Journal of Pediatrics & Child Health Care

Open Access

Austin Publishing Group

Review Article

Neonatal Sepsis: A Review of the Literature

Nyenga AM[1], Mukuku O[2,3]* and Wembonyama SO[1,3]

[1]Department of Pediatrics, University of Lubumbashi, Lubumbashi, Democratic Republic of the Congo
[2]Institut Superieur des Techniques Medicales, Lubumbashi, Democratic Republic of Congo
[3]School of Public Health, University of Goma, Goma, Democratic Republic of Congo

***Corresponding author:** Olivier Mukuku, Institut Superieur des Techniques Medicales, Lubumbashi, School of Public Health, University of Goma, Goma, Democratic Republic of Congo

Received: May 11, 2021; **Accepted:** June 03, 2021; **Published:** June 10, 2021

Abstract

Neonatal sepsis contributes significantly to neonatal morbidity and mortality and is a major public health challenge around the world. Depending on the mode of occurrence, a distinction is made between maternal-transmitted infection and that acquired in the postnatal period. Although the etiologies maternally transmitted diseases are well understood, those of postnatal acquired infections are variable depending on the epidemiology of each hospital environment. On the one hand, risk factors for maternal-transmitted infections are maternal sepsis, prolonged premature rupture of membranes, chorioamnionitis, and bacteriuria in the mother during pregnancy. On the other hand, risk factors for postnatal acquired infections are prematurity, low birth weight, lack of hygiene, and invasive therapeutic interventions. The diagnosis is based on a series of anamnestic, clinical and biological features. Although the positive diagnosis is based on the isolation of the germ by culture on a body sample (blood, cerebrospinal fluid, urine, etc.); its low sensitivity leads to the use of markers of the acute phase of inflammation such as C-reactive protein, procalcitonin and interleukins. New molecular biology techniques are promising and offer precise diagnosis with rapid results. Empirical management is a function of microbial ecology while definitive treatment is guided by the results of microbial culture.

This article presents the essential elements for understanding neonatal sepsis and discusses new diagnosis and therapeutic management. It offers a thorough reading based on the issue of infections in newborns.

Keywords: Neonatal sepsis; Early onset sepsis; Late onset sepsis; Risk factors; Management

Abbreviations

CSF: Cerebrospinal Fluid; EONS: Early Onset Sepsis; LONS: Late Onset Sepsis; NS: Neonatal Sepsis; PCR: Polymerase Chain Reaction; SIRS: Systemic Inflammatory Response Syndrome

Introduction

Neonatal Sepsis (NS) is defined as a systemic inflammatory response syndrome in the presence or following a suspected or established infection with or without associated bacteremia, documented by a positive blood culture during the first 28 days of life [1,2].

The term 'neonatal sepsis' is used to denote a condition of bacterial, viral or fungal origin associated with hemodynamic changes and other clinical manifestations [3]. Despite several years of expertise, many challenges remain in the diagnostic approach to newborns suspected of having NS. These include the lack of a consensual definition of NS in everyday practice.

Traditionally, the definition of sepsis has included the isolation of a pathogen from a normally sterile body fluid such as blood or Cerebrospinal Fluid (CSF) [4,5]. However, given the understanding of the role of potent pro-inflammatory cytokines in the clinical characterization of sepsis, the term 'Systemic Inflammatory Response Syndrome (SIRS)' has also been used to define sepsis in neonates [2,4]. NS can be caused by bacterial, viral, and fungal microorganisms. Although the current description is clear on bacterial causes, the share of other microorganisms is no less important in the hospital environment. These include Candida and Enteroviruses responsible for severe pictures of NS [6-9].

Two categories are to be distinguished according to the mode of occurrence

Early Onset Sepsis (EONS): these are infections of the newborn resulting from vertical mother to infant transmission which occurs in the perinatal period (before or soon after delivery) and which can appear within the first week of postnatal life [3,10,11]. In this context, infection occurs *in utero* from transplacental transmission or more commonly vertically (ascending) from the vaginal environment after rupture of membranes. In addition, the newborn can become infected when exposed to pathogenic bacteria, viruses or fungi as they pass through the birth canal [12-15].

Postnatal acquired infections (Late Onset Sepsis [LONS]): contamination occurs after delivery following interactions with the hospital or community environment. It usually starts after 72 hours of age. The source of contamination is either nosocomial or community [4,14-16].

Epidemiology

Analysis of several studies reports an estimate of NS of 2,202 (95% CI: 1,099 - 4,360) per 100,000 live births, with mortality between 11% and 19% in high- and middle-income countries [17]. However, the burden of NS varies greatly from one setting to another, depending on the level of organization of the health system and socio-demographic characteristics of the populations.

Citation: Nyenga AM, Mukuku O and Wembonyama SO. Neonatal Sepsis: A Review of the Literature. J Pediatr & Child Health Care. 2021; 6(2): 1042.

The reported incidence of NS ranges from 7.1 to 38 per 1,000 live births in Asia, 6.5 to 23 per 1,000 live births in Africa, and 3.5 to 8.9 per 1,000 live births in America South and the Caribbean. By comparison, reported rates in the United States and Australia vary from 1.5 to 3.5 per 1,000 for EONS and up to 6 per 1,000 live births for LONS, for a total of 6-9 per 1,000 for NS [18-22].

In the world, NS contributes significantly to neonatal morbidity and mortality; it constitutes a major public health challenge. The most common causes of death in the neonatal period are infections (35%), followed by prematurity (28%), intrapartum complications (24%), and asphyxia (23%) [2,23,24]. NS is responsible for 26% of deaths in children under-5, with the highest death rates in sub-Saharan Africa [25]. The data available is a mixture of official sources and studies both hospital and community [18].

In developing countries, statistics may be underestimated due to high rate of home deliveries and low percentage of attendance by skilled health workers. Establishing numbers and causes of neonatal deaths is therefore difficult given that a large number of newborns die at home without ever being in contact with health workers and without ever integrating the statistics.

Nonetheless, many studies report infections as one of the 3 leading causes of death both in the world and in Africa [26–31].

Risk Factors and Etiologies

Risk factors for EONS

Anamnestic risk factors for EONS [11] are classified into two groups in decreasing order of risk (although this classification does not prejudge a systematic therapeutic approach).

Major criteria (strongly linked to NS): chorioamnionitis, twin with mother to infant infection, maternal temperature before or during labor >38°C, spontaneous prematurity <35 weeks, Prolonged Rupture of Membranes (PROM) more than 18 h, premature rupture of membranes before 37 weeks, and maternal group B *streptococcus* infections (GBS) colonization/GBS bacteriuria (during index pregnancy).

Minor criteria (little related to NS): rupture of membranes more than 12 hours but less than 18 hours, spontaneous prematurity less than 37 weeks and more than 35 weeks, abnormal fetal heartbeat or unexplained fetal asphyxia, and tinted or meconium amniotic fluid.

The existence of one of these criteria requires clinical monitoring, particularly close during the first 24 hours of postnatal life. Infection and mortality are inversely related to birth weight and gestational age [3,10].

Microorganisms most implicated in EONS are those found in maternal urogenital and digestive tracts. These are *Streptococcus agalactiae* (Group B *streptococcus*) and *Escherichia coli*. Secondarily, *Monocytogenic listeria*, *Nontypeable Haemophilus influenzae*, and Gram-negative *Enterobacteriaceae* other than Escherichia coli are also implicated [3,10,11,19].

However, the application of a routine maternal screening program and intrapartum antibiotic prophylaxis in some countries has significantly reduced *Streptococcus agalactiae* in maternally transmitted NS [19,32].

Risk factors for LONS

In the hospital environment, several factors predispose to an increased risk of NS. These include stay in intensive care, prematurity, low birth weight, invasive medical procedures, mechanical ventilation, and use of parenteral fluid. Poorly disinfected hands and equipment are important vectors of germs [33,34].

In the community, the risk of NS is determined by poor hygiene in general (of the hands, bottle-feeding and poor umbilical cord care practices) [33,35,36].

Nevertheless, the important role of breastfeeding in preventing postnatal infection is proven [37-40]. Breast milk is believed to be an important vector of exchange between the maternal immune system and the newborn's body. The practice of breastfeeding actively regulates immune and metabolic systems and the microflora in the newborn while providing multiple means of protection against various pathogens [40,41].

Bacterial aetiologies of LONS are very varied and depend on one setting to another. Coagulase-negative *Staphylococci* are the most reported in neonatal intensive care units [42,43]. Other germs such as *methicillin-resistant Staphylococcus aureus* and multidrug-resistant Gram-negative bacteria (*Pseudomonas* and *Klebsiella*) are still common in developing countries unlike developed countries [44]. Some Gram-positive germs classically responsible for EONS (e.g. Group B *streptococcus*) can be found in LONS in the community or due to manual transmission or by contaminated equipment in a hospital environment [3,45,46].

The over- and inappropriate use of antibiotics has favored the emergence of unusual germs and the emergence of multi-resistance to common antimicrobials [47,48]. Viruses are also a major cause of nosocomial infections, but most of the time they are underestimated. These include, in particular, Enteroviruses and Rotaviruses. Systemic fungal infections are increasingly reported, with Candida albicans leading the way [7,8,49].

Clinical Features

Clinical features of NS are vague and ill-defined. Altered feeding behavior (refusal to breastfeed) is a common and early symptom, but not specific. Other signs are thermal disturbances (hypothermia or fever), lethargy, incessant crying, hypotonia, peripheral perfusion disorder (prolonged hair recoloration time), blunt neonatal archaic reflexes, cardiac arrhythmias (bradycardia or tachycardia), metabolic disorders such as hypoglycemia or hyperglycemia, and metabolic acidosis.

In the advanced-stage, signs of organ failure determine the severity of NS [1,3,10]. Symptoms specific to each system are:

- Central nervous system: these are a bulging of the anterior fontanel, a blank stare, a sharp and excessive cry, irritability, a coma, convulsions, and a retraction of the neck. The presence of these signs suggests the hypothesis of meningitis.

- Cardiac system: mainly hypotension and poor perfusion. Studies have emphasized the value of early diagnosis of NS using characteristic heart rate analysis over electrocardiographic monitoring. Griffin et al. [50] found that characteristic abnormal

heart rate such as reduced variability and transient decelerations occurred 24 hours before symptoms appeared in NS. Another group experienced an asymmetric increase in the RR interval in 3-4 days preceding sepsis with a greater increase in the last 24 hours [50,51]. These tests may be useful for early indication of therapeutic management.

- Gastrointestinal system: These include vomiting, diarrhea, abdominal distension, paralytic ileus and ulcerative necrotizing enterocolitis.

- Hepatic system: Common hepatic signs are hepatomegaly and direct hyperbilirubinemia. A newborn with jaundice or direct bilirubinemia after 8 days of postnatal life is more likely to have a urinary tract infection [52,53].

- Renal system: acute renal failure may be noted.

- Haematological system: bleeding and petechiae or purpura may be observed.

- Skin system: Multiple pustule-like rashes, sclerema, mottling and oozing umbilicus have been reported. De Felice et al. used colorimetric analysis of skin color to assess the severity of sepsis [52,54].

Diagnostic Approach of NS

The diagnosis of NS is based on a host of anamnestic, clinical, and biological arguments. History-taking information helps assess risk factors for sepsis in the newborn and in the mother. There is a significant correlation between some factors (maternal, environmental, and neonatal) and the occurrence of sepsis [55–57].

Prediction algorithms and scores have been developed to assess the risk of NS and thereby reduce exposure to empiric antibiotics. In addition, a good number of the cases of sepsis presented a poor clinical practice even asymptomatic in the immediate postnatal period [58–60]. Clinical signs of sepsis in the newborn are nonspecific. Several non-infectious clinical pictures can constitute differential diagnoses. Likewise, features relating to the immaturity of some functions, in this case in prematurity, may coexist with an infectious process whose demarcation will not be easy in clinical practice. Nevertheless, a careful clinical examination makes it possible to formulate the diagnostic hypothesis and thus guide paraclinical investigations [3].

Several biological approaches are being studied in the development of NS. However, many of them do not have sufficient sensitivity and specificity to be used in isolation [61]. Isolation of the pathogen in a normally aseptic body sample (blood, cerebrospinal fluid, urine, etc.) is the gold standard in the diagnosis of sepsis [4,62]. However, the low sensitivity and the waiting time for results, especially for blood culture, limit its effectiveness in deciding whether to start treatment. Therefore, the use of biomarkers of the host's response to infection, especially those of the acute phase of inflammation, is of great utility in clinical practice. The most widely used are white blood cell count, C-reactive protein, procalcitonin and interleukins. Understanding the kinetics of inflammatory markers during the infectious process as well as the significant thresholds is essential for a good interpretation. In addition, a combination of different biomarkers can increase sensitivity and specificity in the diagnosis of sepsis [61–63].

High sensitivity molecular diagnostic techniques are developed to overcome the limitations of microbial cultures. These new techniques target the early detection of the pathogen-specific nucleic acid. These are real-time Polymerase Chain Reaction (PCR), PCR followed by post-PCR treatment (matrix hybridization or mass spectroscopy), and Fluorescence *In Situ* Hybridization (FISH). These techniques have the advantage of being quick and requiring small amounts of blood sample. However, although promising, the cost and complexity of molecular biology analyzes do not currently allow their use in current practice and on a large scale [61,64].

Treatment of NS

Given the etiological diversity of sepsis in newborns, several cases can be envisaged in antimicrobial management. On the one hand, the antimicrobial therapeutic approach of NS can be distinguished according to whether they are suspected cases (empiric treatment) or cases with a pathogen well identified by culture (definitive treatment). On the other hand, the clinical picture and the mode of occurrence (EONS or LONS) must be taken into account in the choice of antibiotics.

To do this, a good anamnestic investigation and a careful clinical examination are essential. Under ideal conditions, a positive bacterial culture before starting treatment is an asset that would effectively and efficiently guide the choice of antibiotic. However, given the prognosis of NS, specimen collection and culture results should not delay initiation of treatment in symptomatic newborns.

Empirical treatment

By consensus, the empirical approach should be guided by data from antibiograms on bacteria commonly isolated in the neonatal care unit or in the community. Empiric treatment for EONS should consist of administration of Ampicillin and an aminoglycoside (most commonly Gentamicin) with a third or fourth generation cephalosporin. Piperacillin-Tazobactan and Ampicillin-Sulbactan are increasingly used in patients admitted to neonatal intensive care. However, given the low penetration of Tazobactan into the blood-brain barrier, its indication is limited in meningitis, whereas the combination of Sulbactam (beta-lactamase inhibitor) with ampicillin seems to have a good diffusion in the central nervous system [3,65,66]. In the case of nosocomial infections, the most susceptible germs are of the group of coagulase negative *Staphylococci* compared to *Staphylococcus aureus* and Gram-negative bacteria. In order to reduce the use of Vancomycin (due to the emergence of resistance), an empirical treatment made of an antistaphylcoccal beta-lactam such as Nafcillin combined with an aminoglycoside is proposed before the results of bacterial cultures [67,68].

Definitive treatment

The definitive antimicrobial treatment will be chosen based on the germ identified (by the culture), its sensitivity (antibiogram) and its bioavailability at the main site (s) of infection. In general, the antibiotic of choice should have better systemic availability and good diffusion through the blood-brain barrier.

Ampicillin or any other antibiotic from the penicillin group is generally effective against group B *streptococcus*. Gentamycin is often used in common practice for a synergistic effect with ampicillin;

whereas ampicillin alone has excellent efficacy against *monocytogenic Listeria* [10,69]. The third generation cephalosporins seem to be well indicated in the treatment of enterobacterial septicemia, especially if a meningeal transplant is suspected [3,70].

Inappropriate use of antibiotics has favored the emergence of strains resistant to several common antibiotics, especially from the beta-lactam class. This explains the increasingly frequent use of vancomycin, carbapenemes and combinations with sulbactan [47,48,71].

Prevention

Preventive measures focus on the asepsis of the newborn. The hygiene of hands and equipment used, the reduction of manipulations and invasive procedures as well as early enteral feeding are important pillars [72]. Newborns at risk should be given special surveillance. Breastfeeding is the ideal natural way to help impart anti-infective, anti-inflammatory and immunomodulatory properties to the newborn. Breast milk contains many bioactive molecules that protect against infection and inflammation in the form of cytokines, nucleotides, hormones, and growth factors. The anti-infective properties of breast milk are based on both soluble factors (immunoglobulins) and cellular elements [37,39]. Sound antimicrobial management and surveillance of antimicrobial resistance would improve the prognosis of NS.

Long-Term Prognosis

In the long term, newborns with sepsis are prone to growth deficits and neurodevelopmental disorders. In the event of NS, newborns with low birth weight are at greater risk of developing cerebral palsy and neurodevelopmental delay [10,73].

On the one hand, sepsis affects the long-term neurodevelopmental prognosis, either by directly affecting the central nervous system or by causing severe systemic inflammatory lesion responsible for bronchopulmonary dysplasia, retinopathy of prematurity, and cerebral hemorrhages [74]. On the other hand, an association between the development of atopic diseases in childhood and a history of NS has been reported [75,76].

References

1. Goldstein B, Giroir B, Randolph A, et al. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatric critical care medicine. 2005; 6: 2-8.
2. Agnche Z, Yeshita HY, Gonete KA. Neonatal sepsis and its associated factors among neonates admitted to neonatal intensive care units in primary hospitals in central gondar zone, northwest ethiopia, 2019. Infect Drug Resist. 2020; 13: 3957–3967.
3. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. Lancet. 2017; 390: 1770–1780.
4. Tripathi S, Malik G. Neonatal Sepsis: past, present and future; a review article. Internet J Med Updat - EJOURNAL. 2010; 5: 45–54.
5. Ahirrao BM, Dravid N, Ahirrao M, Nikumbh D, Gadre A, Gondane S. Diagnostic utility of Haematological Scoring System (HSS) with clinicopathological and bacteriological evaluationin early diagnosis of neonatal sepsis. Ann Pathol Lab Med. 2017; 4: A721–A726.
6. Barton M, Shen A, Brien KO, Robinson JL, Davies HD, Asztalos E, et al. Early Onset Invasive Candidiasis in Extremely Low Birth Weight Infants: Perinatal Acquisition Predicts Poor Outcome. Clinical Infectious Diseases. 2017; 64: 921-927.
7. Kaufman DA, Coggins SA, Zanelli SA, Weitkamp JH. Congenital Cutaneous Candidiasis: Prompt Systemic Treatment Is Associated with Improved Outcomes in Neonates. Clin Infect Dis. 2017; 64: 1387–1395.
8. Morriss F, Lindower J, Bartlett H, Atkins D, Kim J, Klein J, et al. Neonatal Enterovirus Infection: Case Series of Clinical Sepsis and Positive Cerebrospinal Fluid Polymerase Chain Reaction Test with Myocarditis and Cerebral White Matter Injury Complications. Am J Perinatol Reports. 2016; 06: e344–e351.
9. Chuang YY, Huang YC. Enteroviral infection in neonates. J Microbiol Immunol Infect. 2019; 52: 851–857.
10. Walker O, Kenny CB, Goel N. Neonatal sepsis. Paediatr Child Heal (United Kingdom). 2019; 29: 263–268.
11. Blond MH, Poulain P, Gold F, Bingen E, Watier H, Quentin R. Maternal-fœtal bacterial infection. EMC - Gynecol. 2005; 2: 28–90.
12. Read JS, Cannon MJ, Stanberry LR, Schuval S. Prevention of Mother-to-Child Transmission of Viral Infections. Curr Probl Pediatr Adolesc Health Care. 2008; 38: 274–297.
13. O'Keefe C. Viral infections in the neonate. Newborn Infant Nurs Rev. 2010; 10: 195–202.
14. Al-Taiar A, Hammoud MS, Cuiqing L, Lee JKF, Lui KM, Nakwan N, et al. Neonatal infections in China, Malaysia, Hong Kong and Thailand. Arch Dis Child Fetal Neonatal Ed. 2012; 98: F249–F255.
15. Kim F, Polin RA, Hooven TA. Neonatal sepsis. BMJ. 2020; 371: m3672.
16. Giannoni E, Agyeman PKA, Stocker M, Posfay-Barbe KM, Heininger U, Spycher BD, et al. Neonatal Sepsis of Early Onset, and Hospital-Acquired and Community-Acquired Late Onset: A Prospective Population-Based Cohort Study. J Pediatr. 2018; 201: 106-114.e4.
17. Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, Schlapbach LJ, Reinhart K, Kissoon N. The global burden of paediatric and neonatal sepsis: a systematic review. Lancet Respir Med. 2018; 6: 223–230.
18. Vergnano S, Sharland M, Kazembe P, Mwansambo C, Heath PT. Neonatal sepsis: An international perspective. Arch Dis Child Fetal Neonatal Ed. 2005; 90: F220–F225.
19. Hyde TB, Hilger TM, Reingold A, Farley MM, Katherine L, Brien O, et al. Population-Based Surveillance in San Francisco and Atlanta. Heal San Fr. 2011; 110: 1996–2003.
20. Tallur SS, Kasturi AV, Nadgir SD, Krishna BVS. Clinico-bacteriological study of neonatal septicemia in Hubli. Indian J Pediatr. 2000; 67: 169–174.
21. Heath PT, Nik Yusoff NK, Baker CJ. Neonatal meningitis. Arch Dis Child Fetal Neonatal Ed. 2003; 88: F173–F179.
22. Schuchat A, Zywicki SS, Dinsmoor MJ, Mercer B, Romaguera J, Sullivan MJO, et al. Risk factors and opportunities for prevention of early-onset neonatal sepsis: a multicenter case-control study. Pediatrics. 2000; 105: 21-26.
23. Getabelew A, Aman M, Fantaye E, Yeheyis T. Prevalence of Neonatal Sepsis and Associated Factors among Neonates in Neonatal Intensive Care Unit at Selected Governmental Hospitals in Shashemene Town, Oromia Regional State, Ethiopia, 2017. International Journal of Pediatrics. 2018; 2018: 7801272.
24. Kanteng AW NM. Mortalité á L'unité de Néonatologie des Cliniques Universitaires de Lubumbashi ; Congo. Rev. méd. Gd. Lacs. 2012; 1: 232-244.
25. Ranjeva SL, Warf BC, Schiff SJ. Economic burden of neonatal sepsis in sub-Saharan Africa. BMJ global health. 2018; 3: e000347.
26. Chemsi M, Benomar S. Infections bactériennes néonatales précoces. J Pediatr Pueric. 2015; 28: 29–37.
27. Lawn J, Shibuya K, Stein C. No cry at birth : global estimates of intrapartum stillbirths and intrapartum-related neonatal deaths. Bulletin of the World Health Organization. 2005; 83: 409-417.
28. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, et al. Global, regional, and national causes of child mortality in 2008: a systematic

analysis. Lancet. 2010; 375: 1969–1987.

29. OMS. Nouveau nés_réduire la mortalité. 2018.

30. Sankar MJ, Natarajan CK, Das RR, Agarwal R, Chandrasekaran A, Paul VK. When do newborns die? A systematic review of timing of overall and cause-specific neonatal deaths in developing countries. J Perinatol. 2016; 36: S1–11.

31. Nyenga AM, Malonda BN AA, Assumani AN, Mukuku O LO, Al E. Trends in Neonatal Mortality in Lubumbashi (Democratic Republic of Congo) from 2011 to 2018. 2019; 2: 1–5.

32. Russell NJ, Seale AC, O'Sullivan C, Le Doare K, Heath PT, Lawn JE, et al. Risk of Early-Onset Neonatal Group B Streptococcal Disease with Maternal Colonization Worldwide: Systematic Review and Meta-analyses. Clin Infect Dis. 2017; 65: S152–S159.

33. Boghossian NS, Page GP, Bell EF, Stoll BJ, Murray JC, Cotten CM, et al. Late-onset sepsis in very low birth weight infants from singleton and multiple-gestation births. J Pediatr. 2013; 162: 4–9.

34. Doit C, Biran V, Aujard Y. Infections nosocomiales en néonatologie: Nosocomial infections in neonatal units. Infections néonatales. Elsevier Masson SAS. 2015; 91–106.

35. Downey LC, Smith PB, Benjamin DK. Risk factors and prevention of late-onset sepsis in premature infants. Early Hum Dev. 2010; 86: 7–12.

36. Kuti BP, Ogunlesi TA, Oduwole O, Oringanje C, Udoh EE, Meremikwu MM. Hand hygiene for the prevention of infections in neonates. Cochrane Database of Systematic Reviews. 2019; 2019: CD013326.

37. Turck D, Vidailhet M, Bocquet A, Bresson JL, Briend A, Chouraqui JP, et al. Allaitement maternel: les bénéfices pour la santé de l'enfant et de sa mère. Archives de pédiatrie. 2013; 20: S29-S48.

38. Munblit D, Treneva M, Peroni DG, Colicino S, Chow LY, Dissanayeke S, et al. Immune components in human milk are associated with early infant immunological health outcomes: A prospective three-country analysis. Nutrients. 2017; 9.

39. Giannattasio A, Marra V, Zoccali S, Capasso L, Raimondi F. Nutrition and immunity in newborns. Ital J Pediatr. 2015; 41: A33.

40. Field CJ. The immunological components of human milk and their effect on immune development in infants. J Nutr. 2005; 135: 1–4.

41. Donovan SM, Comstock SS. Human milk oligosaccharides influence neonatal mucosal and systemic immunity. Ann Nutr Metab. 2017; 69: 42–51.

42. Marchant EA, Boyce GK, Sadarangani M, Lavoie PM. Neonatal sepsis due to coagulase-negative staphylococci. Clin Dev Immunol. 2013; 2013: 586076.

43. Bizzarro MJ, Shabanova V, Baltimore RS, Dembry LM, Ehrenkranz RA, Gallagher PG. Neonatal sepsis 2004-2013: The rise and fall of coagulase-negative staphylococci. J Pediatr. 2015; 166: 1193–1199.

44. Downie L, Armiento R, Subhi R, Kelly J, Clifford V, Duke T. Community-acquired neonatal and infant sepsis in developing countries: Efficacy of WHO's currently recommended antibiotics - Systematic review and meta-analysis. Arch Dis Child. 2013; 98: 146–154.

45. Janota J. Hand hygiene with alcohol hand rub and gloves reduces the incidence of late onset sepsis in preterm neonates. Acta paediatrica. 2014; 103: 1053-1056.

46. Waters D, Jawad I, Ahmad A, Lukšić I, Nair H, Zgaga L, et al. Aetiology of community-acquired neonatal sepsis in low and middle income countries. Journal of global health. 2011; 1: 154-170.

47. Mve Koh Valère Salomon, Mengouna Jean-Rosaire, Essiben Félix GKH. Colonisation Génitale et Profil de Sensibilité du Streptocoque du Groupe B chez les Femmes Enceintes dans deux Hôpitaux de Yaoundé. Heal Sci Dis. 2017; 18: 21–25.

48. Gbonon V, Guessan RN, Guessennd N, Ouattara D. Ecologie et sensibilité aux antibiotiques des bactéries isolées d'infections materno-fœtales au chu de yopougon (abidjan). Revue Bio-Africa. 2013; 12: 13-18.

49. Habzi A, Benomar S. Les Infections Nosocomiales Néonatales. J Pédiatrie Puériculture. 2001; 14: 419–424.

50. Griffin MP, Lake DE, O'Shea TM, Moorman JR. Heart rate characteristics and clinical signs in neonatal sepsis. Pediatr Res. 2007; 61: 222–227.

51. Fairchild KD. Predictive monitoring for early detection of sepsis in neonatal ICU patients. Curr Opin Pediatr. 2013; 25: 172–179.

52. De Felice C, Flori ML, Pellegrino M, Toti P, Stanghellini E, Molinu A, et al. Predictive value of skin color for illness severity in the high-risk newborn. Pediatr Res. 2002; 51: 100–105.

53. Abourazzak S, Alaoui K, Oulmaati A, Hida M, Bouharrou A. L'approche de l'ictère dans l'infection urinaire néonatale. Arch Pédiatrie. 2010; 17: 72.

54. Kale A, Jaybhaye DL, Bonde V. Neonatal sepsis: An update. Iran J Neonatol. 2014; 4: 39–51.

55. Nyenga A, Mukuku O, Mutombo AM ulang, Luboya ON umb. Neonatal infections: what is the place of obstetric history in the prevention of risk? Pan Afr Med J. 2014; 19: 133.

56. Adatara P, Afaya A, Salia SM, Afaya RA, Konlan KD, Agyabeng-fandoh E, et al. Risk Factors Associated with Neonatal Sepsis: A Case Study at a Specialist Hospital in Ghana. 2019; 2019: 9369051.

57. Kardana IM. Incidence and factors associated with mortality of neonatal sepsis. Paediatr Indones. 2011; 51: 144.

58. Puopolo KM, Draper D, Wi S, Newman TB, Zupancic J, Lieberman E, et al. Estimating the probability of neonatal early-onset infection on the basis of maternal risk factors. Pediatrics. 2011; 128: e1155-e1163.

59. Mukhopadhyay S, Puopolo KM. Risk Assessment in Neonatal Early Onset Sepsis. Semin Perinatol. 2012; 36: 408–415.

60. Kuzniewicz MW, Puopolo KM, Fischer A, Walsh EM, Li S, Newman TB, et al. A quantitative, risk-based approach to the management of neonatal early-onset sepsis. JAMA Pediatr. 2017; 171: 365–371.

61. Ruoss JL, Wynn JL. Biomarkers in the Diagnosis of Neonatal Sepsis [Internet]. Infectious Disease and Pharmacology. Elsevier Inc. 2019; 103–112.

62. Zea-Vera A, Ochoa TJ. Challenges in the diagnosis and management of neonatal sepsis. J Trop Pediatr. 2015; 61: 1–13.

63. Meem M, Modak JK, Mortuza R, Morshed M, Islam MS, Saha SK. Biomarkers for diagnosis of neonatal infections: A systematic analysis of their potential as a point-of-care diagnostics. J Glob Health. 2011; 1: 201–209.

64. Pammi M, Flores A, Leeflang M, Versalovic J. Molecular assays in the diagnosis of neonatal sepsis: A systematic review and meta-analysis. Pediatrics. 2011; 128: e973-e985.

65. Lutsar I, Telling K, Metsvaht T. Treatment option for sepsis in children in the era of antibiotic resistance. Expert Rev Anti Infect Ther. 2014; 12: 1237–1252.

66. Sullins AK, Abdel-Rahman SM. Pharmacokinetics of antibacterial agents in the CSF of children and adolescents. Pediatr Drugs. 2013; 15: 93–117.

67. Chiu CH, Michelow IC, Cronin J, Ringer SA, Ferris TG, Puopolo KM. Effectiveness of a guideline to reduce vancomycin use in the neonatal intensive care unit. Pediatr Infect Dis J. 2011; 30: 273–278.

68. Magers J, Prusakov P, Sanchez PJ. 1144. Evaluation of Nafcillin *vs.* Vancomycin as Empiric Therapy for Late-Onset Sepsis in the Neonatal Intensive Care Unit. Open Forum Infect Dis. 2019; 6.

69. Elbeldi A, Smaoui H, Hamouda S, Helel S, Hmaied F, Ben Mustapha I, et al. Les infections à Listeria monocytogenes à Tunis : à propos de sept cas. Bull la Soc Pathol Exot. 2011; 104: 58–61.

70. Furyk JS, Swann O, Molyneux E. Systematic review: Neonatal meningitis in the developing world. Trop Med Int Heal. 2011; 16: 672–679.

71. Awad HA, Mohamed MH, Badran NF, Mohsen M, Abd-Elrhman ASA. Multidrug-resistant organisms in neonatal sepsis in two tertiary neonatal ICUs, Egypt. J Egypt Public Health Assoc. 2016; 91: 31–38.

72. Shane AL, Stoll BJ. Neonatal sepsis: Progress towards improved outcomes. J Infect. 2014; 68: S24–32.

73. Alshaikh B, Yusuf K, Sauve R. Neurodevelopmental outcomes of very low birth weight infants with neonatal sepsis: Systematic review and meta-analysis. J Perinatol. 2013; 33: 558–564.

74. Bakhuizen SE, De Haan TR, Teune MJ, Van Wassenaer-Leemhuis AG, Van Der Heyden JL, Van Der Ham DP, et al. Meta-analysis shows that infants who have suffered neonatal sepsis face an increased risk of mortality and severe complications. Acta Paediatr Int J Paediatr. 2014; 103: 1211–1218.

75. Peroni DG, Pescollderungg L, Piacentini GL, Pollini F, De Luca G, Boner AL. Neonatal sepsis and later development of atopy. Allergol Immunopathol (Madr). 2009; 37: 281–284.

76. Sobko T, Schiött J, Ehlin A, Lundberg J, Montgomery S, Norman M. Neonatal sepsis, antibiotic therapy and later risk of asthma and allergy. Paediatr Perinat Epidemiol. 2010; 24: 88–92.