Variation in Early-Onset Sepsis Risk Assessment in Asymptomatic Term and Near-Term Infants in Portugal

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Abstract

Introduction: Identification of well-appearing infants at risk for early-onset sepsis presents an ongoing challenge. Several guidelines advise categorical risk assessment strategies, resulting in excessive laboratory tests, admissions, and antibiotic use. Currently, approaches using multivariate risk assessment or serial clinical observation are gaining ground. The primary objective of this study was to describe early-onset-sepsis risk management across a national sample of postnatal wards.

Methods: A Web-based survey was sent to 51 neonatal units in Portugal, between April and June 2021, to assess local management protocol for term and near-term newborns at risk for early-onset sepsis.

Results: Thirty-four responses were obtained (out of a total of 65 161 deliveries in 2020). Sociedade Portuguesa de Neonatologia guidelines were followed in 17 out of 34 units. Most units (31/34) used categorical risk assessment and three used serial clinical observation. The considered risk factors differed and the most frequently identified included chorioamnionitis (33/34) and prolonged rupture of membranes (31/34). The most frequent timing for sepsis evaluation was between 6 and 12 hours of life and included blood count and C-reactive protein in all units. Most units (29/33) opted for empiric antibiotics, according to clinical assessment and C-reactive protein values. Antibiotic therapy is started in all cases of chorioamnionitis in 12 out of 34 units. Asymptomatic infants with negative cultures are treated for five or more days in 16 out of 34 units, and in 22 units this is done in the neonatal unit. The majority (25/34) considers possible to adopt a serial clinical evaluation approach. Main concerns were local staff resources (16/24).

Discussion: There is wide variability regarding early-onset-sepsis risk assessment in Portugal. Therefore, it is crucial to standardize clinical pathways to avoid unnecessary interventions.

Keywords: Disease Management; Guideline Adherence/trends; Infant, Newborn; Infant, Premature; Neonatal Sepsis/ diagnosis; Neonatal Sepsis/drug therapy; Portugal; Risk Assessment; Risk Factors; Surveys and Questionnaires

Keypoints

What is known:

- The adoption of sepsis algorithms based on risk-factor threshold values results in laboratory testing and antibiotic treatment of a large number of uninfected newborns.

- Strategies using multivariate risk assessment and/or serial clinical observation are safe and effective.

Introduction

Early-onset sepsis (EOS) is associated with considerable morbidity and mortality in neonates.^{1,2} Identification of well-appearing infants at high risk of infection and early antibiotic therapy may be lifesaving and remains a major challenge.^{1,2} Several perinatal factors associated with

What is added:

- Major variation exists regarding many aspects of early-onset sepsis screening nationwide.
- Less interventive strategies are gaining ground and acceptance throughout the country.

increased risk of early-onset sepsis include gestational age, maternal intraamniotic infection, length of rupture of membranes (ROM), maternal group B *Streptococcus* colonization, and the administration of appropriate intrapartum antibiotic therapy. However, associations between each individual risk factor and early-onset sepsis are weak.^{2,3}

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Since 1996, several clinical practice guidelines have advised a categorical risk factor assessment strategy.^{2,4-6} Later, a multivariate risk assessment strategy (sepsis risk calculator) was developed using a cohort of 608000 infants to create a predictive model for culture-confirmed early-onset sepsis, based on perinatal risk factors and clinical evaluation during the first 6 to 12 hours after birth.⁷ Recently, a strategy using serial clinical observation and based on clinical status, has been increasingly adopted. The alternative approaches mentioned have been implemented in several centers and may be as effective as the traditional screen-and-treat protocols.^{1,7-10}

The current guideline in Portugal dates back to 2014 and follows a categorical risk factor assessment strategy.¹¹ Empiric antibiotics are recommended in the presence of chorioamnionitis, maternal bacteriemia, or a twin with early-onset sepsis, regardless of clinical status or laboratory results.¹¹ When it comes to other risk factors, in the presence of more than one, the recommendation is to perform a limited sepsis screening, including a leucogram with immature / total neutrophile count and C-reactive protein twice in 48 hours.¹¹ Asymptomatic infants with a positive sepsis evaluation and whose cultures remain negative are to be treated for five days.¹¹ Local hospital protocols have been developed since the 2014 guideline. Different approaches, sets of risk factors, and laboratory studies are in practice. Therefore, detailed knowledge of the several national clinical practices is of major relevance here.

This study aimed primarily to describe early-onset sepsis risk management strategies performed in Portugal among asymptomatic term and late-preterm newborns, in a nationwide sample of newborn nurseries. The secondary objectives of the present study were to identify:

- The prevalence of alternative strategies based on multivariate risk assessment or serial clinical observation;

- Specific perinatal factors used to identify newborns at increased risk of early-onset sepsis;

- Laboratory tests used;

- Use of empirical antibiotic treatment;

- Duration of antibiotic treatment in asymptomatic culture negative infants;

- Whether or not mothers and newborns have been separated for antibiotic treatment.

Methods

An anonymous 21-question survey was constructed using a Web-based application for survey design and database management. The questions target the primary issues clinicians consider relevant when assessing sepsis risk for a well-appearing infant born at 35 or more weeks gestation. Questions required yes / no, multiple choice response, or an open answer. The survey was sent to the directors / coordinators of 51 public and private neonatal units in Portugal between April and June 2021, to inquire about the assessment and management protocols practiced by most clinicians at their institutions.

Data analysis was performed using Microsoft Excel (version 16.63.1).

Results

Survey responses were obtained for 34 neonatal units (four highly differentiated perinatal support hospitals, 21 differentiated perinatal support hospitals, and nine perinatal support hospitals, according to the Portuguese neonatal college categorization), with a cumulative number of 65 161 deliveries in 2020.

All 34 units stated that the obstetric practices included a group B Streptococcus intrapartum antibiotic prophylaxis (IAP) policy. The approach to asymptomatic term or near-term newborns considered at risk for early-onset sepsis varied. The approach in 17 units was based on the 2014 consensus of the Sociedade Portuguesa de Neonatologia and the remaining 17 units followed local institutional sepsis risk protocols. Most units (31/34) used categorical risk assessment practices. Laboratory evaluation of sepsis was performed in 19 units in the presence of chorioamnionitis or at least a combination of two other risk factors for early-onset sepsis, any risk factor in seven units, and more than one risk factor in five units. Three units used alternative strategies based on serial clinical observation strategies, one of them in combination with a sepsis risk calculator.

The risk factors cited to consider a newborn at risk for early-onset sepsis differed among centers. In the 34 units inquired, 28 different combinations of risk factors were used to decide for laboratory evaluation (Table 1). The most frequent risk factors included chorioamnionitis (33/34) and prolonged rupture of membranes (PROM) over 18 hours (31/34), followed by maternal fever (27/34) and twin brother with earlyonset sepsis (27/34) (Table 1).

Empirical antibiotic therapy was started in the presence of chorioamnionitis in 12 units, regardless of clinical status or laboratory evaluation.

Sepsis evaluation was performed between 6 and 12 hours of life in 18 institutions, between 12-24 hours in 14 institutions, and was repeated after 24 hours of life in 12 institutions. None included cord blood sampling.

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Risk factors	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34 Tot
Chorioamnionitis	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	33
Twin with EOS	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~		~		~	~	~					~	27
Preterm birth*	~	~	~	~	~	~	~	~	~	~	~	~	~		~	~	~	~			~	~	~		~				~	~				23
Intrapartum fever	~	~	~	~	~	~	~	~	~	~	~	~		~	~	~		~	~	~	~	~	~		~	~	~		~	~	~			27
PROM (> 18 hours)	~	~	~	\checkmark	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~		~	~	~	~		31
Preterm ROM	~	~	~	\checkmark	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~		~										23
SGB with IAP	~	~	~	~	~	~							~												~									8
SGB IAP < 4 hours	~	~	~	\checkmark	~	~	~	~	~	~	~	1	~	~	~	~	~	~	~		\checkmark		~		~									22
SGB without IAP	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~	~		~				~	~				26
SGB bacteriúria	~	~	~	\checkmark	~		~	~	~	~	~		~	~	~					~		~										~		16
Previous SGB disease ⁺	~	~	~	~	~	~	~	~	~	~	~	1	~	~	~		~		~	~	~		~	~				~				~		23
Peripartum UTI ¶	~	~	~	~		~	~	~	~			1		~		~	~						~	~		~		~			~			17
Maternal lab+ [‡]	1	~	1		1	~	1	~	~	1	~	1	1	1		1	1	1	1	1			1	~		1	1	1			~		1	25

* Preterm birth - spontaneous preterm labor.

Previous SGB disease - previous sibling with group B Streptococcus disease.

Maternal lab + - mother with leukocytosis or positive C-reactive-protein IAP - intrapartum antibiotic prophylaxis; PROM - prolonged rupture of membranes; ROM - rupture of membranes; SGB - group B Streptococcus; UTI - urinary tract infection.

Laboratory evaluation includes full blood count and C-reactive protein in all units. Moreover, seven, six, and five units asked for blood culture, procalcitonin, and immature / total neutrophile ratio, respectively.

There were various criteria for starting antibiotics in asymptomatic infants. The majority (29/34) considered serial clinical assessment and C-reactive protein values, and eight stated specific C-reactive protein cutoff values (three of 1 mg/dL and five of 2 mg/dL). Five units considered leukocytosis and four thrombocytopenia to decide for treatment. When asked for the C-reactive protein threshold value for serial evaluation without antibiotics, three consider 1 mg/dL, seven 2-2.5 mg/dL, eight 3-3.5 mg/dL, four 4 mg/dL, four 5 mg/dL, one 6 mg/dL and six have no established value.

Regarding the length of antibiotics in asymptomatic infants with negative cultures, 15 units mentioned five days, 14 units 72 hours, four units 48 hours and one seven days. In 22 institutions, infants were admitted to the neonatal unit for antibiotic therapy and 12 centers allowed infants to room in with their mothers during therapy.

Infants considered at risk for early-onset sepsis with a negative sepsis evaluation are discharged between 48 and 72 hours of life in the majority (26/34), between 36 and 48 hours in two and after 72 hours in six units.

A total of 25 units considered the adoption of a serial clinical evaluation approach. However, the concern over local staff resources was the primary reason against opting for this approach (16/24). Only four units broached concerns about the sensitivity of clinical evaluations alone.

Discussion

Cumulative evidence has led to a rapid shift in consensus about sepsis evaluations and questioning established protocols. New guidelines are undoubtedly forthcoming. Routine intrapartum antibiotic prophylaxis in mothers with group B Streptococcus colonization and/ or chorioamnionitis has resulted in decreasing rates of early-onset sepsis. Currently the culture-positive earlyonset sepsis rate among term and near-term infants (gestational age > 35 weeks) is estimated to be 0.5-0.7 per 1000 live births.¹²⁻¹⁴ Additionally, in this group of infants, good clinical condition at birth was associated with a 60% to 70% lower risk of early-onset sepsis.⁷

In a clinical report from 2018, the American Academy of Pediatrics considered three acceptable strategies for evaluation of term and late preterm infants at risk of early-onset sepsis: categorical algorithms, multivariate risk assessment, and serial clinical observation, considering the merits and limitations of individual approaches and the necessity of choosing strategies that best match local resources and structure.¹ In 2021, the National Institute for Health and Care Excellence (NICE) guideline considered the use of the multivariate risk assessment as a valid alternative.¹⁵

Categorical risk factor assessment strategies define risk factor threshold values to identify infants at increased risk for early-onset sepsis, and different algorithms have been proposed to decide on laboratory sepsis screening and/or empiric antibiotic therapy. Published evidence suggests that these recommendations lead to frequent laboratory screening and antibiotic exposure of healthy newborns with minimal risk of early-onset sepsis.9,10,16

The multivariate risk assessment strategy uses recommended clinical algorithms based on objective criteria (gestational age, highest maternal intrapartum temperature, maternal group B *Streptococcus* colonization status, duration of rupture of membranes, and type and duration of intrapartum antibiotic prophylaxis).⁷ Posterior studies validated the safety of this strategy due to such positive outcomes as a reduction in blood testing and antibiotic use, without an increase in adverse events.¹³ Concerns remain, however, regarding the increased need for clinical surveillance as well as the external validity of its application for populations that are substantially different from the one used to generate the tool.¹³

The serial clinical observation strategy begins with a categorical or multivariate assessment to identify newborn infants at risk who will then be subjected to serial monitoring. Structured clinical evaluations at predefined intervals are performed and include parameters such as general well-being, skin color, respiratory status, and temperature. Institutions adopting this strategy have developed protocols defining the periodicity of clinical examinations, the included clinical parameters, and clinical findings granting an escalation of care. Several studies suggest that serial clinical observation may be as effective as the traditional screen-and-treat protocol.^{9,12} However, this approach requires considerable resources and evidence is still lacking regarding an optimal schedule for clinical observation, as well as the most clinically meaningful signs and symptoms to be assessed.

Approach to term and near-term infants at risk for early-onset sepsis

Regarding the assessment of categorical risk factors, it is of note that published guidelines are heterogeneous considering the included risk factors, clinical assessment tools, and protocols for evaluation and clinical monitoring.¹⁷ Concerns over the clinical application of these guidelines include lack of specificity and sensitivity of laboratory tests, the need for multiple sepsis screening and blood tests, and excessive antibiotic exposure in healthy infants.¹ Other pertinent factors include newborn and/or parental separation distress, delayed maternal bonding, the establishment of breastfeeding, intravenous line complications, and risk of medical error accompanying the hospital stay.¹⁰ All these factors may have important clinical, personal, and economic implications for infants, their caregivers, clinicians, and the healthcare system. Increasing data indicate the detrimental effects of antibiotics on an infant microbiome and the potentially deleterious

effects of early maternal-infant separation on bonding and breastfeeding, which should be well considered in balancing the risk of early-onset sepsis against unnecessary procedures.^{10,18-22}

The management of chorioamnionitis-exposed newborns is particularly problematic due to the inconsistent definition of chorioamnionitis and the potential earlyonset sepsis-associated risk. Recent data show that the risk of early-onset sepsis in chorioamnionitis-exposed term neonates is not as high as that in infants born at less than 35 weeks of gestation, ranging from 0.47% to 1.24%.⁸ The practice of treating all asymptomatic newborns presenting this risk factor has resulted in hundreds of admissions for every treated case of culture-confirmed sepsis.^{7,23}

In our study, half of the inquired units followed local protocols and the categorical risk approach used by the majority. Although most considered it possible to institute less invasive approaches, the practice is globally very conservative regarding indications for sepsis screening and antibiotic therapy. Similar to other studies, we found substantial variation in risk identification, evaluation, and empirical antibiotic therapy, which can probably be explained by a lack of consensus.^{24,25} Alternative strategies are gaining ground worldwide, and locally three of the responders are following these new approaches.

As for the considered risk factors, it should be noted that despite the consensus over the major risk factors, namely chorioamnionitis and prolonged rupture of membranes, there was still great uncertainty over the inclusion of the remaining risk factors. We found 28 different combinations of risk factors in 34 units, demonstrating the same lack of consensus already mentioned. Regarding group B Streptococcus, eight out of 34 units still performed sepsis screening in the presence of adequate intrapartum prophylaxis, and a majority of units (25/34) included a previous sibling with group B Streptococcus disease or group B Streptococcus bacteriuria as risk factors when these should only grant group B Streptococcus intrapartum antibiotic prophylaxis. Half of the centers considered peripartum urinary tract infection a risk factor, against national and major international recommendations. Additionally, eight units still perform laboratory screening in newborns with only one risk factor although national recommendations allow for a less invasive approach. Even though half of the units followed national guidelines, only 12 units agreed to fully comply with some specific issues, such as repeating laboratory screening after 24 hours and treating all babies with chorioamnionitis as a risk factor. Although the latter is one of the most important

recognized early-onset sepsis risk factors, the decision not to treat these babies complies with the findings of recent studies,^{12,23} and the current recommendation is likely to change in the near future.

Laboratory investigation for infants at risk for earlyonset sepsis

The gold standard for the diagnosis of early-onset sepsis is blood or cerebrospinal fluid cultures. The white blood cell count, immature / total neutrophile ratio, and absolute neutrophil count are commonly used to assess the early-onset sepsis risk. Multiple clinical factors can affect the white blood cells count and differential, and evidence shows that none of the components of white blood cells perform well in predicting early-onset sepsis.²⁶⁻²⁸ Both C-reactive protein and procalcitonin concentrations increase in newborn infants in response to a variety of inflammatory stimuli, while procalcitonin concentrations also increase naturally over the first 24 to 36 hours after birth. Determination of C-reactive protein or procalcitonin is neither sensitive nor specific to early-onset sepsis risk assessment in well-appearing term newborns.1,29

All the units reported total blood count and C-reactive protein as the main laboratory screening tests, and the use of other tests was residual. The great variability in choosing a cut-off value probably reflects the lack of sensibility and specificity of these tests.

Duration of antibiotic therapy in asymptomatic infants at risk for early-onset sepsis

Modern blood culture systems reliably detect bacteremia at a level of 1-10 colony-forming units per mL in a minimum blood volume of 1 mL, and intrapartum antibiotic therapy has no proven effect on the timing of positivity.^{30,31} When blood cultures are sterile, antibiotic therapy should be discontinued by 36 to 48 hours of incubation unless there is clear evidence of site-specific infection.¹

Concerns regarding early-onset sepsis in newborn infants still prompt frequent antibiotic use, and up to 2%-8% of late-preterm and term infants receive antibiotic treatment.^{19,24,25} A recent study revealed that 4.6% of 12 121 infants born at 35 or more weeks gestation were evaluated based on the diagnosis of maternal chorioamnionitis, according to the American Academy of Pediatrics guideline. Moreover, although early-onset sepsis was confirmed by positive culture in only 0.7% of cases, 20% received antibiotics for seven or more days, based on laboratory results, despite posterior negative culture results.³²

In institutions surveyed in this study, antibiotics were

continued for more than 48 hours despite negative cultures in the large majority of units (30/34), and 15 out of 34 units continued treatment for more than five days, in compliance with national guidelines, that are most certainly outdated in this aspect. The risk of intestinal dysbiosis caused by prolonged antibiotics should be seriously considered in this critical period. Studies suggest that, apart from acute consequences, this imbalance might contribute to the development of relevant conditions later in life, including diabetes, obesity, depression, or breast or colon cancer, amongst many others.³³

Starting empiric antibiotics in most neonatal units in Portugal implies admission to a neonatal unit and motherinfant separation. This might come with a significant cost since separation even for such a short period as two hours can lead to long-term deleterious effects on the mother-baby interaction,^{34,} especially during a sensitive postnatal period. The impact of neonatal intensive care unit admission on breastfeeding is also of great relevance, as mothers will encounter greater difficulties in maintaining adequate milk production and will be at greater risk for breastfeeding failure.^{35,36}

Introduction of alternative strategies

The large majority of the units inquired in the current study considered it possible to introduce less aggressive approaches (that is serial clinical observation) in their institution, and a few (4/34) limited antibiotic treatment to 48 hours. The major mentioned difficulty was the lack of resources. However, from a hospital standpoint, admissions for suspected sepsis in asymptomatic babies can pose logistic and staffing challenges as well. This is of particular importance in our reality, where the majority (22/34) of the institutions surveyed admit asymptomatic newborns for antibiotic therapy in the neonatal unit.

Given the number of units inquired, our sample (65 161 of a total of 83 784 deliveries in 2020) can be considered representative of national reality.³⁷ Nevertheless, our study has some limitations:

- Only one person at each institution responded to the survey, and provider variation is likely to exist;

- Some of the survey questions were subject to interpretation which might have impacted the provided answers;

- Differences in definitions of chorioamnionitis were not investigated, and details about less-interventive protocols adopted in some institutions were not obtained.

In summary, different centers use different combinations of risk factors, clinical assessment tools, and protocols

for the evaluation and clinical monitoring of infants at risk of early-onset sepsis. In investigating and treating suspected early-onset sepsis in asymptomatic babies, negative consequences are not immediately apparent, but should not be disregarded. Optimization of earlyonset sepsis screening practices could affect a large population of newborns and more research is needed to further define an optimal approach. Meanwhile, national efforts to optimize practice are warranted, and provided that institutions can redirect resources, well-appearing late-preterm and term infants with risk factors for early-onset sepsis can be assessed using sepsis-calculator, serial clinical observation, or a combination of both, rooming in with their mother. These strategies could be considered as an alternative to categorical risk assessment, always keeping in mind the need for tailoring practice according to local resources. Additionally, and regardless of the above, a serious discussion is needed regarding the therapeutic approach to infants exposed to chorioamnionitis and the duration of antibiotics administration in asymptomatic infants with negative cultures.

Author Contribuitions

IS participated in the study conception or design. IS, CD and IG participated in acquisition of data. IS, IG and RG participated in the analysis or interpretation of data. IS and CD participated in the drafting of the manuscript. IS, IG and RG participated in

the critical revision of the manuscript. All authors approved the final manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this study.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki 2013).

Provenance and peer review

Not commissioned; externally peer reviewed.

Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

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Variação na Avaliação do Risco de Sepsis Precoce em Lactentes Assintomáticos de Termo e Próximos do Termo em Portugal

Introdução: A identificação dos recém-nascidos assintomáticos com risco de sepsis precoce mantém-se controversa. As estratégias baseadas na avaliação categórica de fatores de risco resultam em avaliações laboratoriais, internamentos e antibioticoterapia em excesso. A calculadora de risco de sepsis e a observação clínica seriada têm sido aplicadas crescentemente. O principal objetivo deste estudo foi caracterizar a abordagem do risco de sepsis precoce numa amostra de maternidades nacionais.

Métodos: Foi enviado um questionário eletrónico a 51 unidades de apoio perinatal portuguesas entre abril e junho de 2021, sobre a abordagem do risco de sepsis precoce no recém-nascido com idade gestacional igual ou superior a 35 semanas.

Resultados: Obtiveram-se 34 respostas (65 161 partos em 2020). Seguem os consensos de 2014 da Sociedade Portuguesa de Neonatologia 17 unidades. A maioria (31/34) utiliza a avaliação categórica de fatores de risco e três observação clínica seriada. Os fatores de risco mais utilizados são a corioamnionite (33/34) e a rotura prolongada de membranas. O rastreio séptico é realizado mais frequentemente (18/34) entre as 6 e as 12 horas de vida e inclui hemograma e proteína-C-reativa em todos.

Na maioria (29/34), a instituição de antibioticoterapia baseia-se na clínica e no valor seriado da proteína-Creativa. Instituem antibioticoterapia na presença de corioamnionite independentemente do rastreio séptico 12 unidades. A duração de antibioticoterapia em recémnascidos assintomáticos e com hemocultura negativa é de cinco ou mais dias em 16/34 e em 22 isto implica internamento na unidade. A maioria (25/34) considera aplicável uma estratégia baseada na observação clínica seriada, sendo o principal obstáculo identificado os recursos humanos (16/34).

Discussão: Existe grande variabilidade nacional na abordagem do risco infecioso neonatal, sendo fundamental identificar estratégias que permitam evitar intervenções desnecessárias.

Palavras-Chave: Fatores de Risco; Fidelidade a Diretrizes/ tendências; Gestão Clínica; Inquéritos e Questionários; Medição de Risco; Portugal; Recém-Nascido; Recém-Nascido Prematuro; Sepsis Neonatal/diagnóstico; Sepsis Neonatal/tratamento farmacológico