

Research Article

Early-Onset Neonatal Sepsis: The Challenges of Management

Meryem Dahou^{*}, Mouna Lehlmi, Zineb Korchi, Rabiaa Chaini, Amal Badre, Mounir Chems, Abdelahk Habzi

Department of Neonatal Reanimation (P4), Children's Hospital A. Harouchi, CHU Ibn Rochd, Hassan II University, Faculty of Medicine and Pharmacy of Casablanca, Casablanca, Morocco

Abstract

Early-onset sepsis (EOS) is a worldwide major cause of morbidity and mortality especially in developing countries. The objectives of our study is to estimate the frequency of EOS, explore the different risk factors, the clinical features, the hematological, inflammatory and bacteriological parameters necessary for diagnosis, different causative organisms and ATB susceptibility in EOS. A 10-year retrospective study was used, including 153 cases that met the inclusion criteria. Among the 8908 admissions in NICU, sepsis occurred in 2,28% of cases. The sex ratio was 2,1 (Male: 62%, Female: 38%). Chorioamnionitis occurred in 13,7% of cases, PPRM in 44,4%. Intrapartum fever was found in 7% of cases, and amniotic fluid abnormalities in 36,6%. In neonatal risk factors we found prematurity in 76,15% of cases and VLBW in 21,56%. Respiratory distress was the most common symptom at admission with 66,1%. Bacteriological exam showed a positive Blood culture in 19,6% (30) of cases. The most common organisms isolated were E. coli in 16 cases, Group B streptococcus in 11 cases, and a positive LP in only 1 case isolating E. coli. All patients admitted to the NICU suspected of sepsis had a triple antibiotherapy. In our study, sepsis was responsible for 46,4% of deaths out of which 15 died at the first day of admission. Neonatal sepsis is associated with high rate of neonatal mortality. Poor antenatal care, absence of pregnancies follow-up, prematurity and very low birth weight are risk factors associated with EOS. In order to decrease EOS incidence and improve outcome for neonates, a contribution between Neonatologists and Obstetricians is a must.

Keywords

Neonatology, Early-Onset Sepsis, Risk Factors, Biomarker, Antibiotherapy

1. Introduction

Neonatal sepsis is a serious bacterial infection that occurs in newborns within the first 28 days of life, it's can be classified as early-onset neonatal sepsis and late-onset neonatal sepsis based on the age of onset. Early-onset sepsis (EOS) is defined as onset of features of sepsis within 72 hours of life

while Late-onset sepsis (LOS) is defined as onset of features of sepsis after 72hours of life [24].

Neonatal sepsis is a worldwide major cause of morbidity and mortality especially in developing countries. It presents with symptoms of systemic inflammatory response syndrome (SIRS)

*Corresponding author: Meryem.dahou0@gmail.com (Meryem Dahou)

Received: 8 February 2024; **Accepted:** 9 March 2024; **Published:** 2 April 2024



Copyright: © The Author(s), 2023. Published by Science Publishing Group. This is an **Open Access** article, distributed under the terms of the Creative Commons Attribution 4.0 License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

and can easily lead to septic shock and death [1]. The gold standard for diagnosis is a positive blood culture, which is positive in only 50-80% at best, however, negative blood culture does not rule out the disease [2]. Early treatment with appropriate antibiotics would minimize the risk of severe morbidity and mortality besides reducing the emergence of multidrug resistant organisms in intensive care units by rational antibiotic use [3].

2. Objectives

The purpose of this study is to estimate the frequency of EOS and to explore the risk factors, clinical symptoms, hematological; inflammatory and bacterial parameters, necessary for diagnosis, causative pathogen and antibiotic susceptibility of EOS.

3. Materials and Methods

The present study is a hospital-based retrospective study during 10 years (January 2012-December 2021), conducted in the neonatal intensive care unit (NICU) of pediatrics' department at the university hospital Mother-Infant center ABDERRAHIM EL HAROUCHI in Casablanca, Morocco.

In the period study, the NICU of pediatrics department enrolled 8908 neonates, out of which 185 newborns were admitted for suspected sepsis but only 153 of these met inclusion criteria:

1. Neonatal sepsis present with symptoms of systemic inflammatory response (SIRS) syndrome leading easily to a septic shock.
2. All neonates admitted to our NICU, presenting clinical manifestation of neonatal sepsis in the first 72 hours of life (EOS) and one or more of perinatal risk factors were included.
3. The clinical manifestations suggestive of sepsis, can present in the form of respiratory distress, tachypnea, apnea, oxygen dependence, feeding intolerance, poor feeding, hypotension, shock, poor peripheral perfusion, tachycardia, bradycardia lethargy, temperature instability, seizures, marbles or sclerema.
4. The perinatal risk factors are prolonged premature rupture of membranes, chorioamnionitis, intrapartum fever, prematurity, low birth weight.

The collection of Data in our study was based on a farm return (cf. Annexes 1) that was designed from the neonates' medical files, written in English and filled up from neonates' records found in the register and medical files available in the NICU department, and analyzed using EXCEL 2016.

4. Results

4.1. Epidemiological Data

During the study period from January 2012 to December

2021, 8908 neonates were hospitalized in the NICU.

Out of the enrolled patients, 2,28% (185/8908) were admitted for suspected sepsis. Out of these, 82,7% (153/185) were eligible to the inclusion criteria. The sex ratio was 2,1 (Male: 62%, Female: 38%). 16% of neonates were enrolled in the first 24 hours, 32% within 24H-48H and 52% within 48H-72H of life. 76% were inborn. 71,2% (109) of mothers had an age between 18-35 years, 24,1% (37) were aged more than 35 years and 4,57% (7) were aged less than 18 years. The mean maternal age was 29,5 years.

4.2. Clinical Data

4.2.1. The Maternal Risk Factors

They were Prolonged premature rupture of membranes (PROM) in 44,4% (68), intrapartum fever in 7% (11) and chorioamnionitis in 13,7% (21), and amniotic fluid abnormalities in 36,6% (56).

4.2.2. Neonatal Parameters

The neonatal risk factors for neonatal sepsis were:

Prematurity in 76,4% (117), the distribution of GA among neonates was:

1. GA < 28 WA = 5,1%.
2. GA 28- <32 WA = 27%
3. GA 32-<37 WA = 44,3%.
4. GA >37 WA = 23,6%.

24,83% (38) of neonates had a very low birth weight <1500g.

56,2% (86) had a weight between 1500-2499g and 18,95% (29) a weight ≥2500g. Low Apgar at 5-minute in 21,56% (33).

4.2.3. Neonates' Clinical Presentation

Respiratory distress was the most common symptom at admission with 66,1% (102). 3,2% (5) were admitted for fever and 4,3% (7) for neurological distress. Other signs were seen too such as hemorrhage syndrome in 7,1% (11), low sucking reflex in 14,4% (23), sclerema in 3% (5), apnea in 9% (14), tachycardia in 22,2% (34) and jaundice in 7,8% (12), hypothermia in 47 % (72), Hyperglycemia was found 13,70% (21) and hypoglycemia in 9,1% (14) of cases. 13,07% (20) had oliguria and 2,4% (4) had anuria.

At physical exam:

Respiratory exam: tachypnea occurred in 64,05% of cases, 15,03% had bradypnea. 47,05% (72) of neonates had a Silverman score ≥3: 37,2% (57) had a Silverman score between 3-5, and 15,6% (24) had a Silverman score >5. Pulmonary auscultation showed that 14,43% of neonates had ronchis and 8,49% had cracklings.

Cardiac exam tachycardia and bradycardia in 22,87% and 10,45% respectively. CRT was prolonged in 39,86% of cases. Cyanosis was found in 28,21% of cases and sclerema in 3% of cases.

Neurological exam: 24,83% (38) of neonates were sleepy

and 7,1% (11) were unconscious. Hypotonia was found in 63,33% (68) of neonates, Seizures were found in 2,6% (4) of neonates. 3,9% (6) had sunken FA, Archaic reflexes were low in 24,8% (38), absent in 16,9% (26).

Abdominal exam: Hepatomegaly was present in 3,9% (6) of cases, Splenomegaly was present in 1,9% (3) of neonates. The exam of the umbilicus showed a meconium staining umbilicus in 18,9% (29).

4.3. Laboratory Data

Bacteriological exam showed a positive Blood culture in 19,6% (30) of cases. The most common organisms isolated were *E. coli* in 16 cases, group B streptococcus (GBS) in 11, and a positive lumbar puncture in only 1 case isolating *E. coli*.

1. CBC showed a leukopenia ($< 5000/\text{ml}$) in 27,45%, leukocytosis (superior at $25000/\text{ml}$) in 8,49% and thrombocytopenia in 31 of cases, Anemia occurred in 25,49% (39) of cases. CRP was positive in 26,7% (41) of cases.
2. The Chest radiograph: Pneumonia occurred in 4,57% (7) of cases, Alveolitis occurred in 7,18% (11) of cases, PNO was found in 1,3% (2) of cases and Hyaline membrane disease was found in 17,64% (27) of cases.

4.4. Treatment

At the admission 67,32% (103) of neonates were immediately intubated, 4,57% (7) were put on CPAP and 44,23% received oxygen. All patients admitted to the NICU suspected of sepsis had a triple antibiotherapy: Amoxicillin + Gentamycin + Ceftriaxone.

Dobutamine was used alone in 27,45% (42) of cases and was associated with norepinephrine in 22,2% (34) of cases. Dopamine was used in 12,4% (19) of cases and Epinephrine was used in 15,68% (24) of cases. The mean duration of drugs use was 3,18 days [1-13].

A Central line catheter (CLC) was used in 54,24% (83) of neonates. 23,1% (36) of neonates received hydrocortisone with a mean duration of 2,25 days [1-5]. 26,9% of neonates were under diuretics.

All neonates admitted to the NICU had parenteral nutrition, 36,6% (56) had an exclusive parenteral nutrition, in 46,40% (71), parenteral nutrition was combined with artificial feeding, mixed feeding or breastfeeding. All neonates had nursing management and were put in incubator. In our study, the median length of hospitalization was 9,3 days. 44,4% (68) of patients had a secondary infection during their hospitalization.

The sepsis was responsible for 46,4% (71) of deaths out of which 15 died at the first day of admission.

53,59% (82) of neonates admitted have been discharged within 20 days. Among these: 27 neonates had no complications and 3 neonates had complications: 1 neonate developed a cognitive delay in language and speech at 5 years of follow-up, 1 neonate developed psychomotor delay, 4 had developed a seizure and was put under treatment, 1 neonate

developed learning disabilities at 7 years of follow-up. 19 cases were lost to follow-up.

5. Discussion

The term neonatal sepsis, refers to a clinical syndrome characterized by the blood stream infection of neonates and inflammatory response mounted by the neonate. It is associated with hemodynamic changes and other clinical manifestations and results in substantial morbidity and mortality [4, 5].

According to the report on the expert meeting on neonatal and pediatric sepsis of EMA (2010), neonatal sepsis can be defined by the presence of at least two clinical symptoms and at least two laboratory signs in the presence of or as a result of suspected or proven infection (positive culture, microscopy or PCR) [6]. Neonatal sepsis present with symptoms of systemic inflammatory response (SIRS) syndrome and can easily lead to septic shock [7]. Neonatal sepsis remains a serious problem in neonatal intensive care unit (NICU), resulting in significant morbidity and mortality. Incidence of neonatal sepsis varies from 1 to 5 cases per 1000 live births in developed countries but gets higher in developing countries which varies from 49 to 170 per 1000 [8]. In our study, 82,7% (153/185) of neonates met our protocol defined neonatal sepsis, which is higher than Jajoo et al. That found a total of 47% (82/174) and Velaphi SC. Et al. with 47% (1231/2624) [2, 9].

The male gender is predominant with a sex ratio of 2,1 which agree with the majority of studies conducted in the literature and showed that sepsis is more likely to present within male gender [9-13].

5.1. Risk Factors

The risk factors increasing the incidence of early onset sepsis can be divided in 2 categories, maternal and infant:

5.1.1. Maternal Risk Factors

Chorioamnionitis: In our study, 13,7% of mothers were obstetrically diagnosed with chorioamnionitis which is lower than the findings by Michael S. et al. Study that found chorioamnionitis in 24% of cases and Giannoni E et al. In 37% of cases [16, 17].

Intrapartum fever: was present in 7,1% (11) of mothers at delivery in our study which is comparable with Betty C. et al. Study that found proportion of 8,3%. In a study conducted in Saudi Arabia, 12,1% of mothers had intrapartum fever. In north Ethiopia, Gebremedhin D et al. found 28,2% of mothers with intrapartum fever [18, 11].

Premature rupture of membranes (PROM): In our study PROM was found in 44,4% (68) of pregnancies, which is lower compared to Mukhopadhyay S. et al that found a proportion of 50,5% and higher compared to Kiatchoosakun P. et al study in northeast Thailand with only 7,5% of mothers and Abdulrahman A et al. with only 12,1% [10, 18, 19].

Intrapartum antibiotic prophylaxis: In our study 11,1% (17) of mothers received IAP which was similar with Velaphi SC. et al. study with a proportion of 8.1% but different Mukhopadhyay S. et al with a proportion of 67,9% [9, 19].

These results give evidence of the bad and irregular follow-up of pregnancies.

Delivery: was vaginal in the majority of cases 67,79% (104) and caesarean section in 32,02% (49) which joined the results found in the literature [17, 18, 11]. Some authors reported cesarean section to be a risk factor of EOS which can be explained by the hematogenous contamination of the fetus [20].

Amniotic fluid: Purulent amniotic fluid was found in 4,81% (5) of neonates which is comparable with the results found in Gebremedhin D. et al. study with a proportion of 9 % but lower than the proportion found in Betty C. et al. with 30% of neonates [3, 11]. Meconium stained amniotic fluid was found, in our study, in 20,09% (32). Jajoo et al. study joined purulent and meconium stained fluid in one proportion 19,5% [1].

5.1.2. Infant Risk Factors

The most important neonatal factor predisposing to infection

that could result in sepsis are prematurity and low birthweight. EOS rates are inversely proportional to gestational age and birth weight, with the highest incidence occurring in the smallest infants [4, 21]. Low Apgar score at 1 or 5 minutes and birth asphyxia are also associated with a high risk of EOS [22].

Prematurity: In our population, 76,4% (117) of neonates were premature, a result that is similar with the ones found in Naulikha et al. study, with a proportion of 89,1 % and in Betty C. et al study where 80,6% of neonates were premature [3, 12]. Another study conducted also in Austria comparing GBS to E. coli in EOS found that 42% of neonates with GBS EOS were premature and that 72,7% of neonates with E. coli EOS were premature [23]. Giannoni E. et al. study also confirmed a highest incidence of EOS in extremely preterm infants [16].

Birth weight: 81,03% of neonates in our population had a low birth weight and 24,83% of these had a very low birth weight, these results are in agreement with the findings by Velaphi SC. et al. study with a proportion of 27,3% of neonates born with a very low birth weight and Abdulrahman A. et al. with a proportion of 27,3% and with 22,5% in Kiatchoosakun P. et al. [10, 9].

5.2. Clinical Presentation

Table 1. Distribution of EOS clinical manifestations among different studies.

		Our study (%)	India [25]	Bangladesh [31]	Nigeria [24]	South Africa [30]
Respiratory distress	Respiratory distress	66,1	43,9	26,6	58,9	14,8
Abnormality of temperature	Hypothermia	47	47,5	7,8	14,8	34
	Fever	3	16,7	28,1	1	15,5
Abnormality of glycemia	Hyperglycemia	13,2	-	-	9,3	-
	Hypoglycemia	9,7			13,2	-
	Cyanosis	28,2	-	14,1	-	-
Skin abnormality	Sclerema	3		-	1,78	-
	Jaundice	7,8		48,4	17,8	-
	Pallor	25,4		21,9	12,5	-
Abnormality of cardiac frequency	Tachycardia	22,8	-	-		
	Bradycardia	10,5			-	-

5.3. Laboratory Tests

5.3.1. Bacteriological Screening

Blood culture: A positive neonatal blood culture remains the gold standard for diagnosing neonatal sepsis, recognizing

that maternal antimicrobial therapy may inhibit bacterial growth [24]. In our study, the culture was positive in 19,6% (30) of cases compared to 36% in Gurung B et al. study and 18% in Jajoo et al. study and only 5,7% in Naulikha JM, et al. and 21% in Emrah C et al. [25, 2, 26].

The pathogens are:

Groupe B streptococcus: I pregnancy, GBS is harbored

asymptotically in mucous membrane sites, including the genital, rectal, and pharyngeal mucosa. In the United States, rates of maternal colonization are estimated to be 26% [14]. Maternal GBS colonization results in infant colonization in approximately 50% of cases, and infants become colonized either intrapartum or through bacterial translocation despite intact membranes. An estimated 85% of EOS cases are now averted by intrapartum antibiotic prophylaxis, but the frequent use of antibiotics in the delivery setting may be driving higher proportions of neonatal sepsis attributable to ampicillin-resistant *E. coli* over time [14]. In our study GBS was found in 36% of cases.

Escherichia coli: *E. coli* is the second leading cause of EOS in neonates, accounting for about 24% of all EOS episodes, with 81% of cases occurring in preterm infants [14]. When VLBW infants are considered alone, *E. coli* is the most frequent cause of EOS, accounting for 33.4 % of episodes in a large, multicenter study [15]. The incidence of sepsis caused by Gram-negative organisms may be increasing in part due to the frequency of maternal antibiotic prophylaxis for GBS. Coliforms, including *E. coli*, are frequently colonizers of the maternal vaginal canal, and infants acquire them at or just before delivery. Infants infected with K1 antigenic strains have increased morbidity and mortality compared to infants infected with other strains, and disease severity is related to the amount and persistence of K1 antigen in the cerebrospinal fluid [14]. In our study *E. coli* was found in 53,3% of cases.

Lumbar puncture (LP): In asymptomatic term infants investigated for EOS, no cases of meningitis were reported in three large observational studies. Meningitis was similarly very uncommon (0% to 0.3%) in preterm infants investigated for EOS because of respiratory distress. However, newborns with positive blood cultures are more likely to have meningitis. Furthermore, 8% to 40% of infants with early onset meningitis are reported to have negative blood cultures. These data suggest that an LP should be performed at the outset when there is a strong clinical suspicion of EOS or when signs of meningitis (seizures, bulging fontanelle, irritability, altered neurological status) are present. An LP must be done whenever the blood culture is positive. In our study, LP was performed in 41,7% of cases and only 1 culture was positive for *E. coli*.

5.3.2. Inflammatory Screening

Complete blood count (CBC): Total WBC counts give a poor positive indicative value for sepsis. In our study, 27,45% (42) of patients had leukopenia which is similar with Abdulrahman A et al. study that found a proportion of 25,8%. Leukocytosis occurred in only 8,49% (13) of neonates which is comparable with Abdulrahman A et al study with a proportion of 12,9% but lower than the findings by Ogundare E et al. study with 23,2% [1, 18]. Thrombocytopenia was found in 31,37% (48) of neonates in comparison with Abdulrahman A et al. findings with a proportion of 12,9% but lower than the findings by Ogundare E et al. study with 71,4% [1, 18].

CRP: has its best predictive value if measured within 24 to 48 h of onset of infection [14]. In our study, CRP was only positive in 26,79% of cases which is comparable with the findings by Abdulrahman et al. study with a proportion of 33,3% [18]. The fact that CRP was positive in a low proportion of neonates, can be explained by the major proportion of prematurity in our population.

5.3.3. Chest Radiograph

In our study, Pneumonia occurred in 4,57% (7) of cases which is lower than Betty C. et al that found pneumonia in 66,7% (24) of cases.

5.4. Treatment

5.4.1. Indications for Starting Antibiotics

The indications for starting antibiotics in neonates at risk of early onset sepsis include the following: Presence of 3 risk factors for early onset sepsis.

1. Presence of foul-smelling liquor.
2. Presence of 2 antenatal risk factor with a positive septic screen.
3. Strong clinical suspicion of sepsis.

Duration of antibiotics: Clinical sepsis (Based on clinical suspicion and/or sepsis screen positivity): 7-10 days, Culture positive sepsis (not meningitis): 14 days. Meningitis: 2 weeks after sterilization of CSF culture or for a minimum of 2 weeks for gram positive meningitis and 3 weeks for gram negative meningitis, whichever is longer [5]. In EOS, when an organism is identified, the antibiotic regimen should be tailored appropriately. Duration of therapy remains controversial; however, discontinuation of empirical antibiotic therapy should be considered after two to three days of negative cultures if clinical status remains stable.

5.4.2. Hemodynamic support:

Fluid resuscitation: Generally, fluid resuscitation is the recommended initial treatment for sepsis and should take place within the first hour of suspected septic shock [27].

Drugs:

Dopamine is generally the first-line vasopressor for fluid-refractory septic shock because of its positive effect on blood pressure with a low likelihood of adverse effects compared with other vasopressors [27].

Epinephrine and norepinephrine infusions for refractory shock in neonates have been studied to a very limited extent.

Neonates with vasodilatory shock may have a positive response to the alpha-adrenergic vasoconstrictive effect of these agents. A recent report in term neonates showed the addition of noradrenaline to existing therapy (after fluid loading and dopamine or dobutamine infusion) resulted in increased blood pressure and decreased tissue lactate.

Pellicer A. et al. study found low-dose epinephrine was found as effective as low/moderate-dose dopamine for increasing blood pressure, cerebral blood volume, and cerebral oxygen delivery in VLBW infants [28].

Dobutamine is not as commonly used as dopamine, but it may play a role in septic shock due to poor perfusion from reduced myocardial contractility. Along with epinephrine, norepinephrine and vasopressin are being studied for their role in dopamine refractory hypotension [27]. In our study, Dobutamine was used alone in 27,45% of cases, norepinephrine was used in 22,2% of cases and dopamine in 12,4% of cases which is difficult to compare to Berardi et al. study that found 25,6% of neonates to receive catecholamine support [29].

5.4.2. Hydrocortisone (HC)

Hydrocortisone is reserved for pressor resistant septic shock. It is a last-line option for the management of refractory hypotension and also may help facilitate weaning off of vasoactive medications. Hydrocortisone use may correct underlying adrenal insufficiency, contributing to septic shock and resistant hypotension. In our study, Hydrocortisone was used in 23,1% (36) of cases.

6. Conclusion

Neonatal sepsis in the newborn infant continues to be a difficult clinical challenge for neonatologists everywhere in the world and a major cause of morbidity and mortality. Through our study, the major risk factors contributing in rising neonatal sepsis are poor antenatal care, absence of pregnancies follow-up, prolonged rupture of membranes, prematurity, very low birth weight and delay in management of neonates. Clinical features of neonatal sepsis in neonates are non-specific, and the laboratory tests are not 100% sensitive nor specific, however the blood culture remains the gold standard for confirmation of diagnosis and definition of the different organisms involved. The choice of antibiotics should be based on the causative organisms and the patterns of antibiotic susceptibility. The mortality rate in our study is high and the burden of sepsis is majored by nosocomial infection. In order to decrease sepsis frequency and improve outcome for neonates, we hope for an efficient contribution between Neonatologists and Obstetricians, especially for those who develop septic shock.

Abbreviations

EOS: Early-Onset Sepsis
 ATB: Antibiotic
 NICU: Neonatal Intensive Care Unit
 PPROM: Prolonged Premature Rupture of Membranes
 VLBW: Very Low Birth Weight
 LOS: Late-Onset Sepsis
 SIRS: Systemic Inflammatory Response Syndrome
 GA: Gestational Age
 WA: Weak of Amenorrhea
 CRT: Capillary Refilling Time
 CBC: Complete Blood Count

CRP: C-reactive Protein
 CPAP: Continuous Positive Airway Pressure
 CLC: Central Line Catheter
 GBS: Group B Streptococcus
 PCR: Polymerase Chain Reaction
 LP: Lumbar Puncture
 IAP: Intrapartum Antibiotic Prophylaxis
 E. COLI: Escherichia Coli

Conflicts of Interest

The authors declare no conflicts of interest.

References

- [1] Kari A., Anderson-Berry L., Delair F., Davies H., Early-Onset Neonatal Sepsis, *Clinical Microbiology Reviews*, 2014, 27(1): 21-27. <https://doi.org/10.1128/CMR.00031-13>
- [2] Schrag SJ, Farley MM, Petit S, et al. Epidemiology of Invasive Early-Onset Neonatal Sepsis, 2005 to 2014, *Pediatrics*, 2016, 138(6): 2016-2013. <https://doi.org/10.1542/peds.2016-2013>
- [3] Capasso L., Borrelli AC., Ferrara T., Coppola C., Cerullo J., Izzo F., Caiazza R., Lama S., Raimondi F., Immunoglobulins in neonatal sepsis: has the final word been said? *Early Human Development* 90S2 2014: 47-49. [https://doi.org/10.1016/S0378-3782\(14\)50013-8](https://doi.org/10.1016/S0378-3782(14)50013-8)
- [4] Akdag A., Dilmen U., Haque K., Dilli D., Erdevi O., Goekmen T., Role of Pentoxifylline and/or IgM-Enriched Intravenous Immunoglobulin in the Management of Neonatal Sepsis, *Am J Perinatol* 2014, 31: 905-912. <https://doi.org/10.1055/s-0033-1363771>
- [5] Fjalstad W., Stensvold J., Bergseng H., Simonsen S., Salvesen B., Rønnestad E., et al., Early-onset Sepsis and Antibiotic Exposure in Term Infants, *Pediatric Infectious Disease*, 2016, 35: 1-6. <https://doi.org/10.1097/INF.0000000000000906>
- [6] Shahreen R. et al., Early Initiation of Breastfeeding Protects Against Early-onset Sepsis Among Newborns: Evidence from Rural Bangladesh, *PLoS Med*, 2019, 16(8): e1002904. <https://doi.org/10.1371/journal.pmed.1002904>
- [7] Banupriya N. et al, Effect of Zinc Supplementation on Early Outcome of Neonatal Sepsis - A Randomized Controlled trial, *Indian J Pediatr*, 2016, 83(4): 289-93. <https://doi.org/10.1007/s12098-015-1939-4>
- [8] Moffett M., Kitts L., Henderson J., Medication Therapy for Early-Onset, Neonatal Sepsis *AACN Advanced Critical Care*, 2016, 27(3): 253-258. <https://doi.org/10.4037/aacnacc2016503>
- [9] Stephannie V., Patrick J., Neonatal Sepsis, *Clinical Pediatric Emergency Medicine*, 2016, 17(2): 129-133. <https://doi.org/10.1016/j.cpem.2016.03.006>
- [10] Fuchs A. et al., Antibiotic Use in Neonates and Children: 2016 update, WHO-review. <https://doi.org/10.1080/20469047.2017.1408738>

- [11] Stoll BJ. Early-Onset Neonatal Sepsis: A Continuing Problem in Need of Novel Prevention Strategies, *Pediatrics*, 2016, 138(6): 30-38. <https://doi.org/10.1542/peds.2016-3038>
- [12] Blatt S., Schroth M., Neonatal sepsis: Clinical considerations, *J Child Sci* 2017, 1: 54-59. <https://doi.org/10.1055/s-0037-1603802>
- [13] Kuzniewicz MW. Et al., A Quantitative, Risk-Based Approach to the Management of Neonatal Early-Onset Sepsis, *JAMA Pediatrics*, 2017, 171(4): 365-371. <https://doi.org/10.1001/jamapediatrics.2016.4678>
- [14] Nidhi C., Sukirti T., Utkarsh J., Potential Biomarkers for Effective Screening of Neonatal Sepsis Infections: An overview, *Microbial Pathogenesis*, 2017, 107: 234-242. <https://doi.org/10.1016/j.micpath.2017.03.042>
- [15] Mendoza-Palomar N. et al., *Escherichia coli* early-onset sepsis: trends over two decades, *Eur J Pediatr*, 2017, 176(9): 1227-1234. <https://doi.org/10.1007/s00431-017-2975-z>
- [16] Towers CV., Yates A., Zite N., et al. Incidence of Fever in Labor and Risk of Neonatal Sepsis. *Am J Obstet Gynecol*, 2017, 216(596): 1-5. <https://doi.org/10.1016/j.ajog.2017.02.022>
- [17] Shane AL., Sánchez PJ., Stoll BJ., Neonatal sepsis, *Lancet*, 2017, 390(10104): 1770-1780. [https://doi.org/10.1016/S0140-6736\(17\)31002-4](https://doi.org/10.1016/S0140-6736(17)31002-4)
- [18] Jefferies AL. et al., *Paediatrics & Child Health*, 2017, 22(4): 229-234. <https://doi.org/10.1093/pch/pxx023>
- [19] Bell SG. Et al., Procalcitonin and Neonatal Sepsis: Is This the Biomarker We Are Looking For? *Neonatal network* 2017, 36(6): 380-384. <https://doi.org/10.1891/0730-0832.36.6.380>
- [20] Stocker M., Herk W., El Helou S., Dutta S., Fontana M., Schuerman F. et al., *Lancet* 2017, 390: 871–81. [https://doi.org/10.1016/S0140-6736\(17\)31444-7](https://doi.org/10.1016/S0140-6736(17)31444-7)
- [21] Nguyen N. et al., Early onset neonatal sepsis is associated with a high heart rate during automatically selected stationary periods, *Acta paediatrica*, 2017, 106(5): 749-754. <https://doi.org/10.1111/apa.13782>
- [22] Yadav, Nikita Singh; Sharma, Saroj; Chaudhary, Dhiraj Kumar; Panthi, Prabhat; Pokhrel, Pankaj; Shrestha, Anil; Mandal, Pappu Kumar (2018). Bacteriological profile of neonatal sepsis and antibiotic susceptibility pattern of isolates admitted at Kanti Children's Hospital, Kathmandu, Nepal. *BMC Research Notes*, 11(1), 301. <https://doi.org/10.1186/s13104-018-3394-6>
- [23] Swaanenburg JC., Rutten WP., Holdrinet AC., Strik R., The determination of reference values for hematologic parameters using results obtained from patient populations, *Am J Clin Pathol* 1987, 88(2): 182-191. <https://doi.org/10.1093/ajcp/88.2.182>
- [24] Ogundare E, Akintayo A, Aladekomo T, Adeyemi L, Ogunlesi T, Oyelami O. Presentation and outcomes of early and late onset neonatal sepsis in a Nigerian Hospital, *Afri Health Sci*, 2019, 19(3): 2390-2399. <https://doi.org/10.4314/ahs.v19i3.12>
- [25] Jajoo M, Kapoor K, Garg LK, Manchanda V, Mittal SK. To study the incidence and risk factors of early onset neonatal sepsis in an out born neonatal intensive care unit of India, *J Clin Neonatol*, 2015, 4(2): 91-95. <https://doi.org/10.4103/2249-4847.154106>
- [26] Giannoni E. et al., Neonatal Sepsis of Early Onset, and Hospital-Acquired and Community-Acquired Late Onset: A Prospective Population-Based Cohort Study, *Journal of pediatrics*, 2018, 201: 106-114. <https://doi.org/10.1016/j.jpeds.2018.05.048>
- [27] Rashwan NI, Hassan MH, Mohey El-Deen ZM, El-Abd Ahmed A, Validity of Biomarkers in Screening for Neonatal Sepsis – A Single Center Hospital based Study, *Pediatrics and Neonatology*, 2019, 60(2): 149-155. <https://doi.org/10.1016/j.pedneo.2018.05.001>
- [28] Scheel M. et al., Hit or Miss? A review of early-onset sepsis in the neonate, *Crit Care Nurs Clin N Am* 2018, 30(3): 353-362. <https://doi.org/10.1016/j.cnc.2018.05.003>
- [29] Chemsì M, et al. La ponction lombaire dans l'infection néonatale bactérienne précoce: performance et décision. [Lumbar puncture in early bacterial neonatal infection: performance and decision]. *Journal de pédiatrie et de puériculture*, 2018, 7. <https://doi.org/10.1016/j.jpp.2017.11.002>
- [30] Velaphi SC, Westercamp M, Moleleki M, Pondo T, Dangor Z, Wolter N, et al., Surveillance for incidence and etiology of early onset neonatal sepsis in Soweto, South Africa, *PLoS ONE*, 2019, 14(4): e0214077. <https://doi.org/10.1371/journal.pone.0214077>
- [31] Begum, S., Baki, M., Kundu, G., Islam, I., Kumar, M., & Haque, A. (2012). Bacteriological Profile of Neonatal Sepsis in a Tertiary Hospital in Bangladesh. *Journal of Bangladesh College of Physicians and Surgeons*, 30(2), 66–70. <https://doi.org/10.3329/jbcps.v30i2.11406>