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ORIGINAL ARTICLE

Conservative management of newborns with 35 weeks or more of gestational age at risk for early-onset sepsis: a Brazilian cohort study

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Abstract
Objective: To evaluate the conservative management of newborns born at ≥35 weeks of gestational age, at risk for early-onset neonatal sepsis (EOS).
Methods: Retrospective, analytic cohort study (2016 to 2019), including newborns ≥35 weeks of gestational at risk of EOS, asymptomatic at birth, managed conservatively in full rooming-in: serial physical examination and clinical observation for at least 48 h. They were classified into three groups, according to the clinical course: asymptomatic (group A), symptomatic for other reasons (group B), and with sepsis (group C). Risk factors, clinical signs and differential diagnoses of sepsis, length of stay, and discharge conditions were evaluated.
Results: The authors evaluated 769 asymptomatic newborns at risk of EOS. (mean birth weight 2999 ± 485 g and gestational age 37.6 ± 1.7 weeks, respectively) corresponding to 12.2% of rooming-in admissions. The most prevalent risk factors were colonization by Group B *Streptococcus* (29%), prolonged rupture membrane duration (21.9%) and preterm labor (21.4%). Most of all of them (53.9%) remained asymptomatic (group A). Group B corresponded for 45.3%, and the most common clinical signs were hypothermia (24.5%), tremors (8.7%) and vomiting (8%). Environmental dysthermia (50.7%), prematurity (20.0%), and feeding intolerance (15.7%) were common in Group B. Laboratory tests were performed in 3.5%. Five patients (one confirmed) comprised group C (0.8/1,000 live births). There were no deaths. The median length of stay was 64 h (IQR 50-93).
Conclusion: The rate of clinical/confirmed EOS was low. Most of the symptomatic patients only needed clinical evaluation to rule out sepsis. Management was shown to be safe.

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Introduction

Neonatal infections are extremely relevant due to the high rate of associated morbidity and mortality. Early-onset neonatal sepsis (EOS) is defined as an infection that occurs from birth to 48−72 h of life.[1] Unless there is strong evidence of another source of contamination, early infection originates from the maternal microbiota. Therefore, several maternal factors are considered risk factors for EOS, such as urinary tract infection, chorioamnionitis, premature rupture of ovular membranes, and maternal colonization with group B Streptococcus (SGB).[2]

The gold standard for the diagnosis of EOS is a positive blood or cerebrospinal fluid (CSF) culture.[1,2] An accurate diagnosis of EOS in the absence of positive cultures is not easy, as the clinical findings and laboratory screening tests are nonspecific, and they may be confused with conditions specific from birth and neonatal adaptation to the extrauterine environment.[3,4]

The clinical suspicion of EOS, sometimes based only on the presence of risk factors in asymptomatic infants, often leads to the admission of newborns to a neonatal unit, and the institution of empirical antibiotic therapy in many patients who are not truly infected, leading to the possibility of further deleterious effects.[5] Thus, to not let a case of EOS go unnoticed, many infants are categorized as being at high risk and exposed to unnecessary treatment.[2]

Almost three decades ago, the present study's neonatal unit implemented conservative management based on risk stratification associated with identifying clinical conditions in newborns born at $\geq$ 35 weeks, discouraging empirical treatment in asymptomatic patients.[6] Moreover, in the last three decades, the success of obstetric interventions, such as maternal *Streptococcus agalactiae* carrier identification, and adequate antimicrobial peripartum prophylaxis, as well as recognition of undesirable effects of early exposure of newborns to antibiotics, are the main reasons that have motivated new studies and new management guidelines. It was only in 2018 that the assessment of newborns at risk of EOS, based on their clinical conditions, was recognized by the AAP as a possibility for management.[7]

In this context, this study aimed to evaluate the clinical course and discharge conditions of newborns $\geq$ 35 weeks of gestational age at risk of EOS, asymptomatic at birth and managed conservatively.

Methods

An analytical cohort study, with retrospective data analysis, was carried out in a tertiary-level university hospital with approximately 3000 deliveries/year. Inborn infants born at 35 weeks of gestational age or more, born between July 2016 and July 2019, at risk of EOS, who were asymptomatic at birth and referred to the rooming-in ward, were included. The criteria for rooming-in admission in the hospital are well-appearing infants, gestational age $\geq$ 35 weeks, and birth weight $\geq$ 2000 grams.

The sample size estimation was for convenience. Clinical data were collected from medical records from a database identifying newborns at risk of EOS.

The identified risk factors of EOS were: maternal SGB colonization, prolonged rupture of membranes water ($\geq$ 18 h), preterm labor, intrapartum maternal fever alone (T $\geq$ 38 °C), maternal sepsis, foul smelling amniotic fluid, current urinary infection untreated or treated within 48 h before delivery, the previous sibling with a confirmed diagnosis of early group B *Streptococcus* sepsis, and clinical chorioamnionitis.[8]

The indications for intrapartum prophylactic antibiotics used in the neonatal unit were those recommended by the CDC.[9]

The selected newborns were divided into three groups according to their clinical course. Group A: They remained asymptomatic during the 48 h of clinical observation. Group B: those who presented clinical signs suggestive of sepsis, but this diagnosis was ruled out after an investigation by serial clinical examination and laboratory analysis, if needed, without using antibiotics. Group C: those who showed clinical signs and received the diagnosis of EOS were admitted to the neonatal unit and received targeted treatment.

The diagnoses of proven EOS and clinical sepsis were performed using the Diagnostic Criteria for Infection Related to Health Care of the National Health Surveillance Agency of Brazil- ANVISA.[10]

Complementary tests were performed in the case of patients with persistent symptoms suggestive of EOS to establish the diagnosis or to define the differential diagnosis of the clinical signs. Thus, depending on the case, the following tests were obtained: White blood cell count (WBC), C-reactive protein (CRP), blood culture, cerebrospinal fluid (CSF) analysis, and chest X-ray.

For WBC evaluation, the absolute neutrophil counts (ANC) and the immature-to-total (I/T) neutrophil ratio were analyzed, according to Manroe et al.[11] CRP was quantified by nephelometry and analyzed considering a value $<$ 10 mg/l as normal.[12] Blood cultures were collected, when indicated, in two samples. Chest radiography was performed when there was a clinical indication for respiratory distress and suspected pneumonia.

All asymptomatic newborns at birth were conservatively followed up for the first 48 h of life in rooming-in. The protocol included a serial physical examination by an attending physician (at birth, at 12h, and thereafter, every 24 h until discharge), and by assessing the nursing staff, with clinical evaluation, measurement of axillary temperature, and other vital signs every six hours. Blood culture samples of the newborn at risk of EOS were indicated in the following maternal conditions: clinical chorioamnionitis; preterm labor with unknown maternal SGB screening; a mother with the definite or suspected septic condition during labor and delivery; mothers with intrapartum axillary temperature $\geq$ 38.0 °C; pregnant women with suspected or confirmed urinary tract infection in insufficient treatment (less than 48 h of treatment; time to rupture of ovular membranes $\geq$ 18 h in infants $<$ 37 weeks; or in cases where mothers have an indication for antibiotic prophylaxis for SGB, but they do not receive the treatment or it occurred at an inappropriate time ($<$ 4 h).

Patients who remained asymptomatic for up to 48 h of life and with a partial negative result of blood cultures, were discharged from rooming-in to home. Patients with isolated symptoms and no signs of aggravation were reassessed and, if the clinical sign was explained by a reason other than sepsis, they were kept under observation in the rooming-in. If

the clinical signs were multiple, severe, or persistent, they were admitted to a neonatal intensive care unit and underwent complete infectious screening and antibiotic therapy. In cases of negative blood cultures within 48 h and clinical improvement, they were discharged. In case of suspicion of clinical sepsis or confirmation by the positivity of blood culture and/or CSF, antimicrobial treatment was continued.

Categorical variables were expressed as absolute and relative frequency (%). Continuous variables were expressed as the mean and standard deviation or median and interquartile range (IQR), according to the distribution of values. Rates were expressed as a percentage or per thousand live births, as appropriate. When comparing groups, categorical variables were compared using the chi-square or Fisher test and continuous variables using the Mann-Whitney test, according to the normality distribution of the variable. The accepted significance level was $p < 0.05$.

The study was approved by the Research Ethics Committee (Certificate of Presentation of Ethical Appreciation: 89429418.8.0000.5404).

Results

A total of 769 newborn infants were evaluated, equivalent to 12.2% of the total number of patients admitted to the rooming-in ward (*n* = 6,274).

The cohort consisted predominantly of full-term newborns with a mean birth weight of approximately 3.0 kg (2.999 ± 485 g) and with a mean gestational age of 37.6 ± 1.7. The proportion of preterm newborns was approximately one-third (36.3%), The median stay in rooming-in was 64 h (interquartile range 50−93 h) and was significantly longer in group B than in group A: (72 h IQI 53-110 × 60 h IQI 50-72, $p < 0$, 0001). The median hospital stay in group C corresponded to 240 h (IQR 204-456).

The risk factors for EOS found are described in Table 1. The most frequent factors were SGB colonization (29.0%), prolonged rupture membrane duration (22.0%) and preterm labor (21.5%). The presence of more than one EOS risk factor occurred in 13.3% of the population. Intrapartum maternal antibiotic prophylaxis was performed in 52.4% (*n* = 403) of the patients, using penicillin G (*n* = 338), cefazolin (*n* = 41), ampicillin (*n* = 5) or clindamycin (*n* = 19), with a median of 9 h (IQR 4-24) before delivery.

According to their clinical course, Group A (*n* = 415), newborns who remained asymptomatic, corresponded to 53.9%. Group B (*n* = 349) was equivalent to 45.3% of the sample, which represented those infants who had some clinical signs suggestive of sepsis, but who had a diagnosis ruled out. Group C had only five newborns, who were diagnosed with EOS, and they corresponded to 0.65% of cases and a rate of 0.8/1000 born living ≥ 35 weeks of gestation.

In group B, the clinical manifestations, in order of frequency, were: hypothermia (24.5%), tremors (8.7%), vomiting (8%), difficulty in sucking (6.1%), respiratory distress (5 .3%), hypoactivity (4.8%), hypotonia (2.7%), hyperthermia (1.8%), irritability (1.2%), cyanosis (0.9%), convulsion (0.5 %), apnea (0.5%), abdominal distension (0.4%), oliguria (0.4%), tachycardia (0.3%) and altered perfusion (0.1%).

The differential diagnosis of EOS was carried out carefully through a meticulous clinical evaluation, and, in some patients, laboratory and imaging tests were performed. Those who presented transient and self-limiting symptoms did not undergo laboratory and/or radiological examinations. The differential diagnoses of EOS performed in group B are shown in Table 2.

Only 3.5% of the newborns were submitted to WBC (*n* = 27), and eight of them had an altered ANC index. Only one had both altered ANC and I/T values, and none had platelet alterations. CRP measurement was performed in 21 patients (2.7%), with abnormal results in five patients, four of them diagnosed with EOS. One patient in group B had an altered CRP value, however, the diagnosis of sepsis was ruled out because she had only one episode of transitory and self-limited hyperthermia secondary to environmental factors, in addition to the other normal laboratory parameters.

Chest radiography was performed in patients who maintained respiratory symptoms in the serial evaluations. Thirty-one exams were performed, 17 of which were altered. The radiological findings were compatible with transient tachypnea of the newborn (*n* = 9), pneumothorax (*n* = 3), clavicle fracture (*n* = 3), cystic adenomatous malformation (*n* = 1), cardiomegaly (*n* = 1). It is noteworthy that

Table 1 Maternal risk factors for early-onset neonatal sepsis identified in the cohort of newborns at risk admitted to rooming-in ward in the four-year period (2016 to 2019).

Risk factor	N-769 (%)
Streptococcal B carrier	223 (29.0)
Amniotic rupture ≥ 18h	169 (22.0)
Premature labor	165 (21.5)
Fever	34 (4.4)
Sepsis	21 (2.7)
Current urinary infection	21 (2.7)
Foul smelling amniotic fluid	20 (2.6)
Clinical chorioamnionitis	9 (1.2)
Previous sibling with early streptococcal sepsis	4 (0.5)
More than one risk	103 (13.4)

Values are expressed in absolute (N) and relative (%) frequency.

Table 2 Distribution of differential diagnoses of early neonatal sepsis in group B newborns.

Diagnosis	N-349 (%)
Environmental dysthermia	177 (50.7)
Prematurity	70 (20)
Feeding intolerance	55 (15.7)
Hypoglicemia	50 (14.3)
Hiperexcitability signs	48 (13.7)
Transitory tachipnea of the newborn	29 (8.3)
Suckling difficulties	21 (6)
Seizure	3 (0.8)
Pneumothorax	3 (0.8)
Congenital heart disease	3 (0.8)
Intestinal obstruction	2 (0.5)
Other	18 (2.3)

Values are expressed in absolute (N) and relative (%) frequency.

none of the patients had a radiological image compatible with pneumonia.

CSF sampling was performed on seven newborns (0.9%). None of them had microorganism growth in the CSF culture. The only patient whose CSF sample showed a cytological and biochemical abnormality, together with altered hematological screening and a clinical picture of seizure, corresponded to an infant with meningitis without an isolated agent, treated for 21 days with Oxacillin and Cefotaxime due to an ultrasound diagnosis of ventriculitis.

Following the institutional protocol, two blood culture samples were collected from 172 patients, which represents 22.3% of the sample. Positive results occurred in only one case.

Patients in group C (n = 5) were transferred to the neonatal unit and received treatment for EOS, initially with penicillin G and amikacin until the biological agent and site of infection were defined. Only one infant had the diagnosis of EOS confirmed by culture, with two samples of early growth (12 h and 17 h) positive blood cultures of *S. epidermidis*. The infant was treated with Vancomycin for seven days. There was one case of meningitis as described above. The remaining patients were diagnosed with clinical sepsis and treated for 7 days.

There were no deaths among the evaluated patients.

Discussion

The conservative management evaluated in this study, used since 1996, proved to be safe and effective, as there were no deaths caused by delays in diagnosing or treating the true ill patients.

One of the first studies in assessing conservative management in newborns at risk of EOS was carried out by Escobar et al in 1995/1996, which showed that the risk of EOS in the absence of symptoms was very low: in a cohort of 18,299 infants weighing more than 2,000 g, only 2.2% presented criteria of proven, probable or possible EOS. This manuscript was published in 2000, and this result, at that time, motivated the present study's team to proceed with conservative management and to value the clinical manifestations of the disease, despite the presence of risk factors for EOS.[13] In the neonatal unit of the present study, the overall prevalence of EOS in NB $\geq$ 35 weeks evaluated in another evaluation was also low - a rate of 4/1000 living births and that of proven EOS was 0.3/1000 live births,[14] as in a more recent North American study.[3]

In this study, even though a third of the pregnant women were colonized by *S. agalactiae*, the majority received adequate prophylactic antibiotics, which leads us to deduce that the low incidence of proven EOS, as well as the absence of Streptococcal EOS in this study, are linked to adequate prophylaxis. This effect on EOS reduction was already described in the literature.[15]

As the authors have shown, despite all the evaluated newborns having at least one risk factor of EOS, which differs from the study by Escobar et al., most of them remained asymptomatic and healthy during the 48 h of observation in rooming-in. This shows that a more aggressive approach to these newborns, collecting laboratory tests and even initiating antimicrobial therapy, is unnecessary. Regardless of the risk factor, clinical manifestation has been unanimously considered the main diagnostic criterion for the disease.[16] Other studies have also shown that EOS in asymptomatic children is uncommon.[17,18]

In the same period of this evaluation, another study performed in the same neonatal unit showed that 71.7% of EOS episodes had clinical signs of disease at birth and 100% of patients were symptomatic within the first 48 h of life.[14] The importance of clinical monitoring for at least 48 h is based on previous studies, which indicate that 80 to 100% of newborns with culture-proven sepsis developed symptoms within the first 48 h of life.[19,20] Wortham et al. demonstrated that 87% of patients with EOS present symptoms within the first 6 h of life.[18] Thus, Otollini et al. and Cantoni et al. did not find any case of early EOS in asymptomatic newborns at risk for the disease, after extensive investigation running laboratory tests.[19,21]

It is known that the assessment of WBC and serum CRP levels has a low positive predictive value and should not be considered alone in the assessment of EOS, especially in asymptomatic newborns.[22] Even though screening laboratory tests are commonly requested in Brazil and worldwide, the study's judicious indication of the collection of such tests is noteworthy as only 3.5% of the cohort underwent WBC and CRP. The usefulness of WBC changes in asymptomatic newborns with a GA $\geq$35 weeks considered at risk of EOS was evaluated by Ottolini et al., who showed that the indications for test collections based only on the presence of risk factors are not advised, which may cause harm to the patient.[19] It is important to note that the 2018 AAP guideline no longer indicates the collection of blood counts and CRP in asymptomatic infants at risk, as was the case in previous guidelines.[7,9]

In the same way that the request for laboratory tests must be judicious, antimicrobials in cases without any clinical symptoms must also be prescribed cautiously according to the evaluation of the culture results and the clinical evolution of the patients. For decades, the harm associated with the non-rational use of antimicrobials remained unknown or even ignored by the neonatal health team arguing that the treatment would reduce the number of deaths from infection. However, it is known that the inadvertent use of antimicrobials is associated with a cumulative risk to patients and even a greater chance of death.[23]

In addition to the deleterious effects on patients undergoing inadvertent treatment, the empirical use of antimicrobials based on risk factors also has economic and social impacts.[2] In most neonatal care settings, there is a mother-infant separation for exam sampling and treatment, implicating breastfeeding practices and bonding.[24]

The indiscriminate hospitalization of all patients based only on risk stratification would lead to an overload of the occupancy rate of the neonatal unit, estimated at a 30% increase. This would incur extra costs to the Brazilian Ministry of Health of R$680,000/day for the payment of hospital costs and would result in a total expense of R$2,040,000 in the period evaluated (2016 to 2019). In the US, Mukhopadhyay et al., described the costs of the protocol based on the risk categories suggested by the CDC and estimated the cost of this procedure at $110,000 to $150,000 per 1000 living births.[25] A Brazilian study performed a cost analysis between EOS assessment methods and the assessment based on clinical signs proved to be economically advantageous.[26]

In addition to the serial clinical evaluation protocol performed in this study, the AAP also recognizes the employment of the Neonatal Early-Onset Sepsis Calculator as a possibility

for the management of EOS. Recent studies have shown that the use of a calculator was also able to reduce the number of laboratory tests, as well as a reduction in the use of antibiotics when compared to the CDC 2010 recommendation.[17,27] Applying this instrument to asymptomatic infants at risk for EOS, Eason et al. demonstrated that there was an impressive reduction in antibiotic use (63 vs. 3%).[27]

It is important to highlight that, according to more recent publications on more conservative management of patients at risk for EOS, the New Zealand consensus guidelines for the management and prevention of EOS have recommended only careful serial observation in infants at risk for sepsis since 2004. The same guideline suggests that laboratory investigations and immediate initiation of treatment are only necessary if the newborn presents clinical signs of sepsis.[28] This protocol also applies to asymptomatic infants who were born to mothers with chorioamnionitis, differently from what is recommended by the AAP.[7]

In the current study, none of the nine infants exposed to clinical chorioamnionitis developed signs of early sepsis. However, this number corresponded to only 1.2% of the sample. Funisitis, despite representing a more accurate diagnosis of chorioamnionitis, is a late diagnostic method and is not readily available when managing the infant.[29]

This research has some limitations due to its retrospective nature, and the authors were not able to carry out a follow-up and evaluation of outcomes and/or complications after hospital discharge. However, there was no record of readmission for sepsis in the period.

In conclusion, the management proved to be safe, with no deaths, and most of the infants at risk of EOS were discharged and went home 48 h after clinical observation. Furthermore, the authors found a low rate of clinical or proven EOS, and most newborns who presented any clinical symptoms during the observation period required only a rigorous clinical evaluation to rule out sepsis.

Despite well-established protocols and recommendations by the AAP and CDC, the consensual management of patients at risk factors for this disease is still a challenge in Brazil and in several countries. Conservative treatment proved to be advantageous and could serve as an example for other neonatal units in Brazil. This study demonstrated that these newborns at risk of early sepsis (EOS) can be managed safely and effectively managed through a serial and rigorous clinical evaluation, carried out by a properly trained health team. This has the effect of not overloading the health system or relying on high technology for its effectiveness. In addition, such management is in line with government public policies in promoting maternal and child health.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. Lancet. 2017;390:1770—80.
2. Mukhopadhyay S, Puopolo KM. Management of the asyntomatic newborn at risk for sepsis. In: Benitz WE, Smith BP, 1st ed. Polin RA, editor, Neonatology Questions and Controversies: Infectious Disease and Pharmacology, 291, Philadelphia: Elsevier Inc; 2019:3—15.
3. Wynn JL, Wong HR, Shanley TP, Bizzarro MJ, Saiman L, Polin RA. Time for a neonatal-specific consensus definition for sepsis. Pediatr Crit Care Med. 2014;15:523—8.
4. Newman TB, Puopolo KM, Wi S, Draper D, Escobar GJ. Interpreting complete blood counts soon after birth in newborns at risk for sepsis. Pediatrics. 2010;126:903—9.
5. Fjalstad JW, Stensvold HJ, Bergseng H, et al. Early-onset sepsis and antibiotic exposure in term infants. Pediatr Infect Dis J. 2015;35:1—6.
6. T. Er, Pinto A.C. Sepse neonatal. In: Marba S.T., Filho F.M. Manual de Neonatologia UNICAMP- CAISM, Centro de Atenção Integrado à Saúde da Mulher. 1a ed. Rio de Janeiro: Ed. Revinter; 1998.p. 273-80.
7. Puopolo KM, Benitz WE, Zaoutis TE. Management of neonates born at ≥ 35 0 /7 weeks' gestation with suspected or proven early-onset bacterial sepsis. Pediatrics. 2018;142: e20182894.
8. The American College of Obstetricians and Gynecologists - Committee on Obstetric Practice No. 712. Intrapartum management of intraamniotic infection C. Obstet Gynecol. 2017;130:e95—e101.
9. Verani JR, McGee L, Schrag SJ. Prevention of perinatal group B streptococcal disease - revised guidelines. MMWR. 2010;59(RR-10):1—36.
10. Brasil. Ministério da Saúde. Agência Nacional de Vigilância Sanitária. Critérios Diagnósticos de Infecção Relacionada à Assistência à Saúde, vol. 3. Agência Nacional de Vigilância Sanitária; 2022,.https://www.gov.br/anvisa/pt-br/centraisdeconteudo/publicacoes/servicosdesaude/publicacoes/caderno-3-criterios-diagnosticos-de-infeccao-associada-a-assistencia-a-saude-neonatologia.pdf/view.
11. Manroe BL, Weinberg AG, Rosenfeld CR, Browne R. The neonatal blood count in health and disease.I. Reference values for neutrophilic cells. J Pediatr. 1979;95:89—98.
12. Benitz WE, Han MY, Madan A, Ramachandra P. Serial serum C-reactive protein levels in the diagnosis of neonatal infection. Pediatrics. 1998;102:e41.
13. Escobar GJ, Li DK, Armstrong MA, et al. Neonatal sepsis workups in infants ≥ 2000 grams at birth: a population-based study. Pediatrics. 2000;106:256—63.
14. Camargo JF, Caldas JP, Marba ST. Early neonatal sepsis: prevalence, complications and outcomes in newborns with 35 weeks of gestational age or more. Rev Paul Pediatr. 2021;40: e2020388.
15. Russell NJ, Seale AC, O'Sullivan C, et al. Risk of early-onset neonatal group B streptococcal disease with maternal colonization worldwide: systematic review and meta-analyses. Clin Infect Dis. 2017;65:S152—9.
16. Sahni M, Franco-Fuenmayor ME, Shattuck K. Management of late preterm and term neonates exposed to maternal chorioamnionitis. BMC Pediatr. 2019;19:1—6.
17. Kuzniewicz MW, Puopolo KM, Fischer A, et al. A quantitative, risk-based approach to the management of neonatal early-onset sepsis. JAMA Pediatr. 2017;171:365—71.
18. Wortham JM, Hansen NI, Schrag SJ, et al. Chorioamnionitis and culture-confirmed, early-onset neonatal infections. Pediatrics. 2016;137:e20152323.
19. Ottolini MC, Lundgren K, Mirkinson LJ, Cason S. Utility of complete blood count and blood culture screening to diagnose neonatal sepsis in the asymptomatic at risk newborn. Pediatr Infect Dis J. 2003;22:430—4.
20. Benitz WE, Wynn JL, Polin RA. Reappraisal of guidelines for management of neonates with suspected early-onset sepsis. J Pediatr. 2015;166:1070—4.
21. Cantoni L, Ronfani L, Da Riol R, Demarini S. Physical examination instead of laboratory tests for most infants born to mothers

colonized with group B streptococcus: support for the centers for disease control and prevention's 2010 recommendations. J Pediatr. 2013;163:568—73.
22. Procianoy RS, Silveira RC. The challenges of neonatal sepsis management. J Pediatr. 2020;96:80—6. (Rio J).
23. Mukhopadhyay S, Sengupta S, Puopolo KM. Challenges and opportunities for antibiotic stewardship among preterm infants. Arch Dis Child Fetal Neonatal Ed. 2019;104: F327—32.
24. Mukhopadhyay S, Taylor JA, Von Kohorn I, et al. Variation in sepsis evaluation across a national network of nurseries. Pediatrics. 2017;139:e20162845.
25. Mukhopadhyay S, Dukhovny D, Mao W, Eichenwald EC, Puopolo KM. 2010 Perinatal GBS prevention guideline and resource utilization. Pediatrics. 2014;133:196—203.
26. Benincasa BC, Silveira RC, Schlatter RP, Balbinotto Neto G, Procianoy RS. Multivariate risk and clinical signs evaluations for early-onset sepsis on late preterm and term newborns and their economic impact. Eur J Pediatr. 2020;179:1859—65.
27. Eason J, Ward H, Danko O, Richardson K, Vaitkute R, McKeon-Carter R. Early-onset sepsis: can we screen fewer babies safely? Arch Dis Child. 2021;106:86—8.
28. Campbell N, Eddy A, Darlow B, Stone P, Grimwood K. The prevention of early-onset neonatal group B streptococcus infection: technical report from the New Zealand GBS consensus working party. N Z Med J. 2004;117:U1023.
29. Ji H, Bridges M, Pesek E, Graham K, Tan L, Chabra S. Acute funisitis correlates with the risk of early-onset sepsis in term newborns assessed using the kaiser sepsis calculator. Pediatr Dev Pathol. 2019;22:523—31.