

Benedito Rodrigues da Silva Neto
(Organizador)

Saúde Pública e Saúde Coletiva: Dialogando sobre Interfaces Temáticas 4



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**Saúde Pública e Saúde Coletiva:
Dialogando sobre Interfaces Temáticas 4**

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APRESENTAÇÃO

A coleção “Saúde Pública e Saúde Coletiva: Dialogando sobre Interfaces Temáticas” é uma obra composta de cinco volumes que tem como foco principal a discussão científica por intermédio de trabalhos diversos que compõe seus capítulos. Cada volume abordará de forma categorizada e interdisciplinar trabalhos, pesquisas, relatos de casos e/ou revisões que transitam nos vários caminhos da saúde pública e saúde coletiva.

Sabemos que a equipe de saúde cumpre um papel fundamental não apenas no laboratório e no hospital, mas no contexto da sociedade e do seu avanço, por isso cada vez estudos integrados são relevantes e importantes para a formação acadêmica. Deste modo neste trabalho que compreende o quarto volume da obra reunimos trabalhos desenvolvidos com enfoque direcionado ao serviço social, prática profissional, determinantes sociais da saúde, avaliação social, saúde mental; política de saúde, cuidado pré-natal, vulnerabilidade social, aleitamento materno, planejamento, modelo de gestão, infecções sexualmente transmissíveis dentre outros.

Viabilizar novos estudos em saúde pública é de extrema importância para países em desenvolvimento, da mesma forma que é preciso cada vez mais contextualizar seus aspectos no ensino e extensão. Isso nos leva à novas metodologias, abordagens e estratégias que conduzam o acadêmico à um aprendizado mais específico e consistente.

Deste modo a obra Saúde Pública e Saúde Coletiva apresenta uma teoria bem fundamentada nos resultados práticos obtidos pelos diversos professores e acadêmicos que arduamente desenvolveram seus trabalhos que aqui serão apresentados de maneira concisa e didática. Sabemos o quão importante é a divulgação científica, por isso evidenciamos também a estrutura da Atena Editora capaz de oferecer uma plataforma consolidada e confiável para estes pesquisadores exporem e divulguem seus resultados.

Benedito Rodrigues da Silva Neto

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DIAGNOSTIC CONDUCT AND MANAGEMENT OF NEONATAL SEPSIS: A SYSTEMATIC REVIEW

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ABSTRACT: Introduction: Neonatal sepsis is divided into neonatal infection: early when associated with maternal origin and likely diagnosed within 72 hours after birth, and later, which is the form associated with the hospital with the diagnosis after 72 hours. Neonatal sepsis is a leading cause of death in infants, especially premature infants who are more susceptible to infections than children in others ages. **Objectives:** To perform a systematic review of the current data on the diagnostic behavior and proper management of neonatal sepsis. **Methods:** The study consists of a literature review, held in the database PubMed

Central: PMC and Scielo, with the search algorithm “neonatal”, “sepsis” and “morbidity”. The following filters were used: “last five years” and “humans”. Articles published between 2013 and 2017, published in English, Portuguese and Spanish, available in full text format were included. We excluded studies that do not refer to sepsis in the neonate and that define the definition of late neonatal sepsis as that which occurs 48 hours after birth. **Results and Discussion:** Blood culture is the gold standard for the diagnosis of neonatal sepsis. Ampicillin and gentamicin were allocated as the first choice of the initial antimicrobial regimen for neonatal infections. Third generation cephalosporins should be used severely. The use of antiviral and antifungal agents may reduce mortality and morbidity due to specific viral and fungal disease. **Conclusion:** We conclude that the gold standard for the diagnosis of neonatal sepsis continues to be blood culture. Ampicillin and gentamicin are the first choice for treatment. **KEYWORDS:** Neonatal. Sepsis. Morbidity.

CONDUTA DIAGNÓSTICA E MANEJO DA SEPSE NEONATAL: UMA REVISÃO SISTEMÁTICA

RESUMO: Introdução: A sepse neonatal é dividida em infecção neonatal: precoce quando

associada à origem materna e provavelmente diagnosticada até 72 horas após o nascimento, e posteriormente, que é a forma associada ao hospital com o diagnóstico após 72 horas. A sepse neonatal é uma das principais causas de morte em bebês, especialmente bebês prematuros que são mais suscetíveis a infecções do que crianças em outras idades. **Objetivos:** Realizar uma revisão sistemática dos dados atuais sobre o comportamento diagnóstico e manejo adequado da sepse neonatal. **Métodos:** O estudo consiste em uma revisão de literatura, realizada na base de dados PubMed Central: PMC e Scielo, com o algoritmo de busca “neonatal”, “sepsis” e “morbidade”. Os seguintes filtros foram utilizados: “últimos cinco anos” e “humanos”. Incluíram-se artigos publicados entre 2013 e 2017, em inglês, português e espanhol. Foram excluídos os estudos que não se referem à sepse no neonato e trazem a definição de sepse neonatal tardia como aquela que ocorre 48 horas após o nascimento. **Resultados e Discussão:** A hemocultura é o padrão ouro para o diagnóstico de sepse neonatal. Ampicilina e gentamicina foram alocadas como a primeira escolha do regime antimicrobiano inicial para infecções neonatais. As cefalosporinas de terceira geração devem ser usadas rigorosamente. O uso de agentes antivirais e antifúngicos pode reduzir a mortalidade e a morbidade devido à doença viral e fúngica específica. **Conclusão:** Concluímos que o padrão ouro para o diagnóstico da sepse neonatal continua sendo a hemocultura. Ampicilina e gentamicina representa a primeira escolha para o tratamento.

PALAVRAS-CHAVE: Neonatal. Sepse. Morbidade.

1 | INTRODUCTION

Neonatal sepsis is defined as a systemic response to infection, characterized by a clinical syndrome with different manifestations. Such syndrome is divided into early and late neonatal infection, being this associated with the probable maternal origin and diagnosed within 72 hours after birth, and the latter associated with the hospital environment, being diagnosed after 72 hours. Neonatal sepsis is one of the main causes of death of newborns worldwide. It is one of the factors that contributes most to the increase of the neonatal mortality rate. The incidence of neonatal early-onset sepsis has declined with the widespread use of intrapartum antibiotic therapies, yet early-onset sepsis remains a potentially fatal condition, particularly among very low-birth weight infants.

The clinical manifestations of the newborn are nonspecific, with maternal and neonatal risk factors for suspected sepsis and for initiating the investigation. Differential signs of septicemia in the neonate are difficult to recognize and the disease is often at an advanced stage when the newborn is brought to the health care provider's attention. The risk factors associated with sepsis, especially the late sepsis, include: prematurity (immaturity of the immune system), invasive procedures performed at the Neonatal Intensive Care Unit (NICU), use of prolonged mechanical ventilation, antibiotic therapy, long hospital stay and hospital infection prevention standards.

Globally, 3.1 millions of neonates die per year, 12% of them due to sepsis or

meningitis. Neonates are at risk to acquire infections, especially preterm and low-birth-weight newborns. In addition to the high morbidity and mortality associated with neonatal sepsis, these patients are at high risk for long-term disabilities, particularly neurodevelopment impairment.

Therefore, several interventions, including intravenous immunoglobulin, glutamine, anti-staphylococcal monoclonal antibodies and granulocyte/granulocyte-macrophage colony-stimulating factors have been evaluated for reduction in rates of neonatal sepsis, but have not shown efficacy.

Newborns, especially preterms, are more susceptible to infections than children at any other age period. Innate immunity is affected by impaired cytokine production, decreased expression of adhesion molecules in neutrophils and a reduced response to chemotactic factors. Also, transplacental passage of antibodies starts during the second trimester and achieves its maximal speed during the third trimester. As a result, most preterm newborns have significantly reduced humoral responses. Cytotoxic T-cell activity is also impaired during the newborn period. The multiple skin punctures and invasive procedures that preterm newborns commonly undergo increase even more the risk of infections in this population.

Due to the association with high rates of morbidity and mortality, appropriate empirical antibiotic therapy of immediate onset as initial management in the therapeutic management of sepsis is justified. Knowledge of both common pathogens that cause septicemia and antimicrobial susceptibility is essential in selecting the appropriate treatment. As the completion of the diagnosis of sepsis is difficult empirical therapy begins until it can confirm or rule out such injury. However, there has been an increase in the prevalence of sepsis in less developed countries with poorer health, which can be explained by the increase in antimicrobial resistance as a result of inadequate treatment.

During the analysis of the studies, we verified that one of the great challenges for the proper management of cases of neonatal sepsis is the lack of consensus regarding the diagnostic protocols, making the medical decision process difficult, since there is a divergence between the guidelines on when and how to start the correct therapy.

The objective of this article is the review of established concepts and the search for current data about the diagnostic behavior and proper management of neonatal sepsis.

2 | METHODS

Kind of study

This research is a systematic review and aims to select studies and promote an

up-to-date overview of diagnostic management and proper management of neonatal sepsis. And it was elaborated from its classic structure, with the following stages:

- Identification of the theme and formulation of the guiding question;
- Research in the literature and selection of studies found;
- Analysis of included studies and interpretation of results;
- Review of the report and summary of knowledge.

The proposed theme is relevant because it allows to acquire management knowledge about neonatal sepsis, promoting a better qualification of pediatric health professionals.

From this, the guiding question was formulated, which was applied as a theoretical basis parameter for the development of this article. Thus, the following question was defined: “What are the established concepts about the diagnosis and therapeutic management of neonatal sepsis?”

The bibliographic research was carried out in the PubMed Central: PMC and Scielo database, considering the scope of worldwide access of such platforms and their due recognition in scientific circles. The search algorithms were «neonatal sepsis» AND «diagnosis» AND «management». And, the following filters were used: «last five years», seeking a greater update on the subject and, «human» because it corresponds with greater credibility to the object of study. No language restrictions were applied, in view of the contemplation of a greater scope of data.

Criteria for eligibility

We will include articles published between 2013 and 2017, published in English, Portuguese and Spanish, available in full text format. We will also select studies that address the factors that define the morbimortality of neonatal sepsis, as well as the treatment modalities that prevail worldwide.

We will exclude studies that do not refer to sepsis in the neonate and which present the definition of late neonatal sepsis as that which occurs 48 hours after birth.

3 | RESULTS

In figure 1, we present the flow diagram, as recommended by the PRISMA statement showing the process of selecting the studies included in our analysis. Specifically, our research identifies a total of 236 articles (after removing as duplicates). According to titles and abstracts, 79 of them were selected for further evaluation. After a review of the full text, 35 were eligible for inclusion in our review. All articles were identified as diagnostic accuracy studies, unmanaged approach and declare this research goal in the introduction. The papers have been published in the last five years.

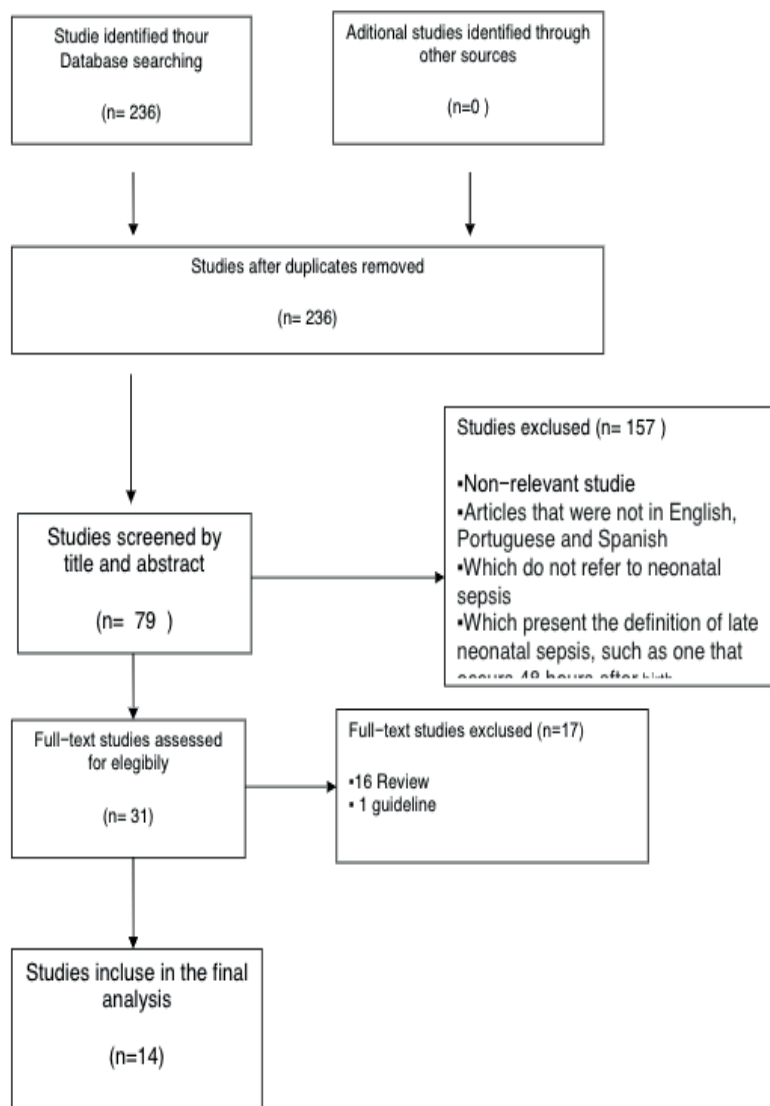


Figure1: Schematic diagram for article selection

Medeiros et al. approached infants in the study were classified according to the type of sepsis they developed: Early Sepsis, corresponding to 71.4%, early and late sepsis, corresponding to 16.3% and Late Sepsis, equal to 12.2%. Furthermore, they described the characteristics of the infants and the occurrence of sepsis and these were distributed in two groups, according to the sepsis they presented: early or other sepsis (including infants who only presented late sepsis and infants who presented both early and late sepsis). Early sepsis corresponded to n=35 and other sepsis (late or both) n= 14.

Coetzee et al. The diagnosis of neonatal sepsis is not always straightforward, and the initiation and continuation of antimicrobials in these situations relies on good clinical judgment. The need for empirical antimicrobials is driven by the existence of risk factors for early-onset sepsis and clinical symptoms and signs of late-onset sepsis. Antimicrobial stewardship programs should be in place to guide clinicians to either stop, change, or continue antimicrobials. Institution-specific knowledge of the most common pathogens and the antimicrobial susceptibility pattern is important to

prevent the emergence of further antimicrobial resistance.

Mukhopadhyay et al. reported the incidence of neonatal early-onset sepsis has declined with the widespread use of intrapartum antibiotic therapies, yet early-onset sepsis remains a potentially fatal condition, particularly among very low-birth weight infants. Clinical signs of neonatal infection are non-specific and may be absent in the immediate postnatal period. Maternal and infant clinical characteristics, as well as infant laboratory values, have been used to identify newborns at risk, and to administer empiric antibiotic therapy to prevent progression to more severe illness.

Rubarth et al related that low gestational age, mechanical ventilation and an intra-vascular catheter were significantly associated with sepsis and it is necessary to develop a multidisciplinary approach for routine surveillance of nosocomial infections, to improve the asepsis of therapeutic procedures, and to implement the more appropriate use of antibiotics. And it were described some risk factors associated with LOS were: mechanical ventilation, intravascular catheter, surgical procedures, birth weight ≤ 1500 g, gestational age ≤ 28 weeks and Apgar score ≤ 3 at 5 minutes. Culture proven sepsis developed in 43.4% of neonates. *Klebsiella pneumoniae* and *Enterococcus faecalis* were the predominant bacteria.

Mhada et al mentioned culture-proven sepsis was seen in 24% of study participants. Bacterial pathogens isolated were predominantly *Staphylococcus aureus*, *Klebsiella* spp and *Escherichia coli*. *Klebsiella* spp was the predominant blood culture isolate in neonates aged less than seven days, while *Staphylococcus aureus* was more common among those older than seven days.

Kabweet al mentioned in Of the 313 neonates with suspected sepsis, 54% were male; 20% were born from HIV-positive mothers; 33% had positive blood cultures, of which 85% were precocious sepsis. The *Klebsiella* species was the most prevalent isolate, representing 75% of the cases, followed by coagulase-negative staphylococci, *Staphylococcus aureus*, 5% *Escherichia coli* and *Candida* species. For *Klebsiella* species, antibiotic resistance varied from 96% to 99% for the World Health Organization recommended first-line therapy (gentamicin and ampicillin / penicillin) to 94% -97% for third-generation cephalosporins.

According to Bhat et al, the most striking finding of this study is that institution of early therapy based on SES results significantly reduced mortality. A total of 452 babies were considered for the study and 190 babies were recruited under the SES arm and 195 babies in the control arm. The impact on mortality by SES is due to speed of diagnosis in comparison to culture. In this study, SES detected pathogens in 3 to 4 times the number of cases than culture in neonates with suspected sepsis, in both the arms. Thus it can be inferred that the SES detected all cases of significant bacteremia and fungaemia.

Lee et al showed that his to logical chorioamnionitis it was the most frequent prenatal infectious / inflammatory exposure, affecting 60 children (43.5%). In addition, 43 infants (31.2%) were exposed to an infection of the maternal genitourinary tract.

Three children (5%) exposed to histological chorioamnionitis had early sepsis, thus, this was the most frequent prenatal infectious / inflammatory exposure, affecting 60 children (43.5%) of the study.

Orbach et al pointed out that, in the cases reported that maternal intrapartum fever occurred, it was a factor in the decision for cesarean urgency. Three of the four infants were unable to survive and their clinical course involved failure of the multiple organ system complicated with disseminated and deep intravascular coagulopathy. He also reported that pulmonary hemorrhage, leading to hypovolemic shock and failed respiration, was the direct cause of death in two cases studied.

Lutsar et al. Pointed out that, in the cases reported that maternal intrapartum fever occurred, it was a factor in the decision for cesarean urgency. Three of the four infants were unable to survive and their clinical course involved multiple system failure. Lutsar et al highlighted the clinical criteria most frequently observed in the diagnostic approach to sepsis, such as perfusion, increased need for oxygen and mottled skin, each seen in about of 40% of the study group. Multiple organs complicated with disseminated and deep intravascular coagulopathy. He also reported that pulmonary hemorrhage, leading to hypovolemic shock and failed respiration, was the direct cause of death in two cases studied.

Title	kind of study	Results
The correlation between invasive care procedures and the occurrence of neonatal sepsis	Cohort study	Early sepsis had a higher prevalence than late sepsis.
Risk Assessment in Neonatal Early-Onset Sepsis	Clinical trial	The incidence of early neonatal sepsis has decreased with the widespread use of intrapartum antibiotic therapies, but early-onset sepsis remains a potentially fatal condition.
Neonatal sepsis as a risk factor for neurodevelopmental changes in very low birth weight preterm infants	Prospective cohort study	Mean birth weight and mean gestational age are important risk factors for sepsis.
Sepsis neonatal no Hospital Nacional Muhimbili, Dar es Salaam, Tanzânia; etiologia, padrão de sensibilidade antimicrobiana e resultado clínico.	Cross-sectional study	Bacterial pathogens isolated were predominantly <i>Staphylococcus aureus</i> , <i>Klebsiella</i> spp and <i>Escherichia coli</i> .
Role of Presepsin in the Diagnosis of Late-Onset Neonatal Sepsis in Preterm Infants	Prospective study	The initial levels of presepsin in the LOS group were significantly higher than in the control group.
Etiology, Antibiotic Resistance and Risk Factors for Neonatal Sepsis in a Large Referral Center in Zambia	A cross-sectional observational	The <i>Klebsiella</i> species was the most prevalent isolate, followed by coagulase-negative staphylococci, <i>Staphylococcus aureus</i> , <i>Escherichia coli</i> and <i>Candida</i> species.

The impact of prenatal and neonatal infection on neurodevelopmental outcomes in very preterm infants	Retrospective analysis	Histological chorioamnionitis was the most frequent prenatal infectious / inflammatory exposure.
Pulmonary hemorrhage due to Coxsackievirus B infection-A call to raise suspicion of this important complication as an end-stage of enterovirus sepsis in preterm twin neonates	Case report	Cases reported that maternal intrapartum fever occurred, was a factor in the decision of emergency cesarean section.
Current management of late onset neonatal bacterial sepsis in five European countries	Prospective observational study	Clinical criteria most frequently observed in the diagnostic approach to sepsis, such as perfusion, increased need for oxygen and mottled skin. C-reactive protein and platelet count were also observed.

Table 1: Management in early and late neonatal sepsis

Title	kind of study	Results
Highlighting the principles of diagnosis and management	Clinical trial	The specific knowledge of the institution of the most common pathogens and the antimicrobial susceptibility pattern are important to avoid the emergence of more antimicrobial resistance.
Feasibility and acceptability of gentamicin in the Uniject prefilled injection system for community-based treatment of possible neonatal sepsis: the experience of female community health volunteers in Nepal	Non-experimental research design	The use of gentamicin showed positive results in the empirical management of sepsis.
Bacterial sepsis in the neonate		It is necessary to develop a multidisciplinary approach for the routine surveillance of nosocomial infections, to improve the asepsis of therapeutic procedures and to implement more appropriate use of antibiotics.
A quantitative and risk-based approach to the management of early-onset neonatal sepsis	Cohort study	The introduction of an empiric antibiotic and blood culture are important for a good prognosis of sepsis.
Syndrome Evaluation System (SES) versus Blood Culture (BACTEC) in the Diagnosis and Management of Neonatal Sepsis - A Randomized Controlled Trial	Randomized Controlled Trial	The institution of early therapy based on SES scores significantly reduced mortality.

Table 2: Early and late neonatal metastasis

4 | DISCUSSIONS

One of the most frequent infectious conditions in the neonatal period is called sepsis. Considered an important cause of morbidity and mortality in this phase of life, Neonatal Sepsis is a serious clinical syndrome that mainly affects preterm newborns

The immune system of the newborns is immature, which contributes to the

occurrence of infections associated with health care in this age group, and neonatal sepsis is extremely prevalent, both in its early and late forms. The diagnostic difficulty and laboratory confirmation contribute to high mortality and morbidity rates, such as longer stay in the intensive care unit and greater incidence of complications.

The consequences are multisystemic and the clinical evolution, which is commonly fulminant. The microorganisms are of maternal origin, being the most found: Streptococcus group B and Escherichia coli. However, late-onset infections are related to postnatal conditions and excessive manipulation and ICU procedures to which the newborns are exposed, such as catheters, mechanical ventilation equipment, venous punctures, nutrition parenteral, horizontal transmission through the unhygienic hands of caregivers and care staff.

The laboratory tests available most of the time are not conclusive, leaving doubts on the prescription of antibiotic therapy and leading to unnecessary treatment in large numbers of newborns. It is extremely important, when identified, to target specific antibiotic therapy to the causative germ. The treatment period will vary according to the initial antimicrobial response. It is recommended 10 to 14 days of treatment, with clinical improvement.

Another review conducted by Santos et al (2015) reports that neonatal infections continue to cause morbidity and mortality in infants. The most common agents in early-onset sepsis are Group B Streptococcus and Escherichia coli, whereas in late sepsis coagulase-negative Staphylococcus predominates. Initially the work for neonatal infection is a complete blood count and blood culture, with the option to perform analyzes and culture of the fluid, if clinically indicated. Serial determinations of biomarkers (C-reactive protein, procalcitonin or neutrophil CD64) can be used adjunctively in diagnostic treatment of infection. The basis for the initial antimicrobial treatment of sepsis remains ampicillin and gentamycin for neonatal infections.

According to Sivanandan et al (2011) [4] in a study that explored the choice and duration of antimicrobial therapy for sepsis and neonatal meningitis, it was noted that the choice of antibiotics should be based on the organisms and the patterns of sensitivity to antibiotics. While the duration of empirical antibiotic therapy in neonates should be from 48 to 72 hours depending on the culture results for suspected sepsis, even more evidence the current recommendation is that 10 to 14 days of antimicrobial treatment is appropriate for positive sepsis for blood culture without meningitis.

According to Andres Camacho-Gonzalez et al (2013) reports that neonatal sepsis remains a feared cause of morbidity and mortality in the neonatal period. Maternal, neonatal, and environmental factors are associated with the risk of infection, and a combination of prevention strategies, careful neonatal screening, and early initiation of therapy are necessary to prevent adverse outcomes. Therefore, prevention of neonatal sepsis is the goal - through the implementation of what is known and the development of new prevention strategies. Early recognition of chorioamnionitis, with appropriate antimicrobial therapy for the mother, decreases

maternal fetal transmission.

Andi L. Shane et al (2013) in a review on neonatal sepsis: progress toward better outcomes, neonates are predisposed to perinatal infections due to multiple exposures and a relatively compromised immune system. The burden of disease attributed to neonatal infections varies according to geographic region and maternal and neonatal risk factors. Risk factors for early neonatal sepsis include prematurity, immunological immaturity, maternal colonization by group B streptococcus, prolonged rupture of membranes, and maternal intra-amniotic infection.

According to Zea-Vera A et al (2015) in which he explored the study on challenges in the diagnosis and management of neonatal sepsis. Neonatal sepsis is the third leading cause of neonatal mortality and a major public health problem, especially in countries under development. Although recent medical advances have improved neonatal care, many challenges remain in the diagnosis and management of neonatal infections. The diagnosis of neonatal sepsis is complicated by the frequent presence of non-infectious conditions resembling sepsis, especially in premature infants, and by the absence of optimal diagnostic exams. Because neonatal sepsis is a high-risk disease, especially in premature infants, physicians are required to administer antibiotics empirically to children with risk factors and / or signs of suspected sepsis.

Iris Lee et al. Considered the relation of clinical suspicion of infection and sepsis to prolonged hospitalization time and a tendency to association with intraventricular hemorrhage but did not reach the standard for statistical significance. He also noted that sepsis and clinical suspicion of infection were still associated with a higher rate of white matter injury or death. Neonatal infection, in contrast, was not associated with two-year neurobehavioral outcomes but was associated with several structural changes in the brain. The fact that neonatal infections are associated with brain structural changes, but not neurobehavioral outcomes, may be related to the timing, extent, or other unique characteristics of these infections. In addition to defects in brain structure metrics, neonatal infection was also associated with higher rates of white matter injury. Although no differences in behavioral outcomes were observed, these associations may highlight the importance of neonatal sepsis as a marker for children at increased risk of severe brain injury in the perinatal period.

According to the research, we can observe that there are several ways of evaluate and prevent septic but simple measures such as use of correct aseptic techniques, a integrated team look plus a holistic care and decision making professionals could decrease the mortality rate by neonatal sepsis.

When finalizing, based on the data revealed in the articles surveyed, observed the need for improvement of health professionals working in the neonatal intensive care units, not feeling promote the prevention and control of infection during the practices. In relation to the nursing, we suggest that it become more present and participatory, since it is has the greatest contact with the newborn.

5 | CONCLUSIONS

We conclude that blood culture remains the most used diagnostic method. However, biomarkers, such as presepsin, have proven to be reliable. However, much remains to be investigated to achieve the diagnosis immediately. It was observed that ampicillin and gentamicin are the first choice for the treatment of early neonatal sepsis, since the management of the late one will depend on the local epidemiology. In addition, serial determinations of PCR, procalcitonin and CD64 neutrophils may be used as adjuvants in the management of neonatal infection.

This review may facilitate the early diagnosis of sepsis, and in turn may possibly improve early therapeutic interventions and the diagnostic approach to sepsis. The future prospects of this study include a better update on the subject, because, because it is an infection, there are many changes in the pathophysiology of microorganisms, especially in relation to antimicrobial resistance mechanisms. A consensus is also expected on the best diagnostic methods and management of sepsis.

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