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> ACESSE AQUI A REVISTA ONLINE

ORIGINAL ARTICLE

Diagnosis of early neonatal sepsis in a neonatal referral unit: 10-year cohort

Diagnóstico de sepse neonatal precoce em Unidade Neonatal de referência – Coorte de 10 anos

Diagnóstico de sepsis neonatal temprana en una unidad de referencia neonatal - Cohorte de 10 años

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ABSTRACT

Background: The neonatal mortality corresponds to almost half of deaths in children under 5 years old, according to information from the World Health Organization, the neonatal sepsis is the cause of a significant portion of these deaths. The non-specific clinical findings and the low sensitivity of blood culture hinder the diagnosis of sepsis and contribute to the overuse of antibiotics. **Objective:** to describe the epidemiological profile and diagnosis of HAI and early neonatal sepsis in a referral neonatal unit. **Methods:** This is a cohort made in a neonatal unit of reference for high obstetric risk and neonatal care. **Results:** It was observed that most cases of sepsis and health-related infections (HAIs) were used as clinical sepsis without a specific location, with a higher incidence in neonates of lower weight, that is the main isolated Gram-positive microorganism. The Empirical antibiotic therapy was introduced in these cases and propaedeutics performed contributed to the definitive diagnosis or suspension of antimicrobials, when the suspicion of infection was ruled out. **Conclusion:** A low percentage of microorganism isolation was observed in cases of early neonatal sepsis with a large number of clinical neonatal sepsis cases treated with antimicrobials. The need for a more accurate diagnosis to reduce empirical impacts is emphasized, and the use of tools that use clinical symptoms and maternal risk factors to reduce their use is recommended.

Keywords: *Neonatal sepsis; Streptococcus agalactiae; newborn, infant; Diseases; Antimicrobial agents.*

RESUMO

Introduction: A mortalidade neonatal corresponde a quase metade dos óbitos em crianças menores de 5 anos, segundo informações da Organização Mundial da Saúde, a sepse neonatal é a causa de uma parcela significativa desses óbitos. Os achados clínicos inespecíficos e a baixa sensibilidade da hemocultura dificultam o diagnóstico de sepse e contribuem para o uso excessivo de antibióticos. **Objetivo:** descrever o perfil epidemiológico e o diagnóstico de IRAS e sepse neonatal precoce em uma unidade neonatal de referência. **Métodos**: Trata-se de uma coorte realizada em uma unidade neonatal de referência para alto risco obstétrico e assistência neonatal. Resultados: Observou-se que a maioria dos casos de sepse e infecções relacionadas à saúde (IRAS) foi utilizada como sepse clínica sem localização específica, com maior incidência em neonatos de baixo peso, que é o principal microrganismo Gram-positivo isolado. A antibioticoterapia empírica foi introduzida nesses casos e a propedêutica realizada contribuiu para o diagnóstico definitivo ou suspensão dos antimicrobianos, quando a suspeita de infecção foi afastada. **Conclusão:** Observou-se baixo percentual de isolamento do microrganismo nos casos de

sepse neonatal precoce com grande número de casos clínicos de sepse neonatal tratados com antimicrobianos. Enfatiza-se a necessidade de um diagnóstico mais preciso para reduzir os impactos empíricos, e recomenda-se o uso de ferramentas que utilizem sintomas clínicos e fatores de risco maternos para reduzir seu uso.

Palavras-chave: *Neonatal sepsis; Streptococcus agalactiae; recém-nascido, bebê; Doenças; Agentes antimicrobianos.*

RESUMEN

Antecedentes: La mortalidad neonatal corresponde a casi la mitad de las muertes en niños menores de 5 años, según información de la Organización Mundial de la Salud, la sepsis neonatal es la causa de una porción significativa de estas muertes. Los hallazgos clínicos inespecíficos y la baja sensibilidad de los hemocultivos dificultan el diagnóstico de sepsis y contribuyen al uso excesivo de antibióticos. **Objetivo:** describir el perfil epidemiológico y diagnóstico de IAAS y sepsis neonatal temprana en una unidad neonatal de referencia. **Métodos:** Se trata de una cohorte realizada en una unidad neonatal de referencia de alto riesgo obstétrico y atención neonatal. **Resultados:** Se observó que la mayoría de los casos de sepsis e infecciones relacionadas con la salud (IAAS) se utilizaron como sepsis clínica sin localización específica, con mayor incidencia en neonatos de menor peso, que es el principal microorganismo grampositivo aislado. En estos casos se introdujo la antibioticoterapia empírica y las propedéuticas realizadas contribuyeron al diagnóstico definitivo o suspensión de antimicrobianos, cuando se descartó la sospecha de infección. **Conclusión:** Se observó un bajo porcentaje de aislamiento de microorganismos en casos de sepsis neonatal temprana con un gran número de casos clínicos de sepsis neonatal tratados con antimicrobianos. Se enfatiza la necesidad de un diagnóstico más preciso para reducir los impactos empíricos y se recomienda el uso de herramientas que utilicen síntomas clínicos y factores de riesgo maternos para reducir su uso.

Palabras llave: *Sepsis neonatal; Streptococcus agalactiae; bebé recién nacido; Enfermedades; Agentes antimicrobianos.*

INTRODUCTION

There is a great heterogeneity among studies regarding the definition of sepsis due to the nonspecificity of clinical signs in newborns. Sepsis should be seen as a clinical syndrome, with a systemic inflammatory response secondary to an infectious agent.[1-3] The *National Healthcare Safety Network* (NHSN) of the *Centers for Disease Control and Prevention* (CDC) considers only clinical manifestations associated with the isolation of a microorganism.[4] However, due to the low sensitivity of blood culture, the criteria outlined by the National Health Surveillance Agency (ANVISA) define early healthcare-associated infections (HAIs) as those of probable maternal origin that occur in the first 48 hours of life and consider clinical manifestation associated with laboratory changes.[5] According to the World Health Organization (WHO), an average of 130 million neonates are born every year and neonatal mortality corresponds to 47% of deaths in children under 5 years old. Of these, about 4 million die and infection is the cause of 36% of these deaths. The majority of all neonatal deaths (75%) occur during the first week of life and about 1 million die in the first 24 hours.[6] In Brazil, neonatal mortality corresponds to 70% of infant deaths and 50% to early neonatal mortality with socioeconomic conditions having a great influence, despite a 61.7% reduction between the years 1990 and 2017.[7]

Guidelines based on risk factors have been used to reduce the use of antimicrobials, but it is considered that more than 95% of neonates treated for sepsis do not require antibiotic therapy.[8-10]

The aim of this study is to describe the epidemiological profile and diagnosis of HAI and early neonatal sepsis in a neonatal unit of reference and to propose actions in the service's routine to reduce antimicrobial use in neonatal units.

METHODOLOGY

Study design and location

This is a prospective cohort study carried out at a neonatal referral unit, which is a reference university hospital for high obstetric risk and neonatal care.

Inclusion and exclusion criteria

All newborns with epidemiological surveillance criteria admitted to the neonatal referral unit of Hospital das Clínicas da Universidade Federal de Minas Gerais were included for follow-up. The high-risk surveillance criteria of newborns are birth weight less than 1,500 g, use of invasive ventilation, use of central venous catheter, neonates in postoperative procedures, and presence of infectious clinical condition with clinical manifestation.[5]

Data collection

Data collection was performed systematically by specialized and trained professionals from the Hospital Infection Control Service (HICS) of the institution from 2008 to 2018. In addition to demographic information, mandatory variables were collected, in accordance with Brazilian legislation for outcome indicators that define the prevention actions of an HICS and include information for calculation of infection rate and density of incidence of infections, infections by topography, infections and incidence density of infections by devices and surgical site, profile of microorganisms and sensitivity to antimicrobials, use of antimicrobials, and lethality associated with infections. The definitions of HAI follow the criteria defined for infections in neonatology by ANVISA,[5] based on the NHSN criteria of the CDC.[4]

Data analysis

The information collected was routinely stored into the HICS internal database. A descriptive analysis was performed using Excel for Mac version 2008 12.3.1 with the calculation of the density of incidence of HAIs by weight range, HAI frequency in 48 hours of life by topography, and early clinical and laboratorial sepsis with incidence density and by microorganisms, in addition to a control chart with incidence density of HAIs in the period.

Ethical considerations

The Institutional Research Ethics Committee approved the project in 2008, which was updated in 2016.

RESULTS

The control chart of early HAI, regardless of the presence of infection focus, throughout the study period is shown in figure 1. It is observed that the incidence density has remained mostly below the alert line over the years, with an average incidence density around 4 per 1,000 patient-days and outbreaks between the year of 2010 and 2012.

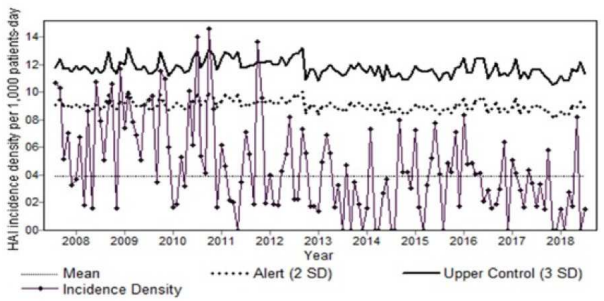

Figure 1. Incidence density control chart for infections related to early health care, (neonatal referral unit, Brazil, 2008 to 2018).

The early HAI density was higher in neonates weighing up to 750 g. In this weight range, the density was 7.2 per 1,000 patient-days, with little variation (4 to 4.7 per 1,000 patient-days) in the other ranges (Table 1).

Table 1. Incidence density of early HAI, by weight range (neonatal referral unit, Brazil, 2008 to 2018.

Birth weight (g)	Patient-days n(%)	Total HAI n (%)	HAI Incidence density
Up to 750	3496	25	7,2
751–1,000	10870	51	4,7
1,001– 1,500	14078	60	4,3
1,501–2,500	24848	107	4,3
> 2,500	23006	93	4
Total	76298	336	4,4

Note. HAI, healthcare-associated infections.

Mid test also presented a significant difference, with higher HAI Incidence Density in neonates ≤ 750g (p<0,05). Most infections were defined as bloodstream infection (sepsis), with no specific focus defined. In addition, most bloodstream infections were defined without laboratory confirmation (clinical sepsis). In some infections, a low incidence of laboratory-confirmed infections was also observed (Figure 2).

Considering only the diagnosis of bloodstream infection (early sepsis), a higher incidence density is observed in extremely low weight patients (with 6.6 episodes of early sepsis per 1,000 patient-days in patients below 750 g and 3.8 episodes of early sepsis per 1,000 patient-days between 750 and 1,000 g (Table 2), but with a higher incidence in patients above 1,500 g (Figure 3).

The main agents of early sepsis identified are Gram-positive microorganisms, as shown in Figure 3 with a low incidence of *Streptococcus agalactiae*. There is a higher incidence of *Staphylococcus aureus* compared to *St. agalactiae* (Figure 4).

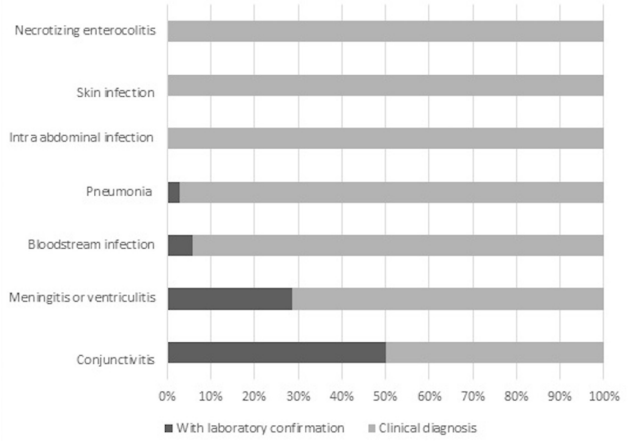

Figure 2. Distribution of early HAI by topography, clinical, and laboratory-confirmed infections (neonatal referral unit, Brazil, 2008 to 2018).

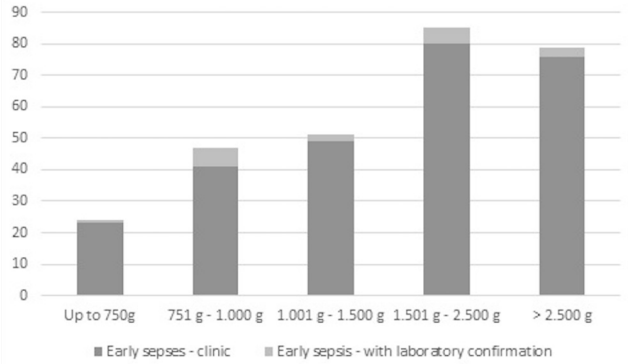

Figure 3. Incidence density of early sepsis per birth weight (neonatal referral unit, Brazil, 2008 to 2018).

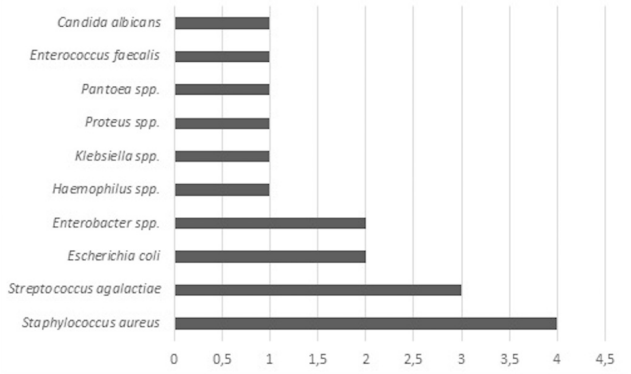

Figure 4. Distribution of microorganisms in laboratory-confirmed early neonatal sepsis (neonatal referral unit, Brazil, 2008 to 2018).

Table 2. Incidence density of early neonatal sepsis, by weight range, (neonatal referral unit, Brazil, 2008 to 2018).

Birth weight (g)	Patient days n(%)	Early-Onset Clinical Sepsis n(%)	Early-Onset laboratorial Confirmed Sepsis n(%)	Total Early-Onset Sepsis n (%)	Incidence density Early-Onset Clinical Sepsis	Incidence density Early-Onset laboratorial Confirmed Sepsis	Total Incidence density Early-Onset Sepsis
Up to 750	3496	23	1	24	6,6	0,3	6,9
751–1,000	10870	41	6	47	3,8	0,6	4,3
1,001– 1,500	14078	49	2	51	3,5	0,1	3,6
1,501–2,500	24848	80	5	85	3,2	0,2	3,4
> 2,500	23006	76	3	79	3,3	0,1	3,4
Total	76298	269	17	336	3,5	0,2	4,4

DISCUSSION

The incidence of early HAI in newborns is related to risk factors associated to prenatal, peripartum, and newborn care. A higher incidence of infections was observed in newborns above 1,500 g, with 200 HAIs reported, 164 of which were episodes of early sepsis. This is due to the characteristics of the population assisted at the service, as a reference in fetal medicine, with a high frequency of neonates with malformations in this weight range.

However, higher incidence density of HAI and early sepsis have been reported in neonates with extremely low birth weight, especially with birth weight below 750 grams, with 7.2 episodes of HAI per 1,000 patient-days and 6.9 episodes of early sepsis per 1,000 patient-days. These data are compatible with the world literature. It is estimated that 60–80% of neonatal deaths occur in newborns with low birth weight, being inversely proportional to the weight range and gestational age. The mortality of newborns in premature infants is three times higher than that of full-term newborns and sepsis is one of the main causes of neonatal death.[6,11]

It was observed that most infections in this study were reported as early clinical sepsis, which means without laboratory confirmation. Due to the low sensitivity of blood cultures, the diagnosis of early neonatal sepsis is overestimated, as newborns show nonspecific signs, compatible with other differential diagnoses. The start of empirical antibiotic therapy is introduced and the propedeutic performed contributes to the definitive diagnosis and can even define the suspension of an antimicrobial.[11,12] In Brazil, ANVISA[5] defines neonatal sepsis as nonspecific clinical signs associated with changes in blood count and C-reactive protein, and treatment, as defined by the attending physician, reflects a higher incidence density of HAIs and neonatal sepsis and greater empirical use of antimicrobials. Only 17 of the 336 cases of early neonatal sepsis had isolation of microorganisms in blood culture, with a low incidence density of laboratory-proven early sepsis of 0.2 per 1,000 newborns, compared to the incidence density of early clinical sepsis of 3.5 per 1,000 newborns.

The literature describes that newborns who receive systemic antibiotic therapy for sepsis with negative culture improve 6–16 times better than babies who receive sepsis therapy with culture confirmation,[12] which can be attributed to the lower detection of bacteremia of some microorganisms, using small volumes of blood obtained from newborns and the technique of collecting and sowing in an appropriate culture medium. In addition, it is considered that the use of maternal antibiotics before or during delivery may interfere with the detection of bacteremia in the newborn.

Even in developed countries, the frequency of isolation of microorganisms in newborn blood cultures is low. In a surveillance study of early sepsis in Norway, only 91 of the 1,538 cases had microbiological evidence with growth in blood culture, which corresponded to 0.54 per 1000 live births who were exposed to empirical antibiotic therapy.[13] This corroborates the data from the present study, with a low percentage of isolation of microorganisms, including *St. agalactiae* and even a lower incidence density of laboratory-proven early sepsis.

The most frequently reported organisms isolated in early neonatal sepsis are *St. agalactiae* (50%), Gram-negative bacilli of maternal flora (25%), predominantly *Escherichia coli*, and, in similar proportions, other *Streptococcus* ssp. and *S. aureus* (6% and 5%, respectively). *Listeria monocytogenes* is reported less frequently (0.9–6%).[4,11]

After the introduction of intrapartum prophylaxis to cover *St. agalactiae*, the rates of early GBS infection in the USA decreased from 0.6 to 0.21 per 1,000 live births.[14] *St. agalactiae* remains the primary medium of early sepsis and can cause maternal urinary tract infection, intra-amniotic infection, or endometritis and is associated with premature and stillbirth labor. Approximately 50% of colonized women transmit the bacteria to their newborns. In the absence of intrapartum antibiotic prophylaxis, 1% to 2% of newborns develop infection, and colonization by this agent is considered the main maternal risk factor.[15] In the hospital where the present study was carried out, intrapartum prophylaxis for *St. agalactiae* is routinely indicated, according to international recommendations.[15-17] Considering the cases of neonatal sepsis with microorganism isolation, the most prevalent agent in early-onset sepsis was *S. aureus*, in contrast to what was reported in the cited literature, even with GBS prophylaxis.[4,11,15-17] It is considered that the present sample was limited, but the absence of isolation of multiresistant microorganisms is emphasized.

Since 1996, the CDC recommended the screening for *St. agalactiae* after 35 weeks of gestation.[17] In 2019, the American College of Obstetricians and Gynecologists recommends performing a universal screening for GBS between 36 and 37 weeks of gestation.[15] Thus, it is recommended that all pregnant women undergo predelivery screening for GBS at 36 weeks of gestation, unless in cases where intrapartum antibiotic prophylaxis is indicated due to GBS bacteriuria during pregnancy, previous history of newborn preinfected with GBS, prematurity, and amniorrhexis time above 18 hours. Although a 4-hour duration of antibiotic prophylaxis is recommended, 2 hours of exposure to antibiotics has been shown to reduce the vaginal colony count by GBS and decrease the frequency of a clinical diagnosis of neonatal sepsis.[15] In the service where this study was carried out, screening for GBS is performed because it is a reference service of high prenatal risk. However, low isolation of the agent was observed, also considering that there is an adequate indication of peripartum antimicrobial prophylaxis.

The American Academy of Pediatrics (AAP) published in 2018 recommendations that guide the care of term newborn and premature newborns at risk of sepsis. The main obstetric measures necessary for the effective prevention of GBS continue to include universal prenatal screening by vaginal-rectal culture, correct collection and processing of samples, appropriate implementation of intrapartum antibiotic prophylaxis, and coordination of pediatric care.[18,19] In 2019, the AAP published recommendations based on risk factors and the use of a risk calculator to define the management of the newborn in order to reduce propedeutics and unnecessary antimicrobial use, with a greater recommendation for clinical observation.[20]

Other maternal risk factors considered in the risk assessment for early newborn sepsis are bacteriuria or *St. agalactiae* urinary tract infection, previous child with invasive GBS disease, prolonged rupture of membranes (≥ 18 h), and maternal fever (temperature ≥ 38°C; often interpreted as a chorioamnionitis sign). The greatest risk of early-onset sepsis occurs in babies born of women with chorioamnionitis who are also colonized with GBS and have not received intrapartum antimicrobial agents.[18-20]

The difficulty in identifying neonates with early signs of sepsis from other neonates is highlighted, because noninfectious conditions have the same nonspecific findings. Although early sepsis is overestimated, it can be fatal if not treated immediately. This favors an increase in the diagnosis of clinical sepsis and a consequent increase in the use of antibiotic therapy in these neonates. The strategy of evaluating the risk factors associated with clinical manifestations reduces the incidence of unnecessary use of antibiotic therapy and increases the sensitivity of the clinical diagnosis.[12] Thus, several authors have

published flowcharts for clinical management of newborns based on maternal risk factors.[8-10]

In addition to the proposed flowcharts, Wynn et al.[21] carried out a multicenter study with surveillance data from 348 neonatal units and adapted the criteria for the definition of clinical sepsis with those of organ dysfunction in newborns with adaptation of the Sequential Organ Dysfunction Assessment (SOFA) but for late-onset sepsis and proposed a criteria for respiratory, cardiovascular, renal, immunological, and hematology dysfunction that can contribute to the diagnosis of sepsis in this population. However, the definition of organ dysfunction in the neonatal population is hampered by the nonspecificity of symptoms.

In 2011, Puopolo et al.[22] published a model with validation of which variables would be included in the sepsis risk calculator model: gestational age (continuous), amniorrhexis duration (continuous), maternal temperature (continuous), colonization by GBS (categorical), and use of intrapartum prophylactic (categorical) antimicrobials. Escobar et al.[23] presented results of the implementation of the electronic risk calculator for newborns ≥34 weeks of gestation, to predict sepsis based on quantitative maternal risk factors and clinical symptoms after birth, with a significant reduction in several countries in the use of antibiotics due to suspected sepsis. The mentioned study used maternal and neonatal data, with definition of risk stratification that considers three groups of newborns: treating empirically (4.1% of all live births, 60.8% of all cases of sepsis, incidence of sepsis of 8.4/1,000 live births), observe and evaluate (11.1% of births, 23.4% of cases, 1.2/1,000), and continuous observation (84.8% of births, 15.7% cases, incidence 0.11/1,000). The authors concluded that the association of maternal risk factors with neonatal clinical signs allowed to define the most efficient approach in the assessment and indication of treatment of neonatal sepsis, with a reduction in the use of antibiotics in 80,000 to 240,000 newborns in the USA each year.

A prospective study in the United Kingdom,[24] with newborns older than 34 weeks, considered maternal and neonatal risk factors, clinical manifestations, use of antibiotics, and results of blood cultures. Babies were treated following National Institute for Health and Care Excellence (NICE) recommendations and compared to those who used antimicrobials based on the risk calculator. The results showed that 16% started antibiotics according to NICE recommendations, compared with 4.3% indicated by the risk calculator, observing a relative reduction of 74%.

In recent years, other studies using the risk calculator have been utilized and compared with recommendations based on conventional flowcharts. A systematic review and meta-analysis carried out by Achten et al.[25] assessed the use of antibiotic therapy in the suspicion of early-onset sepsis guided by the risk calculator compared to conventional strategies and showed that all studies found a lower relative risk for antibiotic therapy. The authors concluded that the use of the risk calculator in newborns of mothers with a risk factor for sepsis showed a significant reduction in the use of antimicrobials by 44% (RR 0.56%, 95% CI 0.53 to 0.59) compared to previous studies, with conventional recommendations based on the presence of risk factors. In this study, the use of antimicrobials was also evaluated in the presence only of chorioamnionitis, with an 80% reduction in the use of antimicrobials when using the risk calculator (RR 0.20%, 95% CI 0.04 to 0.91).

The present study was carried out in a single center, in a developing country, despite having a Hospital Infection Control Committee that performs active surveillance, performed by trained professionals and with standardized international criteria. However, the national criteria recommended by ANVISA[5] still consider clinical sepsis in the identification of neonatal sepsis.

It is considered that the use of the neonatal risk calculator can reduce interventions such as propedeutics and use of unnecessary antibiotics and favor early discharge. Thus, the use of a calculator based on risk factors is recommended, since clinical sepsis is considered and reported based on nonspecific signs, with optimization of propedeutics and rational empirical use of antimicrobials.

CONCLUSION

A low percentage of microorganism isolation was observed in cases of early neonatal sepsis with a large number of clinical neonatal sepsis cases treated with antimicrobials. The need for a more accurate diagnosis to reduce empirical treatments and the use of a risk calculator based on variables that include clinical symptoms and maternal risk factors are recommended to reduce inappropriate antimicrobial use.

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