factor A and anti-lipoteichoic acid (LTA) antibodies.^{108–110} Initial animal studies, as well as phase I and II trials in humans, showed that capsular directed antibodies and anti-clumping factor A were well tolerated and had the potential to reduce staphylococcal sepsis.^{111,112} However, a meta-analysis showed that their efficacy in decreasing staphylococcal infections was limited and recommended against their use¹¹³. Recently, Weisman and colleagues showed safety and tolerance of pagibaximab (anti-LTA antibody) at doses of 60 and 90 mg/kg in VLBW infants, with those receiving 90 mg/kg per dose showing no staphylococcal sepsis.¹¹⁰ Although these are exciting results, randomized controlled studies are needed to further confirm these findings.

Granulocyte/Granulocyte-macrophage Colony Stimulating Factors

Granulocyte-macrophage stimulating factor (GM-CSF) increases T-Helper 1 immune responses and enhances bactericidal activity by stimulating neutrophils and monocytes. Animal studies have shown that both GM-CSF and granulocyte colony stimulating factor (G-CSF), given prior to bacterial inoculation, decreases mortality. A single blinded multicenter study looking at the use of GM-CSF and the development of sepsis showed that although the absolute neutrophil count on the treatment arm increased significantly faster ($p=0.002$), there was no difference in sepsis-free survival to day 14 from study entry (risk

difference -8%; 95% CI -18% to 3%).¹¹⁴ A meta-analysis that included 4 small studies had similar results (RR: 0.89; 95% confidence interval (CI), 0.43 to 1.86).⁹⁶

Glutamine

Based on promising adult studies, glutamine supplementation has been suggested as a potential intervention to reduce neonatal sepsis. A randomized double-blinded study from the NICHD NRN among 1,433 ELBW infants showed no difference in mortality and late-onset sepsis outcomes (RR: 1.07; 95% CI 0.97, 1.17; P=0.18).¹¹⁵ Similar results were obtained in a meta-analysis of 5 trials that included 2,240 neonates looking at the effects of glutamine in the incidence of culture proven invasive infection (RR 1.01; 95% CI 0.91, 1.13).¹¹⁶ Glutamine supplementation is not currently recommended as a strategy to decrease or prevent neonatal sepsis.

Probiotics

Evidence continues to grow regarding the use of probiotics to prevent necrotizing enterocolitis (NEC)^{117,118}, but data on use of probiotics for prevention of neonatal sepsis are limited and contradictory. A major problem with the use of probiotics is the lack of standardization and federal regulation. If probiotics are considered food additives, no formal evaluation is required and a wide variety of products are available. Some investigators have stressed the need for FDA review and approval especially if probiotics are to be used in at risk VLBW infants. While small studies have indicated potential benefits of probiotics in decreasing neonatal sepsis, a recent meta-analysis (RR 0.90, 95% CI 0.76 to 1.07) and a systematic review (RR: 0.98, 95% CI: 0.81–1.18) found no evidence that probiotics decreased sepsis in preterm VLBW infants.^{117,119}

Lactoferrin

Lactoferrin is a glycoprotein present in human milk that contains immunomodulatory properties by increasing cytokine production in the gut and associated lymphoid tissue, as well as by showing antibiotic-like activities against Gram-negative and Gram-positive bacteria. A recent multicenter randomized study in 472 VLBW neonates demonstrated decreased bacterial and fungal LOS among newborns treated with lactoferrin (5.9% in lactoferrin group vs 17.3% in controls p=0.002).¹²⁰ Further studies are needed to confirm these findings and to evaluate optimal dosage as well as short-term and long-term safety.

Fluconazole Prophylaxis

Studies have documented that fluconazole prophylaxis among high-risk VLBW infants is effective in reducing the number of severe infections. Kaufman and colleagues found a 22% decrease in risk of fungal colonization among infants weighing less than 1000 grams who were on fluconazole prophylaxis. In addition, they found no fungal invasive infections in those who received fluconazole compared to 20% in the placebo group¹²¹. Similar results were obtained by the Italian Task Force in 322 neonates who were randomized to receive fluconazole or placebo.¹²² The success in decreasing the incidence of fungal infections in the neonatal units has not been translated into decreased mortality; however, all prospective studies of fluconazole prophylaxis have consistently revealed decreasing mortality

trends.^{121–124} In addition, Healy and colleagues in a retrospective 4-year study, looking at the incidence of invasive candidiasis, showed that there were no attributable deaths among patients who received fluconazole prophylaxis compared to 21% of those who did not.¹²⁵ Current recommendations advocate for the use of fluconazole prophylaxis in infants with birth weights of less than 1000 grams in neonatal units with high rates of invasive candidiasis.¹²⁶ Recently, Kaufman and colleagues reported an 8–10 year follow-up study evaluating the long-term and neurodevelopmental outcomes of fluconazole prophylaxis. They found no significant neurodevelopmental impairment, or difference in head circumference growth and cholestasis in patients on prophylaxis when compared to placebo.¹²³ A larger study is needed to verify these findings. Another important aspect of fluconazole prophylactic use has been the concern regarding emergence of fluconazole resistant strains; however, studies have failed to show such an association and a significant increase on fluconazole-resistant *Candida* species have not yet occurred¹²⁵.

Judicious use of Antibiotics

Appropriate use of antibiotics is important to save lives and reduce complications. Indiscriminate use increases risk of multi drug resistant organisms and other complications including disseminated candida infections and necrotizing enterocolitis.^{127,128} Reports of vancomycin resistant enterococcus, beta lactamase producing organisms (*E.coli*, *klebsiella*, *enterobacter*) and highly resistant *acinetobacter*, *burkholderia*, *chryseobacterium meningosepticum* and *serratia* are increasing in the neonatal population, calling for a judicious use of antibiotics.^{129–134} A study looking at antibiotic prescribing practices in four NICU's found that approximately 28% of the establish antibiotic courses and 24% of antibiotic days were inappropriate for the prescribing indication. The most common cause of inappropriate use was excessive continuation of antibiotics, rather than inappropriate initiation; followed by inability to target the specific pathogen once isolated.¹³⁵ General principles for antibiotic use, as well as effective antibiotic stewardship programs, may help decrease misuse of antibiotics in the NICU (Table 6). Such programs require developing antibiotic guidelines, education initiatives, accompanied by pre-prescription approval and post-prescription review (i.e. modification of empiric antibiotic regimen, dose optimization, therapeutic monitoring, oral antimicrobial conversion and drug-drug interactions). Close involvement and communication between an infectious disease specialist, neonatologist, clinical pharmacist, infection control and microbiology personnel is essential for the success of the program.¹³⁶ Efforts to document and measure the success of stewardship programs are important as well as generating non-punitive feedback on antibiotic prescription practices. The neonatal intensive care unit has specific characteristics in antibiotic prescription practices, since multiple providers may be involved in the decision of initiating, continuing or discontinuing antibiotics; adapting programs to such characteristics is important.¹³⁷ Recently, CDC launched the *Get Smart for Healthcare* campaign, which focuses on improving antibiotic use in inpatient/outpatient healthcare facilities and offers tools for implementation and improvement of stewardship efforts (<http://www.cdc.gov/getsmart/healthcare>).

Ampicillin and Gentamicin continue to be the preferred antibiotics for empiric treatment of suspected early-onset neonatal sepsis. Increasing ampicillin resistant *E.coli* in some centers

has lead to increased use of third generation cephalosporins as part of the empirical treatment; however, studies have shown a potential association with increased mortality and the development of multidrug-resistant organisms associated with this practice. In addition, cephalosporins are not active against listeria and enterococcus. In late-onset sepsis coverage with vancomycin should be considered, especially in hospitalized VLBW infants at risk for CoNS infection.

Definitive therapy should be chosen based on antibiotic susceptibilities. Combination therapy for Gram-negative organisms is not required for patients without meningitis, and for patients with an inducible B-lactamase producing organism (*serratia*, indol positive *proteus*, *citrobacter* and *enterobacter*) the use of a carbapenem should be considered. The duration of therapy is based on the disease process (Table 7).

Amphotericin and fluconazole continue to be the antifungal drugs of choice for treatment of neonatal candidiasis. Local susceptibility patterns should be followed if *C. glabrata*, *C. krusei* or *C. lusitaniae* are isolated, since susceptibility of these species to both fluconazole and amphotericin may be decreased. The experience with the use of echinocandins (micafungin, caspofungin, anidulafungin) in neonates continues to increase, but their use is not yet approved in this population, and their poor CNS penetration is also a concern.¹³⁸ Micafungin, is the echinocandin that has been studied the most in the neonatal population and these studies show that higher doses may be required especially for better CNS penetration.^{139–141}.

Conclusion

Neonatal sepsis continues to be a significant cause of morbidity and mortality in term and preterm infants. Although GBS and *E. coli* are the most common pathogens associated with EOS and CoNS are the most frequently isolated agents in newborns with LOS, other organisms as well as multidrug resistant pathogens need to be considered. Development of accurate novel early diagnostic markers will allow clinicians to better assess the risk of infection and need for antibiotic therapy. Adherence to infection control policies including attention to strict hand hygiene, antibiotic stewardship and catheter management are required to decrease the number of infections in hospitalized neonates.

References

1. Verani JR, McGee L, Schrag SJ. Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010; 59:1–36. [PubMed: 21088663]
2. Stoll BJ, Hansen N, Fanaroff AA, et al. Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants. N Engl J Med. 2002; 347:240–7. [PubMed: 12140299]
3. Stoll BJ, Hansen NI, Sanchez PJ, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and *E. coli* disease continues. Pediatrics. 2011; 127:817–26. [PubMed: 21518717]
4. Weston EJ, Pondo T, Lewis MM, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005–2008. Pediatr Infect Dis J. 2011; 30:937–41. [PubMed: 21654548]
5. Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928–2003. Pediatrics. 2005; 116:595–602. [PubMed: 16140698]
6. Vergnano S, Menson E, Kennea N, et al. Neonatal infections in England: the NeonIN surveillance network. Arch Dis Child Fetal Neonatal Ed. 2011; 96:F9–F14. [PubMed: 20876594]

7. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics*. 2002; 110:285–91. [PubMed: 12165580]
8. Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics*. 2010; 126:443–56. [PubMed: 20732945]
9. Baker CJ, Byington CL, Polin RA. Policy statement-Recommendations for the prevention of perinatal group B streptococcal (GBS) disease. *Pediatrics*. 2011; 128:611–6. [PubMed: 21807694]
10. Kumar S, Ingle H, Prasad DV, Kumar H. Recognition of bacterial infection by innate immune sensors. *Crit Rev Microbiol*. 2012
11. Kollmann TR, Crabtree J, Rein-Weston A, et al. Neonatal innate TLR-mediated responses are distinct from those of adults. *J Immunol*. 2009; 183:7150–60. [PubMed: 19917677]
12. Belderbos ME, Levy O, Stalpers F, Kimpen JL, Meyaard L, Bont L. Neonatal plasma polarizes TLR4-mediated cytokine responses towards low IL-12p70 and high IL-10 production via distinct factors. *PLoS One*. 2012; 7:e33419. [PubMed: 22442690]
13. Carr R. Neutrophil production and function in newborn infants. *Br J Haematol*. 2000; 110:18–28. [PubMed: 10930976]
14. Levy O. Innate immunity of the newborn: basic mechanisms and clinical correlates. *Nat Rev Immunol*. 2007; 7:379–90. [PubMed: 17457344]
15. Guilmot A, Hermann E, Braud VM, Carlier Y, Truysens C. Natural killer cell responses to infections in early life. *J Innate Immun*. 2011; 3:280–8. [PubMed: 21411972]
16. Schelonka RL, Maheshwari A, Carlo WA, et al. T cell cytokines and the risk of blood stream infection in extremely low birth weight infants. *Cytokine*. 2011; 53:249–55. [PubMed: 21145756]
17. Tolar J, Hippen KL, Blazar BR. Immune regulatory cells in umbilical cord blood: T regulatory cells and mesenchymal stromal cells. *Br J Haematol*. 2009; 147:200–6. [PubMed: 19796269]
18. Risdon G, Gaddy J, Horie M, Broxmeyer HE. Alloantigen priming induces a state of unresponsiveness in human umbilical cord blood T cells. *Proc Natl Acad Sci U S A*. 1995; 92:2413–7. [PubMed: 7892281]
19. Takahashi N, Kato H, Imanishi K, et al. Change of specific T cells in an emerging neonatal infectious disease induced by a bacterial superantigen. *Microbiol Immunol*. 2009; 53:524–30. [PubMed: 19703246]
20. Sautois B, Fillet G, Beguin Y. Comparative cytokine production by in vitro stimulated mononucleated cells from cord blood and adult blood. *Exp Hematol*. 1997; 25:103–8. [PubMed: 9015209]
21. Palmeira P, Quinello C, Silveira-Lessa AL, Zago CA, Carneiro-Sampaio M. IgG placental transfer in healthy and pathological pregnancies. *Clin Dev Immunol*. 2012; 2012:985646. [PubMed: 22235228]
22. van den Berg JP, Westerbeek EA, van der Klis FR, Berbers GA, van Elburg RM. Transplacental transport of IgG antibodies to preterm infants: a review of the literature. *Early Hum Dev*. 2011; 87:67–72. [PubMed: 21123010]
23. Malek A. Ex vivo human placenta models: transport of immunoglobulin G and its subclasses. *Vaccine*. 2003; 21:3362–4. [PubMed: 12850340]
24. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins during human pregnancy. *Am J Reprod Immunol*. 1996; 36:248–55. [PubMed: 8955500]
25. Zandvoort A, Timens W. The dual function of the splenic marginal zone: essential for initiation of anti-TI-2 responses but also vital in the general first-line defense against blood-borne antigens. *Clin Exp Immunol*. 2002; 130:4–11. [PubMed: 12296846]
26. Brandtzaeg P. The mucosal immune system and its integration with the mammary glands. *J Pediatr*. 2010; 156:S8–15. [PubMed: 20105666]
27. Hogasen AK, Overlie I, Hansen TW, Abrahamsen TG, Finne PH, Hogasen K. The analysis of the complement activation product SC5 b-9 is applicable in neonates in spite of their profound C9 deficiency. *J Perinat Med*. 2000; 28:39–48. [PubMed: 10765513]
28. Suzuki-Nishimura T, Uchida MK. Binding of spin-labeled fatty acids and lysophospholipids to hydrophobic region of calmodulin. *J Biochem*. 1991; 110:333–8. [PubMed: 1663109]

29. Imperi M, Gherardi G, Berardi A, et al. Invasive neonatal GBS infections from an area-based surveillance study in Italy. *Clin Microbiol Infect.* 2011; 17:1834–9. [PubMed: 2172258]
30. Tomlinson MW, Schmidt NM, Rourke JW Jr, McDonald J. Rectovaginal *Staphylococcus aureus* colonization: is it a neonatal threat? *Am J Perinatol.* 2011; 28:673–6. [PubMed: 21544769]
31. Yancey MK, Duff P, Kubilis P, Clark P, Frentzen BH. Risk factors for neonatal sepsis. *Obstet Gynecol.* 1996; 87:188–94. [PubMed: 8559521]
32. Regan JA, Klebanoff MA, Nugent RP, et al. Colonization with group B streptococci in pregnancy and adverse outcome. VIP Study Group. *Am J Obstet Gynecol.* 1996; 174:1354–60. [PubMed: 8623869]
33. Schrag SJ, Zywicki S, Farley MM, et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. *N Engl J Med.* 2000; 342:15–20. [PubMed: 10620644]
34. Tsai CH, Chen YY, Wang KG, Chen CY, Chen CP. Characteristics of early-onset neonatal sepsis caused by *Escherichia coli*. *Taiwan J Obstet Gynecol.* 2012; 51:26–30. [PubMed: 22482964]
35. Bizzarro MJ, Dembry LM, Baltimore RS, Gallagher PG. Changing patterns in neonatal *Escherichia coli* sepsis and ampicillin resistance in the era of intrapartum antibiotic prophylaxis. *Pediatrics.* 2008; 121:689–96. [PubMed: 18381532]
36. Kaczmarek A, Budzinska A, Gospodarek E. Prevalence of genes encoding virulence factors among *Escherichia coli* with K1 antigen and non-K1 *E. coli* strains. *J Med Microbiol.* 2012
37. Schrag SJ, Hadler JL, Arnold KE, Martell-Cleary P, Reingold A, Schuchat A. Risk factors for invasive, early-onset *Escherichia coli* infections in the era of widespread intrapartum antibiotic use. *Pediatrics.* 2006; 118:570–6. [PubMed: 16882809]
38. Al-Hasan MN, Lahr BD, Eckel-Passow JE, Baddour LM. Antimicrobial resistance trends of *Escherichia coli* bloodstream isolates: a population-based study, 1998–2007. *J Antimicrob Chemother.* 2009; 64:169–74. [PubMed: 19435736]
39. Puopolo KM, Eichenwald EC. No change in the incidence of ampicillin-resistant, neonatal, early-onset sepsis over 18 years. *Pediatrics.* 2010; 125:e1031–8. [PubMed: 20385650]
40. Versalovic, J. *Manual of Clinical Microbiology.* 10. ASM Press; 2012.
41. Shetron-Rama LM, Marquis H, Bouwer HG, Freitag NE. Intracellular induction of *Listeria monocytogenes* actA expression. *Infect Immun.* 2002; 70:1087–96. [PubMed: 11854187]
42. Moors MA, Levitt B, Youngman P, Portnoy DA. Expression of listeriolysin O and ActA by intracellular and extracellular *Listeria monocytogenes*. *Infect Immun.* 1999; 67:131–9. [PubMed: 9864207]
43. Smith B, Kemp M, Ethelberg S, et al. *Listeria monocytogenes*: maternal-foetal infections in Denmark 1994–2005. *Scand J Infect Dis.* 2009; 41:21–5. [PubMed: 18855227]
44. CDC. From the Centers for Disease Control. Foodborne listeriosis--United States, 1988–1990. *JAMA.* 1992; 267:2446–8.
45. Schlech WF 3rd. Foodborne listeriosis. *Clin Infect Dis.* 2000; 31:770–5. [PubMed: 11017828]
46. Miyairi I, Berlingieri D, Protic J, Belko J. Neonatal invasive group A streptococcal disease: case report and review of the literature. *Pediatr Infect Dis J.* 2004; 23:161–5. [PubMed: 14872185]
47. Prommalikit O, Mekmullica J, Pancharoen C, Thisyakorn U. Invasive pneumococcal infection in neonates: 3 case reports. *J Med Assoc Thai.* 2010; 93(Suppl 5):S46–8. [PubMed: 21294381]
48. Malhotra A, Hunt RW, Doherty RR. *Streptococcus pneumoniae* sepsis in the newborn. *J Paediatr Child Health.* 2012; 48:E79–83. [PubMed: 21199057]
49. Gomez M, Alter S, Kumar ML, Murphy S, Rathore MH. Neonatal *Streptococcus pneumoniae* infection: case reports and review of the literature. *Pediatr Infect Dis J.* 1999; 18:1014–8. [PubMed: 10571441]
50. Appelbaum PC, Friedman Z, Fairbrother PF, Hellmann J, Hallgren EJ. Neonatal sepsis due to group G streptococci. *Acta Paediatr Scand.* 1980; 69:559–62. [PubMed: 7446105]
51. West PW, Al-Sawan R, Foster HA, Electricwala Q, Alex A, Panigrahi D. Speciation of presumptive viridans streptococci from early onset neonatal sepsis. *J Med Microbiol.* 1998; 47:923–8. [PubMed: 9788817]
52. Dobson SR, Baker CJ. Enterococcal sepsis in neonates: features by age at onset and occurrence of focal infection. *Pediatrics.* 1990; 85:165–71. [PubMed: 2104974]

53. Ault KA. Vaginal flora as the source for neonatal early onset *Haemophilus influenzae* sepsis. *Pediatr Infect Dis J*. 1994; 13:243. [PubMed: 8018185]
54. Hershckowitz S, Elisha MB, Fleisher-Sheffer V, Barak M, Kudinsky R, Weintraub Z. A cluster of early neonatal sepsis and pneumonia caused by nontypable *Haemophilus influenzae*. *Pediatr Infect Dis J*. 2004; 23:1061–2. [PubMed: 15545867]
55. Takala AK, Pekkanen E, Eskola J. Neonatal *Haemophilus influenzae* infections. *Arch Dis Child*. 1991; 66:437–40. [PubMed: 2025040]
56. Didier C, Streicher MP, Chognot D, et al. Late-onset neonatal infections: incidences and pathogens in the era of antenatal antibiotics. *Eur J Pediatr*. 2012; 171:681–7. [PubMed: 22134805]
57. Lim WH, Lien R, Huang YC, et al. Prevalence and pathogen distribution of neonatal sepsis among very-low-birth-weight infants. *Pediatr Neonatol*. 2012; 53:228–34. [PubMed: 22964280]
58. Shane AL, Hansen NI, Stoll BJ, et al. Methicillin-resistant and susceptible *Staphylococcus aureus* bacteremia and meningitis in preterm infants. *Pediatrics*. 2012; 129:e914–22. [PubMed: 22412036]
59. de Silva GD, Kantzanou M, Justice A, et al. The *ica* operon and biofilm production in coagulase-negative *Staphylococci* associated with carriage and disease in a neonatal intensive care unit. *J Clin Microbiol*. 2002; 40:382–8. [PubMed: 11825946]
60. Drudy D, Mullane NR, Quinn T, Wall PG, Fanning S. *Enterobacter sakazakii*: an emerging pathogen in powdered infant formula. *Clin Infect Dis*. 2006; 42:996–1002. [PubMed: 16511766]
61. Tresoldi AT, Padoveze MC, Trabasso P, et al. *Enterobacter cloacae* sepsis outbreak in a newborn unit caused by contaminated total parenteral nutrition solution. *Am J Infect Control*. 2000; 28:258–61. [PubMed: 10840347]
62. Cohen-Wolkowicz M, Moran C, Benjamin DK, et al. Early and late onset sepsis in late preterm infants. *Pediatr Infect Dis J*. 2009; 28:1052–6. [PubMed: 19953725]
63. Bell Y, Barton M, Thame M, Nicholson A, Trotman H. Neonatal sepsis in Jamaican neonates. *Ann Trop Paediatr*. 2005; 25:293–6. [PubMed: 16297304]
64. Leibovitz E, Flidel-Rimon O, Juster-Reicher A, et al. Sepsis at a neonatal intensive care unit: a four-year retrospective study (1989–1992). *Isr J Med Sci*. 1997; 33:734–8. [PubMed: 9434810]
65. Townsend S, Hurrell E, Forsythe S. Virulence studies of *Enterobacter sakazakii* isolates associated with a neonatal intensive care unit outbreak. *BMC Microbiol*. 2008; 8:64. [PubMed: 18423002]
66. Etuweve O, Kulshrestha R, Sangra M, Riordan A. Brain abscesses due to *Citrobacter koseri* in a pair of twins. *Pediatr Infect Dis J*. 2009; 28:1035. [PubMed: 19859021]
67. Townsend SM, Pollack HA, Gonzalez-Gomez I, Shimada H, Badger JL. *Citrobacter koseri* brain abscess in the neonatal rat: survival and replication within human and rat macrophages. *Infect Immun*. 2003; 71:5871–80. [PubMed: 14500508]
68. Benjamin DK Jr, Stoll BJ, Fanaroff AA, et al. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. *Pediatrics*. 2006; 117:84–92. [PubMed: 16396864]
69. Neu N, Malik M, Lunding A, et al. Epidemiology of candidemia at a Children's hospital, 2002 to 2006. *Pediatr Infect Dis J*. 2009; 28:806–9. [PubMed: 19636286]
70. Chitnis AS, Magill SS, Edwards JR, Chiller TM, Fridkin SK, Lessa FC. Trends in *Candida* central line-associated bloodstream infections among NICUs, 1999–2009. *Pediatrics*. 2012; 130:e46–52. [PubMed: 22711720]
71. Bliss JM, Wong AY, Bhak G, et al. *Candida* virulence properties and adverse clinical outcomes in neonatal candidiasis. *J Pediatr*. 2012; 161:441–7 e2. [PubMed: 22504098]
72. Stoll BJ, Hansen N, Fanaroff AA, et al. To tap or not to tap: high likelihood of meningitis without sepsis among very low birth weight infants. *Pediatrics*. 2004; 113:1181–6. [PubMed: 15121927]
73. Jawaheer G, Neal TJ, Shaw NJ. Blood culture volume and detection of coagulase negative staphylococcal septicaemia in neonates. *Arch Dis Child Fetal Neonatal Ed*. 1997; 76:F57–8. [PubMed: 9059190]
74. Neal PR, Kleiman MB, Reynolds JK, Allen SD, Lemons JA, Yu PL. Volume of blood submitted for culture from neonates. *J Clin Microbiol*. 1986; 24:353–6. [PubMed: 3760131]

75. Visser VE, Hall RT. Urine culture in the evaluation of suspected neonatal sepsis. *The Journal of pediatrics*. 1979; 94:635–8. [PubMed: 430312]
76. Wiswell TE, Baumgart S, Gannon CM, Spitzer AR. No lumbar puncture in the evaluation for early neonatal sepsis: will meningitis be missed? *Pediatrics*. 1995; 95:803–6. [PubMed: 7761203]
77. Lakeman FD, Whitley RJ. Diagnosis of herpes simplex encephalitis: application of polymerase chain reaction to cerebrospinal fluid from brain-biopsied patients and correlation with disease. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *The Journal of infectious diseases*. 1995; 171:857–63. [PubMed: 7706811]
78. Simko JP, Caliendo AM, Hogle K, Versalovic J. Differences in laboratory findings for cerebrospinal fluid specimens obtained from patients with meningitis or encephalitis due to herpes simplex virus (HSV) documented by detection of HSV DNA. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2002; 35:414–9. [PubMed: 12145725]
79. Christensen RD, Rothstein G, Hill HR, Hall RT. Fatal early onset group B streptococcal sepsis with normal leukocyte counts. *Pediatric infectious disease*. 1985; 4:242–5. [PubMed: 3889873]
80. Hornik CP, Benjamin DK, Becker KC, et al. Use of the complete blood cell count in early-onset neonatal sepsis. *Pediatr Infect Dis J*. 2012; 31:799–802. [PubMed: 22531231]
81. Murphy K, Weiner J. Use of leukocyte counts in evaluation of early-onset neonatal sepsis. *Pediatr Infect Dis J*. 2012; 31:16–9. [PubMed: 21860335]
82. Tillett WS, Francis T. Serological Reactions in Pneumonia with a Non-Protein Somatic Fraction of *Pneumococcus*. *J Exp Med*. 1930; 52:561–71. [PubMed: 19869788]
83. Hengst JM. The role of C-reactive protein in the evaluation and management of infants with suspected sepsis. *Adv Neonatal Care*. 2003; 3:3–13. [PubMed: 12882177]
84. Philip AG, Mills PC. Use of C-reactive protein in minimizing antibiotic exposure: experience with infants initially admitted to a well-baby nursery. *Pediatrics*. 2000; 106:E4. [PubMed: 10878173]
85. Chiesa C, Signore F, Assumma M, et al. Serial measurements of C-reactive protein and interleukin-6 in the immediate postnatal period: reference intervals and analysis of maternal and perinatal confounders. *Clin Chem*. 2001; 47:1016–22. [PubMed: 11375286]
86. Forest JC, Lariviere F, Dolce P, Masson M, Nadeau L. C-reactive protein as biochemical indicator of bacterial infection in neonates. *Clin Biochem*. 1986; 19:192–4. [PubMed: 3524899]
87. Chiesa C, Natale F, Pascone R, et al. C reactive protein and procalcitonin: reference intervals for preterm and term newborns during the early neonatal period. *Clin Chim Acta*. 2011; 412:1053–9. [PubMed: 21338596]
88. Hofer N, Muller W, Resch B. Non-infectious conditions and gestational age influence C-reactive protein values in newborns during the first 3 days of life. *Clin Chem Lab Med*. 2011; 49:297–302. [PubMed: 21126207]
89. Auriti C, Fiscarelli E, Ronchetti MP, et al. Procalcitonin in detecting neonatal nosocomial sepsis. *Arch Dis Child Fetal Neonatal Ed*. 2012; 97:F368–70. [PubMed: 22933097]
90. Vouloumanou EK, Plessa E, Karageorgopoulos DE, Mantadakis E, Falagas ME. Serum procalcitonin as a diagnostic marker for neonatal sepsis: a systematic review and meta-analysis. *Intensive Care Med*. 2011; 37:747–62. [PubMed: 21380522]
91. Neth O, Jack DL, Dodds AW, Holzel H, Klein NJ, Turner MW. Mannose-binding lectin binds to a range of clinically relevant microorganisms and promotes complement deposition. *Infect Immun*. 2000; 68:688–93. [PubMed: 10639434]
92. Ozkan H, Koksall N, Cetinkaya M, et al. Serum mannose-binding lectin (MBL) gene polymorphism and low MBL levels are associated with neonatal sepsis and pneumonia. *J Perinatol*. 2012; 32:210–7. [PubMed: 21681178]
93. Ng PC, Li K, Wong RP, et al. Proinflammatory and anti-inflammatory cytokine responses in preterm infants with systemic infections. *Arch Dis Child Fetal Neonatal Ed*. 2003; 88:F209–13. [PubMed: 12719394]
94. Resch B, Gusenleitner W, Muller WD. Procalcitonin and interleukin-6 in the diagnosis of early-onset sepsis of the neonate. *Acta Paediatr*. 2003; 92:243–5. [PubMed: 12710654]

95. Genel F, Atlihan F, Gulez N, et al. Evaluation of adhesion molecules CD64, CD11b and CD62L in neutrophils and monocytes of peripheral blood for early diagnosis of neonatal infection. *World J Pediatr.* 2012; 8:72–5. [PubMed: 21874613]
96. Pammi M, Brocklehurst P. Granulocyte transfusions for neonates with confirmed or suspected sepsis and neutropenia. *Cochrane Database Syst Rev.* 2011:CD003956. [PubMed: 21975741]
97. Ng PC, Ang IL, Chiu RW, et al. Host-response biomarkers for diagnosis of late-onset septicemia and necrotizing enterocolitis in preterm infants. *J Clin Invest.* 2010; 120:2989–3000. [PubMed: 20592468]
98. Daniels JP, Gray J, Pattison HM, Gray R, Hills RK, Khan KS. Intrapartum tests for group B streptococcus: accuracy and acceptability of screening. *BJOG.* 2011; 118:257–65. [PubMed: 21040389]
99. Polin RA, Denson S, Brady MT. Strategies for prevention of health care-associated infections in the NICU. *Pediatrics.* 2012; 129:e1085–93. [PubMed: 22451712]
100. Kilbride HW, Wirtschafter DD, Powers RJ, Sheehan MB. Implementation of evidence-based potentially better practices to decrease nosocomial infections. *Pediatrics.* 2003; 111:e519–33. [PubMed: 12671172]
101. Bloom BT, Craddock A, Delmore PM, et al. Reducing acquired infections in the NICU: observing and implementing meaningful differences in process between high and low acquired infection rate centers. *J Perinatol.* 2003; 23:489–92. [PubMed: 13679937]
102. Andersen C, Hart J, Vemgal P, Harrison C. Prospective evaluation of a multi-factorial prevention strategy on the impact of nosocomial infection in very-low-birthweight infants. *J Hosp Infect.* 2005; 61:162–7. [PubMed: 16240469]
103. Shah P, Shah V. Continuous heparin infusion to prevent thrombosis and catheter occlusion in neonates with peripherally placed percutaneous central venous catheters. *Cochrane Database Syst Rev.* 2005:CD002772. [PubMed: 16034876]
104. Birch P, Ogden S, Hewson M. A randomised, controlled trial of heparin in total parenteral nutrition to prevent sepsis associated with neonatal long lines: the Heparin in Long Line Total Parenteral Nutrition (HILLTOP) trial. *Arch Dis Child Fetal Neonatal Ed.* 2010; 95:F252–7. [PubMed: 20530110]
105. Fanaroff AA, Korones SB, Wright LL, et al. A controlled trial of intravenous immune globulin to reduce nosocomial infections in very-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. *N Engl J Med.* 1994; 330:1107–13. [PubMed: 8133853]
106. Ohlsson A, Lacy J. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. *Cochrane Database Syst Rev.* 2010:CD001239. [PubMed: 20238315]
107. Brocklehurst P, Farrell B, King A, et al. Treatment of neonatal sepsis with intravenous immune globulin. *N Engl J Med.* 2011; 365:1201–11. [PubMed: 21962214]
108. Vernachio J, Bayer AS, Le T, et al. Anti-clumping factor A immunoglobulin reduces the duration of methicillin-resistant *Staphylococcus aureus* bacteremia in an experimental model of infective endocarditis. *Antimicrob Agents Chemother.* 2003; 47:3400–6. [PubMed: 14576094]
109. Patti JM, Allen BL, McGavin MJ, Hook M. MSCRAMM-mediated adherence of microorganisms to host tissues. *Annu Rev Microbiol.* 1994; 48:585–617. [PubMed: 7826020]
110. Weisman LE, Thackray HM, Steinhorn RH, et al. A randomized study of a monoclonal antibody (pagibaximab) to prevent staphylococcal sepsis. *Pediatrics.* 2011; 128:271–9. [PubMed: 21788224]
111. Benjamin DK, Schelonka R, White R, et al. A blinded, randomized, multicenter study of an intravenous *Staphylococcus aureus* immune globulin. *J Perinatol.* 2006; 26:290–5. [PubMed: 16598296]
112. Bloom B, Schelonka R, Kueser T, et al. Multicenter study to assess safety and efficacy of INH-A21, a donor-selected human staphylococcal immunoglobulin, for prevention of nosocomial infections in very low birth weight infants. *Pediatr Infect Dis J.* 2005; 24:858–66. [PubMed: 16220082]

113. Shah PS, Kaufman DA. Antistaphylococcal immunoglobulins to prevent staphylococcal infection in very low birth weight infants. *Cochrane Database Syst Rev.* 2009;CD006449. [PubMed: 19370635]
114. Carr R, Brocklehurst P, Dore CJ, Modi N. Granulocyte-macrophage colony stimulating factor administered as prophylaxis for reduction of sepsis in extremely preterm, small for gestational age neonates (the PROGRAMS trial): a single-blind, multicentre, randomised controlled trial. *Lancet.* 2009; 373:226–33. [PubMed: 19150703]
115. Poindexter BB, Ehrenkranz RA, Stoll BJ, et al. Effect of parenteral glutamine supplementation on plasma amino acid concentrations in extremely low-birth-weight infants. *Am J Clin Nutr.* 2003; 77:737–43. [PubMed: 12600870]
116. Tubman TR, Thompson SW, McGuire W. Glutamine supplementation to prevent morbidity and mortality in preterm infants. *Cochrane Database Syst Rev.* 2008;CD001457. [PubMed: 18253992]
117. Alfaleh K, Anabrees J, Bassler D, Al-Kharfi T. Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Cochrane Database Syst Rev.* 2011;CD005496. [PubMed: 21412889]
118. Bonsante F, Iacobelli S, Gouyon JB. Routine Probiotic Use in Very Preterm Infants: Retrospective Comparison of Two Cohorts. *Am J Perinatol.* 2012
119. Deshpande G, Rao S, Patole S, Bulsara M. Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. *Pediatrics.* 2010; 125:921–30. [PubMed: 20403939]
120. Manzoni P, Rinaldi M, Cattani S, et al. Bovine lactoferrin supplementation for prevention of late-onset sepsis in very low-birth-weight neonates: a randomized trial. *JAMA.* 2009; 302:1421–8. [PubMed: 19809023]
121. Kaufman D, Boyle R, Hazen KC, Patrie JT, Robinson M, Donowitz LG. Fluconazole prophylaxis against fungal colonization and infection in preterm infants. *N Engl J Med.* 2001; 345:1660–6. [PubMed: 11759644]
122. Manzoni P, Stolfi I, Pugni L, et al. A multicenter, randomized trial of prophylactic fluconazole in preterm neonates. *The New England journal of medicine.* 2007; 356:2483–95. [PubMed: 17568029]
123. Kaufman DA, Cuff AL, Wamstad JB, et al. Fluconazole prophylaxis in extremely low birth weight infants and neurodevelopmental outcomes and quality of life at 8 to 10 years of age. *J Pediatr.* 2011; 158:759–65 e1. [PubMed: 21168853]
124. Kicklighter SD, Springer SC, Cox T, Hulsey TC, Turner RB. Fluconazole for prophylaxis against candidal rectal colonization in the very low birth weight infant. *Pediatrics.* 2001; 107:293–8. [PubMed: 11158461]
125. Healy CM, Campbell JR, Zaccaria E, Baker CJ. Fluconazole prophylaxis in extremely low birth weight neonates reduces invasive candidiasis mortality rates without emergence of fluconazole-resistant *Candida* species. *Pediatrics.* 2008; 121:703–10. [PubMed: 18381534]
126. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009; 48:503–35. [PubMed: 19191635]
127. Cotten CM, Taylor S, Stoll B, et al. 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; 123:58–66. [PubMed: 19117861]
128. Kuppala VS, Meinen-Derr J, Morrow AL, Schibler KR. Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. *J Pediatr.* 2011; 159:720–5. [PubMed: 21784435]
129. Arslan U, Erayman I, Kirdar S, et al. *Serratia marcescens* sepsis outbreak in a neonatal intensive care unit. *Pediatr Int.* 2010; 52:208–12. [PubMed: 19664012]
130. Dashti AA, Jadaon MM, Gomaa HH, Noronha B, Udo EE. Transmission of a *Klebsiella pneumoniae* clone harbouring genes for CTX-M-15-like and SHV-112 enzymes in a neonatal intensive care unit of a Kuwaiti hospital. *J Med Microbiol.* 2010; 59:687–92. [PubMed: 20185547]

131. Golan Y, Doron S, Sullivan B, Snyderman DR. Transmission of vancomycin-resistant enterococcus in a neonatal intensive care unit. *Pediatr Infect Dis J*. 2005; 24:566–7. [PubMed: 15933574]
132. Linkin DR, Fishman NO, Patel JB, Merrill JD, Lautenbach E. Risk factors for extended-spectrum beta-lactamase-producing Enterobacteriaceae in a neonatal intensive care unit. *Infect Control Hosp Epidemiol*. 2004; 25:781–3. [PubMed: 15484805]
133. Maraki S, Scoulica E, Manoura A, Papageorgiou N, Giannakopoulou C, Galanakis E. A *Chryseobacterium meningosepticum* colonization outbreak in a neonatal intensive care unit. *Eur J Clin Microbiol Infect Dis*. 2009; 28:1415–9. [PubMed: 19685348]
134. Touati A, Achour W, Cherif A, et al. Outbreak of *Acinetobacter baumannii* in a neonatal intensive care unit: antimicrobial susceptibility and genotyping analysis. *Ann Epidemiol*. 2009; 19:372–8. [PubMed: 19364663]
135. Patel SJ, Oshodi A, Prasad P, et al. Antibiotic use in neonatal intensive care units and adherence with Centers for Disease Control and Prevention 12 Step Campaign to Prevent Antimicrobial Resistance. *Pediatr Infect Dis J*. 2009; 28:1047–51. [PubMed: 19858773]
136. Tamma PD, Cosgrove SE. Antimicrobial stewardship. *Infect Dis Clin North Am*. 2011; 25:245–60. [PubMed: 21316003]
137. Patel SJ, Saiman L, Duchon JM, Evans D, Ferng YH, Larson E. Development of an antimicrobial stewardship intervention using a model of actionable feedback. *Interdiscip Perspect Infect Dis*. 2012:150367. [PubMed: 22500166]
138. Chen SC, Slavin MA, Sorrell TC. Echinocandin antifungal drugs in fungal infections: a comparison. *Drugs*. 2011; 71:11–41. [PubMed: 21175238]
139. Smith PB, Walsh TJ, Hope W, et al. Pharmacokinetics of an elevated dosage of micafungin in premature neonates. *Pediatr Infect Dis J*. 2009; 28:412–5. [PubMed: 19319022]
140. Heresi GP, Gerstmann DR, Reed MD, et al. The pharmacokinetics and safety of micafungin, a novel echinocandin, in premature infants. *Pediatr Infect Dis J*. 2006; 25:1110–5. [PubMed: 17133155]
141. Benjamin DK Jr, Smith PB, Arrieta A, et al. Safety and pharmacokinetics of repeat-dose micafungin in young infants. *Clin Pharmacol Ther*. 2010; 87:93–9. [PubMed: 19890251]

Table 1

Risk Factors for the Development of Neonatal Sepsis

SOURCE	RISK FACTOR
Early Onset Neonatal Sepsis	
	Maternal GBS Colonization
	Chorioamnionitis
	Premature rupture of membranes
	Prolonged rupture of membranes (>18 hours)
	Maternal urinary tract infection
	Multiple pregnancies
	Preterm Delivery (<37 weeks)
Late Onset Neonatal Sepsis	
	Breakage of the natural barriers (skin and mucosa)
	Prolonged indwelling catheter use
	Invasive Procedures (eg. Endotracheal intubation)
	Necrotizing Enterocolitis
	Prolonged use of Antibiotics
	H ₂ -receptor blocker or proton pump inhibitor use
Neonatal*	
	Prematurity <ul style="list-style-type: none"> Decrease passage of maternal immunoglobulin and specific antibodies. Immature function of immune system

* Increases the risk for both early and late onset neonatal sepsis

Table 2

Organisms Associated with Early and Late Onset Neonatal Sepsis

Early Onset Sepsis	Late Onset Sepsis
Group B <i>streptococcus</i>	Coagulase negative <i>staphylococcus</i>
<i>Escherichia coli</i>	<i>Staphylococcus aureus</i>
<i>Listeria Monocytogenes</i>	<i>Enterococci</i>
Other streptococci: <i>S. pyogenes</i> , viridans group streptococci, <i>S. pneumonia</i>	Multi drug resistant Gram negative rods (<i>E. coli</i> , <i>Klebsiella</i> , <i>pseudomonas</i> , <i>enterobacter</i> , <i>citrobacter</i> , <i>serratia</i>)
<i>Enterococci</i>	<i>Candida</i>
Non-Typable <i>Haemophilus influenza</i>	

Table 3

Clinical Manifestations in Patients with Early and Late Onset Neonatal Sepsis

Sepsis/Meningitis	
	Temperature Instability
	Respiratory Distress
	Apnea
	Jaundice & Feeding intolerance
	Bulging fontanel
	Seizures
Other	
	Skin lesions: may occur in disseminated staphylococcal, <i>listeria</i> and <i>candida</i> infections.
	Joint and Bone: May be the preceding event

Table 4

Recommended Intrapartum Antibiotic Prophylaxis for GBS-positive Women

Antibiotic	Dose
Penicillin G	5 million units IV as an initial dose followed by 2.5 units every 4 hours
Ampicillin	2 grams IV as an initial dose, followed by 1 gram IV every 4 hours until delivery
Cefazolin	2 grams IV as an initial dose, followed by 1 gram IV every 8 hours until delivery.

Table 5

Evidence of Strategies for Prevention of Neonatal Sepsis

Prevention Strategy	Notes
Lactoferrin	Small studies show reduction of both fungal and bacterial infection. Large studies needed
IVIG	No proven efficacy for prevention of neonatal sepsis
Anti-staphylococcal Monoclonal Antibodies	Monoclonal antibodies against capsular polysaccharide and clumping Factor A have shown no effect in prevention of sepsis. Anti-lipoteichoic acid antibodies may have an effect but further randomized controlled studies are required.
Probiotics	No proven efficacy for neonatal sepsis. Useful as prevention of necrotizing enterocolitis.
GM-CSF/G-CSF ¹	No proven efficacy of neonatal sepsis
Glutamine	No proven efficacy of neonatal sepsis
Fluconazole	Efficacious in prevention of <i>Candida</i> sepsis in VLBW infants

Table 6

Principles for antibiotic use

Empiric initiation of antibiotics	Use only when bacterial infections are likely and discontinue empiric treatment when they have not been identified
Switch antibiotics based on susceptibility patterns	Change the antibiotic agents to those with the narrowest spectrum
Define duration of antibiotic therapy	Establish a final duration of antibiotic management based on the disease process

Table 7

Duration of Antibiotic Therapy in Neonatal Sepsis based on Clinical Presentation

Clinical Presentation	Duration of Antibiotic Therapy
Early Onset Sepsis without meningitis	10 days
Late Onset Sepsis without meningitis	10–14 days
Meningitis: Early or Late onset sepsis	14–21 days*

* Gram-negative rod meningitis: will require at least 21 days of therapy