ORIGINAL ARTICLE

WILEY

Screening for early-onset neonatal sepsis on the Kaiser Permanente sepsis risk calculator could reduce neonatal antibiotic usage by two-thirds

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Received: 15 March 2022
Accepted: 27 July 2022

ABSTRACT

Importance: Effective screening strategies for early-onset neonatal sepsis (EONS) have the potential to reduce high volume parenteral antibiotics (PAb) usage in neonates.

Objective: To compare management decisions for EONS, between CG149 National Institute for Health and Care Excellence (NICE) guidelines and those projected through the virtual application of the Kaiser Permanente sepsis risk calculator (SRC) in a level 2 neonatal unit at a district general hospital (DGH).

Methods: Hospital records were reviewed for maternal and neonatal risk factors for EONS, neonatal clinical examination findings, and microbial culture results for all neonates born at ≥34 weeks' gestation between February and July 2019, who were (1) managed according to CG149-NICE guidelines or (2) received PAb within 72 h following birth at a DGH in Winchester, UK. SRC projections were obtained using its virtual risk estimator.

Results: Sixty infants received PAb within the first 72 h of birth during the study period. Of these, 19 (31.7%) met SRC criteria for antibiotics; 20 (33.3%) met the criteria for enhanced observations and none had culture-proven sepsis. Based on SRC projections, neonates with '≥1 NICE clinical indicator and ≥1 risk factor' were most likely to have a sepsis risk score (SRS) >3. Birth below 37 weeks' gestation (risk ratio [RR] = 2.31, 95% confidence interval [CI]: 1.02–5.22) and prolonged rupture of membranes (RR = 3.14, 95% CI: 1.16–8.48) increased the risk of an SRS >3.

Interpretation: Screening for EONS on the SRC could potentially reduce PAb usage by 68% in term and near-term neonates in level 2 neonatal units.

KEYWORDS

Early onset neonatal sepsis, Kaiser Permanente sepsis risk calculator, NICE guidelines, Parenteral antibiotics

DOI: 10.1002/ped4.12344

INTRODUCTION

Early onset neonatal sepsis (EONS) is an infrequent (global incidence rate of 0.3–0.9/1000 in terms of near-term live births) but serious illness.[1,2] It is defined as blood or cerebrospinal fluid (CSF) culture-proven infection within 72 h of birth.[3] Group B streptococcus (GBS) and *Escherichia Coli* are the most frequent causative pathogens, with the mechanism of pathogenesis attributed to the ascending colonization of the maternal genital tract, and subsequent colonization and infection of the fetus or newborn, often without signs of maternal systemic illness.[4]

EONS frequently present with non-specific clinical signs, including tachypnoea, hypoglycemia, and altered thermoregulation, which overlap with those seen in common non-infectious pathologies such as transient tachypnoea of the newborn and hypoglycemia. Conversely, babies with EONS may initially be asymptomatic.[2] Clinical decision-making about which newborns should receive parenteral antibiotics (PAb) during the 72 h following birth is, therefore, challenging.

Current management strategies involve the screening and treatment of a large number of healthy newborns with PAb. In the UK, EONS screening and treatment have, over the past decade, been guided by clinical recommendations produced by the National Collaborating Centre for Women's and Children's Health and published by the National Institute for Health and Care Excellence (NICE, CG149) (Table 1).[5] The CG149-NICE guidelines list eight risk factors and 23 clinical indicators (six of which are labeled "red flags") to guide clinical decision-making on the PAb used to prevent and treat EONS. The guidance recommends performing investigations and commencing PAb without delay, even before the availability of test results, in all neonates with ≥2 risk factors, clinical indicators, or a combination of these; and in any neonate with a "red flag". UK-based hospital audits suggest that 13%–20% of neonates in the postnatal wards received PAb.[6,7]

Perinatal antibiotic use has been associated with gut microbiome modulation and increased risks of long-term adverse health outcomes, including Type 2 diabetes, inflammatory bowel disease, and food allergies.[6,8] High volume PAb usage in neonates is also associated with increased risks of repeated phlebotomies, cannulations, drug side effects, prescription errors, and maternal-infant separation.[6,8] Moreover, as already well-established, inappropriate use of antibiotics can lead to microbial resistance.

The adoption of the Kaiser Permanente (KP) sepsis risk calculator (SRC) in the USA, and some tertiary neonatal centers in Australia and the UK, for the screening of all term and near-term neonates for EONS risk, has safely reduced intervention and antibiotic treatment by nearly 50% in this group of babies.[6,7,9–12] The KP SRC is a multi-variate risk-prediction model, which calculates the risk for EONS based on local epidemiology, maternal variables, and the neonate's clinical condition. It was developed on 350 case subjects from a cohort of 608 014 infants born at ≥ 34 weeks' gestation at 14 California and Massachusetts hospitals from 1993 to 2007[13] and validated by comparing EONS management between the CDC guidelines and the calculator in 204 485 infants born at ≥34 weeks' gestation at a Kaiser Permanente hospital in Northern California between January 1, 2010, and December 31, 2015.[4] The models were constructed using an interrupted time series design and produce, based on six perinatal risk factors (Table 2), a sepsis risk score (SRS). The SRS, together with a clinical assessment of the baby ("well-appearing", "equivocal" and "clinical illness" as defined in Table 2), is used to inform clinical management. Clinical management recommendations, for each category of SRS, were based on a consensus opinion of the KP clinicians: neonates with SRS <1 are recommended normal care; those with SRS 1–3 are recommended enhanced observation with or without a blood culture while PAb and blood culture are recommended for symptomatic neonates or those with SRS >3.[4] The SRC is freely available at https://neonatalsepsiscalculator.kaiserpermanente.org.

A recent UK study from eight maternity hospitals reported that of 576 infants receiving antibiotics as per CG149-NICE criteria, only 150 (26%) met SRC recommendations.[6] However, caution was advised in the adoption of the SRC into clinical practice,[14] and units desiring to implement the SRC as an aid to clinical decision-making have been recommended to undertake audits to confirm its safety and utility.[4,6,14]

In accordance with these recommendations, our objective was to compare clinical management decisions for EONS in neonates treated with parental antibiotics according to the CG149-NICE guidelines, with those projected through the virtual application of the SRC, in a UK-based district general hospital (DGH). Our aims were to: (1) examine the proportion of neonates receiving parental antibiotics within 72 h following birth that met SRC criteria for antibiotics, and (2) to determine the CG149-NICE risk factors and clinical indicators most frequently associated with an SRS >3.

METHODS

Ethical approval

The study was considered a quality improvement project by the institutional research ethics committee and consequently deemed exempt from formal ethics approval.

TABLE 1 Comparison of the prevalence of National Institute for Health and Care Excellence (NICE) risk factors and clinical indicators in neonates receiving empirical antibiotics for early-onset neonatal sepsis (EONS) according to CG149-NICE guidelines and those meeting Kaiser Permanente criteria for parenteral antibiotics

CG149-NICE risk factors and clinical indicators for EONS	Neonates receiving parental antibiotics according to CG149-NICE guidelines[†] ($n = 60$)	Neonates in column 1 meeting KP SRC criteria for parenteral antibiotics[‡] ($n = 19$)
Risk factors		
Invasive GBS infection in a previous baby	1 (1.7)	1 (5.3)
Maternal GBS colonization, bacteriuria, or infection in the current pregnancy	5 (8.3)	1 (5.3)
Prelabour rupture of membranes	10 (16.7)	8 (42.1)
Preterm birth following spontaneous labor	6 (10.0)	5 (26.3)
Rupture of membranes for >18 h in a preterm birth	1 (1.7)	0 (0.0)
Intrapartum fever >38°C, or confirmed or suspected chorioamnionitis	3 (5.0)	1 (5.3)
Parenteral antibiotic treatment given to the woman (red flag)	5 (8.3)	3 (15.8)
Suspected or confirmed infection in another baby in the case of a multiple pregnancy (red flag)	2 (3.3)	1 (5.3)
Clinical indicators		
Altered behavior or responsiveness	5 (8.3)	1 (5.3)
Altered muscle tone (e.g. floppiness)	1 (1.7)	1 (5.3)
Feeding difficulties/intolerance	6 (10.0)	1 (5.3)
Abnormal heart rate	1 (1.7%)	1 (5.3)
Signs of respiratory distress	21 (35.0)	4 (21.2)
Respiratory distress starting >4 h after birth (red flag)	6 (10.0)	1 (5.3)
Hypoxia	11 (18.3)	2 (10.5)
Jaundice within 24 h of birth	7 (11.7)	3 (15.8)
Apnoea	0 (0.0)	2 (10.5)
Encephalopathy	0 (0.0)	0 (0.0)
Seizures (red flag)	1 (1.7)	1 (5.3)
Need for CPR	0 (0.0)	0 (0.0)
Mechanical ventilation in a term baby (red flag)	1 (1.7)	1 (5.3)
Persistent pulmonary hypertension	0 (0.0)	0 (0.0)
Temperature abnormality	8 (13.3)	2 (10.5)
Signs of shock (red flag)	0 (0.0)	0 (0.0)
Bleeding, thrombocytopenia, or abnormal coagulation	0 (0.0)	0 (0.0)
Oliguria	0 (0.0)	0 (0.0)
Altered glucose homeostasis	7 (11.7)	2 (10.5)
Metabolic acidosis	1 (1.7)	1 (5.3)
Local signs of infection	3 (5.0)	0 (0.0)

Data are shown as *n* (%).
[†]Neonates treated with parental antibiotics, in the 72 h following birth, according to the CG149-NICE guidelines.
[‡]Neonates with KP SRS >3.
Abbreviations: CG149-NICE, Clinical Guideline 149 published by the National Institute for Health and Care Excellence; EONS, early onset neonatal sepsis; GBS, group B streptococcal; KP SRC, Kaiser Permanente sepsis risk calculator; SRS, sepsis risk score.

TABLE 2 Maternal risk factors and infant's clinical presentation description included in the calculation of risk for EONS on the Kaiser Permanente sepsis risk calculator

Variables	Description
Maternal risk factors	
Incidence of EONS at institution	0.1 to 4/1000 live births
Gestational age in weeks and days	34 weeks 0 days to 43 weeks 0 days
Highest maternal antepartum temperature	No specified range
Duration of rupture of membranes in h	0 to 240
Maternal GBS status	Negative, positive or unknown
Type of intrapartum antibiotics	Broad spectrum antibiotics >4 h prior to birth; broad spectrum antibiotics 2–3.9 h prior to birth; GBS specific antibiotics >2 h prior to birth; no antibiotics or any antibiotics <2 h prior to birth
Classification of infant's clinical presentation	
Clinical illness	Persistent need for NCPAP/HFNC/mechanical ventilation (outside of the delivery room) Hemodynamic instability requiring vasoactive drugs Neonatal encephalopathy /Perinatal depression Seizure Apgar Score @ 5 minutes < 5 Need for supplemental $O_2 \geq 2$ h to maintain oxygen saturations > 90% (outside of the delivery room)
Equivocal	Persistent physiologic abnormality ≥ 4 h Tachycardia (Heart rate ≥ 160) Tachypnea (Respiratory rate ≥ 60) Temperature instability (≥ 38°C or < 36.4°C) Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O_2 Two or more physiologic abnormalities lasting for ≥ 2 h Note: abnormality can be intermittent
Well appearing	No persistent physiologic abnormalities

Abbreviations: EONS, early onset neonatal sepsis; GBS, group B streptococcal; HFNC, high-flow nasal cannula; NCPAP, nasal continuous positive airway pressure.

Study design and location

The study was undertaken at Royal Hampshire County Hospital (RHCH), Winchester, UK, a DGH with a level 2 neonatal unit.

Participants and eligibility

All neonates born at ≥34 weeks' gestation between 1 February and 31 July 2019 who were (1) managed according to CG149-NICE guidelines or (2) received PAb within 72 h of birth.

Data collection

Maternal and neonatal hospital records were reviewed for information on maternal and neonatal risk factors for EONS, neonatal clinical examination findings (Tables 1 and 2), C-reactive protein (CRP) levels (in mg/dl) and microbial culture results, gestational age (GA) at birth, and birth weight. Information on the NICE risk factors and clinical indicators prompting neonatal treatment with PAb was reviewed. True EONS was defined by positive blood or CSF culture with the pathogenic organism(s) within 5 days of culture.

Two assessors independently applied the SRC's virtual application on each infant retrospectively (at >72 h post-birth), using our institution's background EONS incidence of 0.5/1000 live births. This rate is identical to the closest estimated incidence from studies of term and near-term infants in high-income countries including the UK and has been previously applied in similar UK-based studies.[6] Contemporaneous notes were used to complete the KP clinical classification.

Statistical analysis

Statistical analysis was performed in IBM SPSS V.25.0. The frequency of NICE risk factors and clinical indicators between the three SRS groups (<1, 1–3, and >3) were compared using Chi-Square tests. We examined which of the six SRC factors, if any, were associated with an SRS >3, using Chi-Square tests and estimated relative risks and 95% confidence intervals for each risk factor. GA at birth,

TABLE 3 Kaiser Permanente sepsis risk scores in neonates receiving parenteral antibiotics within 72 h of birth according to CG149-NICE criteria for early-onset neonatal sepsis, and meeting Kaiser Permanente criteria for normal care, enhanced observations, and parenteral antibiotics

	KP SRS			
		KP SRS according to clinical assessment of the baby		
Groups	**Early onset sepsis risk at birth**	**Well appearing ($n = 4$)**	**Equivocal ($n = 41$)**	**Clinical illness ($n = 15$)**
Total sample ($n = 60$)	0.17 (0.29)	0.08 (0.10)	0.84 (1.33)	3.40 (5.30)
Neonates meeting SRC criteria for normal care ($n = 21$)	0.06 (0.19)	0.02 (0.01)	0.15 (0.05)	na
Neonates meeting SRC criteria for enhanced observations ($n = 20$)	0.10 (0.02)	0.04 (0.02)	0.43 (0.16)	na
Neonates meeting SRC criteria for parenteral antibiotics ($n = 19$)	0.41 (0.38)	0.18 (0.20)	2.08 (1.86)	8.20 (7.34)

Data are shown as median (interquartile range). KP, Kaiser Permanente; SRS, sepsis risk score; SRC, sepsis risk calculator; na, SRS values not computed as $n = 0$ in these cells.

birth weight, and the highest recorded CRP within 72 h of birth were compared between the three SRS groups using analysis of variance.

RESULTS

During the study period, 72 neonates born at ≥34 weeks' gestation received PAb for EONS at <72 h of age. After removing those without a recorded intrapartum maternal temperature ($n = 12$), complete data were available for 60 neonates. None had evidence of culture-proven infections.

The mean birth weight and median GA at birth for the sample were 3269 g (standard deviation, 757) and 38 weeks and 1 day (interquartile range [IQR] 1 day) respectively. CRPs ranged between 2 and 111 mg/dl (median 3.0, IQR 16.0). The median 'highest maternal temperature' during labor was 36.8°C (IQR 0.5). The median 'duration of rupture of membranes (ROM) prior to birth' was 4.08 h (IQR 16.6). None of the neonates were re-admitted, following discharge, with concerns of sepsis.

Proportion of neonates receiving parental antibiotics with SRS >3: comparisons between CG149-NICE and SRC recommendations

The median SRS values for the total sample, and for each of the three clinical assessment categories are presented in Table 3. For the total sample, the median SRS was 0.17 (IQR 0.29).

Nineteen neonates (31.7%) met SRC criteria for treatment with antibiotics. For this group, the median SRS (assuming clinical illness) was 8.20 (IQR 7.34). Twenty neonates (33.3%) met SRC recommendations for enhanced observations; for these, the KP clinical classification was "equivocal" and the median SRS was 0.43 (IQR 0.16). Twenty-one neonates (35.0%) met SRC recommendations for normal care (median SRS 0.02 and 0.15, IQR 0.01 and 0.05 for well appearing and equivocal clinical classifications, respectively).

The distribution of SRC risk factors between the three groups is presented in Table 4. Of the neonates with an SRS >3, 57.9% ($n = 11$) met KP classification criteria for clinical illness as described in Table 2. None of the neonates with an SRS ≤3 had 'clinical illness' or were born to mothers with clinical chorioamnionitis.

CG149-NICE risk factors and clinical indicators associated with SRC recommendations for PAb

The distribution of CG149-NICE risk factors and clinical indicators between the total sample and those neonates with an SRS >3 is presented in Table 1. Of 60 neonates, 27 (46.6%) met CG149-NICE criteria for at least one clinical indicator and at least one risk factor, and 16 (27.1%) met criteria for at least one red flag. Of these, 11 (40.7%) and 7 (43.8%) respectively met SRC recommendations for antibiotics. One neonate (1.7 %) had two NICE risk factors (without clinical indicators) and 11 neonates (18.6%) had two clinical indicators (without risk factors). Four neonates (6.8%) had only one non-red flag clinical indicator (local signs of infection in skin or eye ($n = 2$) and temperature abnormality unexplained by environmental factors ($n = 1$) or risk factor [prelabour ROM ($n = 1$)]. One neonate (1.7%) had neither a clinical indicator nor a risk factor. Although these neonates ($n = 5$, 8.3% of total) did not meet CG149-NICE criteria for suspected EONS, they received PAb within 72 h following birth. The median KP score for this group was 0.07 (IQR 0.06).

TABLE 4 Distribution of predictors included in the Kaiser Permanente sepsis risk calculator's quantitative model for the risk-prediction of early-onset neonatal sepsis in the study sample

Variables	All infants (on antibiotics as per CG149-NICE) ($n = 60$)	Infants meeting SRC recommendations for antibiotics ($n = 19$)	Infants meeting SRC recommendations for enhanced observations ($n = 20$)	Infants meeting SRC recommendations for normal care ($n = 21$)
Gestational age <37 weeks	12 (20.0)	2 (10.5)	2 (10.0)	8 (38.1)
Rupture of membranes ≥18 h[†]	12 (20.0)	9 (47.4)	2 (10.0)	1 (4.8)
Maternal temperature ≥38°C[†]	3 (5.0)	2 (10.5)	1 (5.0)	0 (0.0)
GBS status				
Positive	5 (8.3)	1 (5.3)	2 (10.0)	2 (9.5)
Negative	44 (73.3)	14 (73.7)	14 (70.0)	16 (76.2)
Unknown	11 (18.3)	4 (21.1)	4 (20.0)	3 (14.3)
Maternal antibiotics				
Broad spectrum antibiotics >4 h prior to birth	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Broad spectrum antibiotics 2–3.9 h prior to birth	1 (1.7)	0 (0.0)	0 (0.0)	1 (4.8)
GBS-specific antibiotics >2 h prior to birth	5 (8.3)	2 (10.5)	2 (10.0)	1 (4.8)
No antibiotics or any antibiotics <2 h prior to birth	54 (90.0)	19 (100.0)	18 (90.0)	17 (80.9)
Clinical status of neonate[‡]				
Well	4 (6.7)	0 (0.0)	1 (5.0)	3 (14.3)
Equivocal	41 (68.4)	4 (21.1)	19 (95.0)	18 (85.7)
Unwell	15 (25.0)	15 (78.9)	0 (0.0)	0 (0.0)

CG149-NICE, Clinical Guideline 149 published by the National Institute for Health and Care Excellence; GBS, group B streptococcal.
[†]These predictors are applied as continuous variables in the Kaiser Permanente sepsis risk calculator's quantitative model for the risk prediction of early-onset neonatal sepsis. In this table, the number (%) of neonates with these predictors is presented.
[‡]Clinical status of the neonate, as reported in the neonate's hospital records, at the time of the decision to commence parenteral antibiotics for suspected early-onset neonatal sepsis according to the CG149-NICE guidelines.

There was a significant difference in the frequency of CG149-NICE risk factors between the three SRC groups ($\chi^2 = 20.45$, $P = 0.020$) with the highest frequency of risk factors reported in neonates with SRS >3. Differences in the frequencies of clinical indicators between the three KP groups were not significant ($\chi^2 = 13.78$, $P = 0.620$). Invasive GBS infection in a previous baby and prelabour ROM; and signs of respiratory distress and jaundice within 24 h of birth; were, respectively, the CG149-NICE risk factors and clinical indicators most frequently reported in neonates with SRS >3 and/or clinical illness.

We also examined which of the six SRC risk factors were most significantly associated with an SRS of >3. In our sample, these were (1) GA at birth <37 weeks ($n = 12$, $\chi^2 = 8.49$, $P = 0.004$; risk ratio [RR] = 2.31, 95% confidence interval [CI]: 1.02–5.22) and ROM >18 h prior to birth ($n = 12$, $\chi^2 = 12.63$, $P < 0.001$; RR = 3.14, 95% CI: 1.16–8.48). We did not find the intrapartum maternal pyrexia ($n = 3, \chi^2 = 1.94$, $P = 0.163$), maternal GBS infection ($n = 5, \chi^2 = 0.42$, $P = 0.810$) and maternal antibiotics ($n = 6, \chi^2 = 0.63$, $P = 0.730$) to be significantly associated with SRS >3 in our sample. We did not detect differences in birth weight ($F = 0.3$, $P = 0.270$) and highest neonatal CRP ($F = 1.5$, $P = 0.670$) between the three SRS groups.

DISCUSSION

Our results show that the application of the SRC in a level 2 neonatal unit in a DGH could potentially result in a 68% reduction in antibiotic usage in the 72 h following birth in near-term and term neonates. In our sample, the CG149-NICE criteria triggering PAb in 71.6% of our sample were (1) one risk factor and one clinical indicator, and (2) one red flag. The application of the SRC in this group could result in a 41% decrease in antibiotic usage. Importantly, all "clinically unwell" neonates triggered the SRC recommendations for antibiotic treatment; conversely, in our sample, the KP SRC recommended treatment only for babies in the clinical illness category. No "clinically unwell" neonates were

assigned to the SRC observation or normal care group, indicating an excellent safety profile of the SRC in our cohort. We have also shown that GA at birth <37 weeks and ROM >18 h prior to birth were the SRC risk factors most significantly associated with an SRS >3. Nevertheless, it is important to acknowledge that the 68% reduction in neonatal PAb usage reported by our retrospective application of the KP SRC represents a 'best case scenario' and it is theoretically possible that, if the KP SRC, rather than the CG149-NICE criteria, was used in clinical practice to guide PAb use, this percentage might be lower.

Our findings are consistent with previous reports from the UK and USA. A multi-center study from Wales reported the SRC to potentially avoid empirical antibiotics in three out of four infants. Another UK-based study reported the SRC to potentially reduce antibiotic prescribing in a tertiary neonatal unit in 70% to 80% of babies.[7] These differences between SRC and CG149-NICE recommendations for PAb in neonates may, in part, be because the SRC estimates individualized EONS risk based on continuous, rather than discrete, perinatal risk factors and indicators. The initial KP SRC study showed that, compared with the baseline period, the SRC use resulted in (1) a decrease in empirical antibiotic administration in the first 24 h from 5.0% to 2.6% and (2) no increase in antibiotic use between 24 and 72 h after birth.[4] In addition, the authors reported that SRC use did not delay treatment of infants with EONS presenting with more severe clinical illness and did not increase hospital readmissions for EONS after hospital discharge.[4] Nevertheless, the SRC's authors emphasize the importance of clinical judgment to EONS risk-estimation and management, cautioning against a solely algorithm-driven approach.[4]

Some studies, however, recommend caution in the adoption of the SRC into clinical practice. A meta-analysis of 11 studies, published in 2020,[14] reported between 14 and 22 out of a total of 75 culture-positive EONS cases (across all studies) where the use of the SRC would have resulted in delayed or missed treatment, compared to if NICE guidelines had been followed. The authors highlight differences in microbiology and healthcare practices (particularly in postnatal care and rates of maternal GBS screening) between the UK and the USA as significant factors to be considered before the introduction of the SRC into UK clinical practice.[14] This is consistent with the SRC's recommendations that "if adopting our approach, individual centers must assess local care structures".[4] Moreover, a recent comparison found CG149-NICE criteria to be superior to the SRC in identifying asymptomatic EONS within 4 h of birth.[15] Additionally, it is important to acknowledge the large variation in clinical practice in the screening and treatment of EONS, including in the application of the SRC, and that other team-directed strategy, such as the implementation of weekly 'antibiotic' ward rounds may be effective in reducing PAb prescribing in neonates.[16]

Our study design of retrospective selection to include only those neonates who received PAb according to CG149-NICE criteria, and the short study period with resultant lack of culture-proven sepsis episodes, limited our ability to identify babies in whom the SRC would have resulted in delayed or missed treatment. This also precluded our ability to (1) determine the SRC's sensitivity and specificity in predicting culture-positive EONS and (2) ascertain the proportion of neonates with an SRS >3 who did not trigger CG149-NICE criteria. Additionally, our study was restricted to a level 2 DGH-based neonatal unit and the overall sample size was relatively small, limiting the interpretation of the sub-group analyses, particularly for the maternal pyrexia sub-group ($n = 3$). These considerations limit the generalizability of our findings. Finally, we were unable to make comparisons between the SRC and the recently published NG195 2021 NICE guidelines for neonatal infection[17] because our sample was treated according to the CG149 guidelines.[5] The NG195 guidelines include fewer risk factors ($n = 7$), clinical indicators ($n = 14$), and red flags ($n = 6$) than CG149 and suggest that the KP SRC could be used as an alternative to the NICE framework if its use in clinical practice is prospectively audited.

Nevertheless, our study is, to our knowledge, the first to specifically examine the safety and efficacy of the SRC in a Level 2 neonatal unit in a DGH. It is also the first to examine which NICE risk factors and clinical indicators were most commonly associated with an SRS >3. This is important to consider in local settings before the adoption of the SRC into clinical practice as (1) only five of the eight NICE risk factors are included in the initial estimation of the SRS; and only 16 of the 21 NICE clinical indicators are included in the KP's classification of clinical illness in the infant, and (2) the local prevalence of these indicators are likely to influence clinical judgment, particularly in babies with an equivocal KP SRC clinical classification. It is important to know which risk factors and clinical indicators are associated with a higher SRS score in local settings so as to target quality improvement measures to a reduction in these risk factors and clinical outcomes accordingly. In our sample, nearly half of the neonates receiving PAb within 72 h of birth ($n = 27$; 45%) had one CG149-NICE risk factor and clinical indicator. In this group alone, the application of the SRC would have potentially reduced antibiotic prescribing in 56.2% of neonates.

Compared with CG149 NICE-based practice, the use of the SRC could reduce early antibiotic usage in nearly seven out of 10 term and near-term infants managed for suspected EONS in a DGH. The SRC is a good example of translatable research that is being increasingly adopted into

healthcare practice in the UK, with the potential to avoid unnecessary investigations and antibiotic usage in a large proportion of low-risk newborns.

ACKNOWLEDGMENTS

Michelle Fernandes is supported by a Clinical Research Training Fellowship from the Medical Research Council, UK.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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How to cite this article: Fernandes M, Winckworth L, Lee L, Akram M, Struthers S. Screening for early-onset neonatal sepsis on the Kaiser Permanente sepsis risk calculator could reduce neonatal antibiotic usage by two-thirds. *Pediatr Investig*. 2022;6:171–178. https://doi.org/10.1002/ped4.12344