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Management of neonates with 35 weeks of gestational age or more with infectious risk factors at birth: opportunities for improvement

https://doi.org/10.1515/jpm-2021-0372
Received July 27, 2021; accepted April 10, 2022;
published online May 11, 2022

Abstract

Objectives: The Northern California Kaiser-Permanente Neonatal Sepsis Risk Calculator (SRC) has proved to be safe and effective in reducing laboratory tests, hospital admissions, and administration of antibiotics to patients at risk of early-onset neonatal sepsis (EONS). Many studies have focused on maternal chorioamnionitis as the principal risk factor for EONS. We wanted to know if the use of the SRC could be equally efficient in the context of several other infectious risk factors (IRF), in addition to chorioamnionitis, such as intrapartum maternal fever, GBS colonization and/or prolonged rupture of membranes (PROM).

Methods: Systematic study of neonates with ≥35 weeks gestational age (GA), born in our tertiary university hospital during a period of 18 months. Patients were retrospectively assessed with the SRC and its recommendations were compared with the actual management. A bivariate analysis of perinatal interventions, and outcomes was performed.

Results: A total of 5,885 newborns were born during the study period and 1783 mothers (31%) had at least one IRF. The incidence of culture-proven EONS was 0.5‰. The use of the SRC would have reduced laboratory evaluations (CBC and CRP) from 56.2 to 23.3%, and blood cultures, hospital admissions and antibiotic therapy from 22.9 to 15.5%, 17.8 and 7.6%, respectively. The management based on patients' symptoms would have shown a reduction to 7.5% in all the outcomes of interest.

Conclusions: Both, the SRC and the management based on clinical findings, are safe and efficient to reduce the number of analytical studies, hospital admissions and administration of antibiotics to neonates with IRF.

Keywords: antibiotic therapy; early-onset neonatal sepsis; infectious risk factors; maternal chorioamnionitis; sepsis workup.

Introduction

The optimal management of the asymptomatic term or near-term newborn with infectious risk factors (IRF) remains controversial for clinicians [1]. Traditional IRFs include maternal third trimester urinary tract infection or vaginal or rectal colonization by group B streptococcus (GBS), a previous infant with an early-onset neonatal sepsis (EONS) by GBS, prolonged rupture of membranes (PROM) (longer than 18 or 24 h), intrapartum maternal fever, and chorioamnionitis. In the past, most recommendations and algorithms used for the management of newborns with IRF were based on studies prior to the systematic use of intrapartum antibiotic prophylaxis against GBS, the most frequently pathogen isolated in EONS [2]. On the other hand, chorioamnionitis has received a special attention since it is diagnosed in 0.1–2% of all pregnancies, with a higher incidence at lower gestational ages (GA) [3], increasing the risk of EONS [4]. For this reason, most scientific societies, including the American Academy of Pediatrics [5], a decade ago recommended that all infants born to mothers with chorioamnionitis should be evaluated with laboratory tests, including a blood culture, and should be treated with broad spectrum antibiotics for at least 48 h. More recently, this approach began to be reevaluated [6]. Several studies and expert opinions suggested that such an approach was probably unnecessary in many infants or even harmful, interfering with breastfeeding and the establishment of the maternal-infant bond, altering the patient microbiota with unknown long-term

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consequences, and increasing the risk of side effects of medication or errors related to health care [6, 7]. In addition, other studies with large populations of asymptomatic term or near-term newborns with IRF showed that the probability of developing an EONS was nearly absent [8, 9]. Furthermore, the usefulness of laboratory tests, such as complete blood cell count (CBC) has been questioned [10], and even the performance of routine blood cultures in asymptomatic patients may not be beneficial since the results can be difficult to interpret, as in cases of contaminated cultures or transient bacteremia in patients who already receive antibiotics and in whom the blood culture was not repeated before treatment [1].

Over the past decade, the Northern California Kaiser-Permanente Neonatal Sepsis Risk Calculator (SRC) was developed in North America [11–13], based on objective parameters commonly available at the time of delivery, as well as on the clinical evaluation of the newborn in the first hours of life. The calculator considers the current incidence of bacteriologically confirmed EONS in the center, the newborn GA in weeks and days, the mother's maximum temperature during delivery, her GBS status (positive, negative, or unknown), and whether she received antibiotics during delivery, as well as the type of antibiotics and their duration. The calculator carries out recommendations for the management of patients, in addition, considering the clinical condition of the patient, differentiating clinical illness from equivocal symptoms or well appearing infants [13]. The application of this tool has been shown to be safe in different settings and several authors have reported its efficacy in reducing laboratory tests, hospital admissions and administration of antibiotics to patients [14–16].

The aim of our study was to know the proportion of newborns with IRF born in our maternity, how many of them were evaluated by laboratory tests or blood culture, and how many were admitted and receive antibiotics according to the usual protocols during the study period. Most importantly, we wanted to know if the use of the SRC could reduce the number of sepsis workups and hospital admissions, and if it could safely help to optimize the use of antibiotics in our setting in the context of IRF, including chorioamnionitis, but also intrapartum maternal fever without chorioamnionitis, GBS colonization and PROM, or the combination of them. Additionally, the safety and efficiency of the management based on close clinical observation and regular physical examination of the infant was also studied.

Subjects and methods

We carried out a systematic study of all newborns with a GA ≥35 weeks, born in our tertiary university hospital during a period of 18 months (January/2018 to June/2019). Our center, Las Palmas Children's Hospital, serves a mixed urban and rural population of around 850,000 people in Gran Canaria. This is the only facility with a level 3 NICU, being a reference for the entire province, which includes two other islands with a total of 1.13 million inhabitants. Healthy newborns are cared for in the maternity ward together with their mothers. When surveillance or more complex treatments are necessary, patients are admitted to the neonatal general ward, to the intermediate care ward or to the NICU of the Neonatology Service, according to the severity of their condition.

We reviewed the maternal and neonatal clinical records and collected sociodemographic and clinical data according to a prespecified data collection form. Outborn infants and patients with major congenital anomalies were excluded. We also excluded infants with birth weight less than 2,000 g, as they are generally admitted to the neonatal general ward per protocol, regardless of whether they have IRF or not. During this period, the clinical management of patients was carried out based on local protocols, mostly derived from international recommendations [2, 5] (Supplementary Figure 1). The IRF considered for the present study were maternal GBS status, intrapartum maternal fever ≥38 °C, PROM ≥18 h, and clinical chorioamnionitis diagnosed by the attending obstetrician and registered in the maternal clinical record. All patients with at least one IRF underwent a retrospective risk assessment for EONS according to the SRC. The main outcome of the study was to compare the proportion of laboratory tests, blood cultures, hospital admissions and administration of antibiotics carried out during the period, with those that would have been carried out according to the SRC recommendation, and with those that would have occurred with the management based initially on the patient clinical observation and regular physical examination. In our center, during the period 2017–2019, the incidence of EONS was 0.39‰. However, for the risk calculation, a more conservative value of 0.5‰ was adopted.

The statistical analysis was performed with the SPSS package, version 25 (IBM Corp, Armonk, NY, USA). Continuous variables with normal distribution are expressed as mean and standard deviation (SD) and the differences between groups were studied with the Student's t-test. When not normally distributed they are expressed as median and interquartile range (IQR) and were compared with the Mann-Whitney U test. Qualitative variables are expressed as proportions (%) and were analyzed with the Chi-square or Fisher's exact test, as appropriate. A bivariate analysis of patient characteristics, perinatal interventions, and outcomes was performed. All statistical tests were two-tailed, and statistical significance was established at $p<0.05$.

The study was approved by the Center's Research Ethics Committee (Code: 2019-381-1). Given the use of anonymized data from medical records as part of the quality control of the healthcare activity, written informed consent from parents or caregivers was not deemed necessary.

Results

During the study period, 6,005 deliveries were assisted in our maternity with a total of 6,144 newborns. Of the total deliveries, 5,752 (95.8%) were gestations of ≥35 weeks, with a total of 5,885 newborns. Of these 5,752 mothers, 1,783 (31%) had at least one IRF, affecting to a total of 1,796 newborns (30.5%). For the present study, six newborns with a GA of 35 weeks and a birth weight less than 2,000 g were excluded.

The demographics and clinical characteristics of the mothers and newborns with and without IRF are summarized in Table 1. The age distribution of the mothers was similar in both groups, as was the type of delivery. Mothers with IRF were less frequently diabetic or hypertensive. The proportion of low-birth weight infants was lower among patients with IRF, but they were more frequently hospitalized than the newborn from the general population. Table 2 shows the proportion of newborns with IRF who underwent laboratory tests, and/or blood cultures, who were admitted to the hospital and who received empirical antibiotic therapy due to the risk or suspicion of EONS. It also shows the projection of what would have happened if the SRC or a management based exclusively on the patient's clinical condition had been used. All outcomes of interest would have improved and the administration of antibiotics, specifically, would have been reduced from 22.9% to 7.5–7.6% of patients. Table 3 shows the distribution of the IRF and the proportion of mothers and infants that received antibiotic therapy, as well as the result of the infants' blood cultures, which were positive in 3 cases (0.5‰). Seventeen mothers exhibited all three IRF (GBS colonization, fever, and PROM ≥18 h), but none of their children developed EONS with a positive blood culture.

The clinical evolution of the patients with a positive blood culture is summarized in Table 4. Two of them (cases 1 and 2) presented with clinical symptoms at the time of the first evaluation and the SRC strongly recommended evaluation and administration of antibiotics. Patient one died on day three of life and Patient two was treated for 10 days, and the evolution was favorable (see Table 4 for details). Patient number three, a late preterm of 35-week GA, with unknown maternal colonization at the time of delivery, 1 h of ROM, and afebrile mother, was asymptomatic during the first 16 h of life and the SRC yielded a low risk, recommending routine observation. Subsequently, he exhibited hypoglycemia and poor feeding, and a sepsis workup was indicated showing leukopenia, but normal C-reactive protein (CRP). Although empirical antibiotic therapy was immediately started, the evolution was unfavorable developing disseminated intravascular coagulation, severe brain haemorrhage, and multi-organ failure, dying on day four of life.

No readmissions for EONS were found after hospital discharge. Only a 5-day-old female infant without IRF, who was discharged from the maternity ward at 48 h of age with

Table 1: Demographic and clinical characteristics of mothers and newborns from the general population and the population with infectious risk factors (IRF).

Maternal and newborn characteristics		General population Mothers = 5,752 Newborns = 5,885	Mothers with IRF Mothers = 1,783 Newborns = 1,796
Maternal age, years	<18	46 (0.8)	11 (0.6)
	18–34	3,842 (66.8)	1,200 (67.3)
	>34	1,864 (32.4)	572 (32.1)
Gestational or pregestational diabetes		486 (8.4)	84 (4.7)
Chronic or pregnancy-induced hypertension		462 (8.0)	75 (4,2)
Type of delivery	Vaginal	4,635 (78.8)	1,456 (81.1)
	Forceps	576 (9.8)	144 (8.0)
	Cesarean section	628 (10.7)	185 (10.3)
	Vaginal breech	46 (0.8)	11 (0.6)
Infant birthweight, g	<2,500	612 (10.4)	106 (5.9)
	2,500–4,000	4,910 (83.4)	1,558 (86.7)
	>4,000	363 (6.2)	132 (7.3)
Hospital admission of the newborn		812 (13.8)	412 (22.9)

All values are n (%). IRF, Infectious Risk Factors.

Table 2: Main outcomes and comparison with the projection if the Kaiser-Permanente Neonatal Sepsis Risk Calculator had been used or if the initial management had been based on the clinical findings.

Outcomes	Actual n=1,796	Projection according to the EONS risk calculator n=1,796	Management according to the patient's symptoms n=1,796
Complete blood count and C-reactive protein	1,010 (56.2)	418 (23.3)	135 (7.5)
Blood culture	412 (22.9)	275 (15.3)	135 (7.5)
Hospital admission	412 (22.9)	319 (17.8)	135 (7.5)
Antibiotic therapy	412 (22.9)	136 (7.6)	135 (7.5)

All values are n (%). EONS, Early-onset neonatal sepsis.

Table 3: Distribution of Infectious Risk Factors and relationship with positive blood culture in the newborn.

Infectious risk factor		n=1796	Maternal antibiotic therapy	Newborn antibiotic therapy	Duration of newborn treatment (days)[a]	Positive blood culture of the newborn
Maternal GBS colonization	Negative	866/1796 (48.2)	866/866 (100)	279/866 (32.2)	3 (2–4)	–
	Positive	793/1796 (44.2)	633/793 (79.8)	105/793 (13.2)	3 (2–5)	1 GBS[b]
	Unknown	137/1796 (7.6)	73/137 (53.3)	34/137 (24.8)	3 (2–5)	1 GBS[b]
PROM ≥ 18 h		897/1796 (49.9)	897/897 (100)	205/897 (22.9)	3 (2–5)	1 *Proteus mirabilis*[c]
Fever ≥ 38 °C		360/1796 (20.0)	360/360 (100)	261/360 (72.5)	3 (2–4)	–
Chorioamnionitis		215/1796 (12.0)	215/215 (100)	214/215 (99.5)	2 (2–3)	–

All values are n/N (%). PROM, Prolonged Rupture of Membranes; GBS, Group B Streptococcus. [a]Median and Interquartile Range. Only those patients who received antibiotics are included. [b]Of the two patients who developed early-onset neonatal sepsis by GBS, the mother with a positive vaginal-rectal colonization had received intrapartum antibiotic therapy, but the mother with an unknown result did not. [c]The mother of the infant who developed sepsis by *Proteus mirabilis* had received broad-spectrum antibiotics for more than 4 h.

Table 4: Clinical presentation and evolution of patients with a positive blood culture.

Case	GA (weeks)	Symptoms at the time of the first assessment	Risk of EONS by SRC (‰)	SRC recommendation	Antibiotic start (hours)	WBC count (cells/mm^3)	CRP (mg/dl)	Blood culture	Duration of antibiotic therapy (days)	Outcome
1	41^{+1}	Perinatal asphyxia. Foul smelling amniotic fluid. Meconium aspiration	2.07	Empiric antibiotics Vitals per NICU	1	9,500	7.2	GBS	3	Death
2	39^{+0}	Tachypnea maintained for more than 12 h	0.38	Empiric antibiotics Vitals per NICU	14	9,900	0.8	*Proteus mirabilis*	10	Discharge healthy
3	35^{+6}	Initially asymptomatic. At 16 h of life: Hypoglycemia and poor feeding	0.02	No culture No antibiotics Routine vitals	18	2,300	0.66	GBS	4	Death

GA, Gestational age; EONS, Early-onset neonatal sepsis; SRC, Northern California Kaiser-Permanente Neonatal Sepsis Risk Calculator; WBC, White blood cells; CRP, C-Reactive protein; GBS, Group B Streptococcus.

a normal physical examination, was readmitted on day five of life due to fever, and the blood culture was positive for *Escherichia coli*. She received antibiotic treatment for 10 days with a favorable evolution.

Discussion

As shown in the results section and in Tables 1 and 2, approximately one third of the newborns ≤35 weeks GA in our setting were exposed to some IRF. Some analytical studies (CBC and CRP) were carried out in half of them, representing 17.2% of the total population. In addition, a blood culture was obtained, and antibiotics administered to 412 patients, 7% of the total group of infants. Thus, approximately 137 newborns received antibiotic therapy for each case of bacteriologically confirmed EONS. These figures are similar to those previously reported in the literature, in which, according to commonly used guidelines, 15–20% of newborns ≥35 weeks of GA undergo a sepsis workup for risk or suspicion of EONS, and 5–8% are treated with antibiotics [17–19]. Our results show the potential of both, the SRC and the management based on clinical findings, to reduce the number of analytical studies (CBC, CRP, and blood cultures), hospital admissions and administration of antibiotics to neonates with IRF in our setting. Similar findings have been recently reported by several authors [14–16]. However, it has also been pointed out that even asymptomatic newborns without IRF can develop EONS [20], as was the case of our third patient that developed clinical symptomatology at 16 h of life, being evaluated for sepsis and admitted for antibiotic therapy. He

exhibited neutropenia (634 neutrophils/mm^3) and GBS was isolated in the blood culture. In this case, neither the SRC nor the initial clinical evaluation in the first 12 h of life could anticipate the development of an EONS.

Although some authors have drawn attention to the possible lack of safety of the management based on the SRC [21], in our study we found no inferiority with respect to routine management. The recent systematic review and meta-analysis by Achten et al. concluded that the use of the SRC is useful to reduce the use of antibiotics, without neglecting to diagnose a significant number of newborns with EONS [16].

Perhaps the most controversial infectious risk group regarding its management using the SRC is that of patients with antecedents of maternal chorioamnionitis. At the end of the last century, the incidence of EONS in infants born to mothers with chorioamnionitis was reported between 80 and 200 cases per thousand live newborns [22, 23]. Subsequently, intrapartum antibiotic therapy significantly reduced this incidence and, although it varies according to center, it is currently estimated to be around 4‰ (95% CI 0.5–7.5‰) [24]. This condition, in fact, was not included in the original design of the calculator due to the subjective component of the diagnosis [12]. However, the SRC currently allows adjustment of the baseline risk of sepsis from 0.1 to 4‰. In our center, during the study period, 213 mothers of the 5,752 included (3.7%) were diagnosed with clinical chorioamnionitis and received intrapartum antibiotic therapy. Of the 215 exposed children (two twin pregnancies), none developed culture proven EONS. However, this was the risk group in which newborns received antibiotics most frequently (99.5%), followed by infants whose mothers had intrapartum fever (72.5%). The overall duration of antibiotic therapy was (median and IQR) 3 (2–4) days, similar for all risk groups.

The design of our study, together with the small number of patients with a positive blood culture, do not allow us to study the value of the CBC or CRP in the early diagnosis of EONS, although infants with infection had lower total leukocyte counts (mean [SD]): 7,233 (4,277) vs. 17,607 (6,312) cells/mm^3 (not significant), and higher CRP: 2.8 (3.7) vs. 1.2 (2.3) mg/dl (p=0.005). Previous studies have already shown the low value of the leukocyte count, although patients with confirmed sepsis tend to have lower total leukocyte and neutrophil counts [25]. In our study, 55 newborns (3.1%) received antibiotics for seven or more days, based mainly on the clinical evolution and/or the persistent elevation of acute phase reactants. This could be due to concerns about the possible existence of "blood culture negative sepsis" [26]. In this regard, emphasis should be placed on obtaining appropriate samples to avoid contamination, as well as obtaining sufficient blood for culture since, as previously demonstrated, a 1 mL sample reaches a sensitivity of 100% in the detection of pathogens in blood [27]. In our cohort, only two blood cultures (0.5%) were considered contaminated, one by Micrococcus luteus and another by *Rothia dentocariosa* [28], which represents a good result considering the reported variability among centers, which range between 0.6% and more than 6% [29]. The value of CRP has also been widely questioned due to its low sensitivity and its elevation in multiple non-infectious processes [30]. In the case of the evaluation of late sepsis (>72 h) some authors consider it more useful to increase the volume of blood for culture than its use for the determination of acute phase reactants [31, 32].

Another controversial issue is the possible influence of antibiotics administered to the mother, which could make the newborn's cultures negative. In our center, the culture medium used is the BD BACTEC Peds Plus/F (digested soy-casein broth enriched with CO_2), which contains resins capable of neutralizing the antibiotic activity, although this capacity may vary depending on the dose of the antibiotic and the time of sample collection. In addition, the resins present in this medium could not be able to adequately neutralize preparations containing meropenem or antifungals (fluconazole) [33].

Our study has some limitations. First, it is a hypothetical single-center study with retrospectively collected data, so its internal validity depends on the accuracy of the data collection. Furthermore, culture confirmed EONS is a rare event and more prospective studies would be necessary to accurately assess the sensitivity and specificity of any diagnostic tool to allow the generalizability of the results. But it also has some strengths. Our study comprises a complete cohort of babies born during a defined period of time, including patients with different IRF, not just maternal chorioamnionitis, or infants who received antibiotics, like most similar studies. Modern electronic medical record systems make data collection and patient monitoring relatively easy and reliable.

In conclusion, both the SRC and the management based on clinical findings appear to be appropriate and safe tools for reducing the number of laboratory tests, blood cultures, and hospital admissions, as well as the use of antibiotics in term and near-term newborns with IRF. Nevertheless, the clinical surveillance of infants with IRF remains an essential aspect of clinical practice. The effectiveness of this approach is currently being evaluated prospectively in our center.

Research funding: There was no funding for this research.
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: The Authors declare no conflict of interest.
Informed consent: Informed consent was deemed not necessary for this study given the use of anonymized data from medical records as part of the quality control of the healthcare activity.
Ethical approval: The local Institutional Review Board approved the study.
Data availability: Deidentified individual data are available on request.

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Supplementary Material: The online version of this article offers supplementary material (https://doi.org/10.1515/jpm-2021-0372).