A CALCULATED RISK

risk stratification as a basis for medical management of early-onset sepsis risk

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General Introduction and Thesis Outline

What are the odds

You were lucky to survive your first days of life, and so was I. The first day a human being is alive, is statistically the most probable to be the last [1]. Likewise, no more deaths occur in any other month, than in the first month of life [2]. However, the probability of sickness and death is distributed unequally at birth. For example, those born prematurely are about twice as likely to have a bacterial infection involving the bloodstream in the first 72 hours [3, 4], known as early onset sepsis (EOS) [5]. Similarly, EOS is more likely in those born from a mother suffering from a fever during delivery [4, 6]. So, maybe you were more likely to survive your first days than me. Or the other way around.

Like other humans, doctors are notoriously bad at estimating probabilities [7–9]. This is not because of a lack of intelligence, but caused by multiple biases and the complexity of problems. A myriad of factors can be indicative of the probability of the presence or course of a disease. Partial overlap between these 'risk factors' can further complicate the assessment of the probability. Subjective interpretation of signs and symptoms creates even more difficulty.

Consider the following two fictious but realistic examples:

1. Xander is born prematurely at 35 weeks and 3 days of gestation, 19 hours after 'breaking of the waters'. His mother, carrier of Group B Streptococcus (GBS) bacteria, had a temperature of 37.0 °C during labor. She received antibiotics 5 hours prior to his birth. During his first 4 hours, Xander's respiratory rate is relatively high, at 63 breaths per minute.
2. Yasmin is born on the expected day after 40 weeks, 16 hours after rupture of the membranes. During delivery, her mother had a fever of 38.9 °C, for which she received antibiotics after Yasmin's birth. Like Xander, her respiratory rate is a bit high during the first 4 hours, at 62 breaths per minute.

In both cases, known risk factors for EOS are present to a various degree. But is EOS more probable in one of these cases? How should we decide on the start of treatment? If we experienced a severe case of EOS recently, does this change our estimation of probability, or lead to different decisions?

Clinical decisions depend on complete assessments, involving not only probability, but also the severity and nature of consequences of the decision. Among other factors, these can include the results of absent or delayed treatment, long-term sequelae of disease or treatment, and personal preferences of patient and doctors. These decisions are challenging enough even without the difficulties in estimating probabilities. Therefore, objective estimation of the probability of a disease can be essential in making balanced decisions on the course of action [10]. The combination of computer-aided decision systems and electronic health care records provides the possibility for this objective estimation, and therefore the potential to improve doctor's decision making and patient outcomes [8, 11, 12]. This thesis explores the nature and effects of a computer-assisted decision tool in

clinical management of EOS. Specifically, whether it can improve the decision on whether to start empiric antibiotics in cases like that of Xander, or Yasmin.

Early onset sepsis

Systemic invasion by a micro-organism in a newborn is known as neonatal sepsis, associated with significant morbidity and mortality [5]. This condition can occur within the first days as a result of bacterial infection in the womb, or infection during or shortly after delivery. This is known as 'early onset sepsis' (EOS) [5]. Although a consensus definition is lacking critically lacking [13, 14], EOS is most often defined as a positive blood culture at less than 72 hours of age. With an exception for Figure 1, this definition will be used throughout this thesis. It carries limitations however, which will be discussed.

Overtreatment with antibiotics

EOS is an exceedingly rare condition, especially in late preterm and term infants. In developed countries, incidence rates have dropped from more than 3 to below 0.8 per 1000 livebirths (Figure 1) [3, 15–17]. However, EOS is hard to distinguish from other neonatal problems or normal neonatal physiology after birth. Signs and symptoms are non-specific [18], blood cultures do not provide sufficiently fast results [19, 20], and other conventional laboratory tests are unable to reliably detect or exclude EOS [21]. As a result, physicians often start empiric antibiotic therapy for *suspected* EOS based on the presence of risk factors and/or symptoms. For instance, the Centers for Disease Control and Prevention (CDC) guidelines of 2010 recommend empiric antibiotics for all newborns born

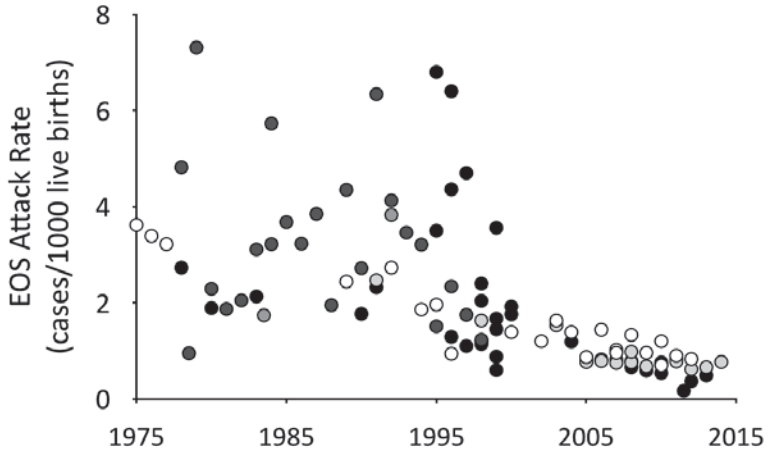

Figure 1. Declining rates of early-onset neonatal sepsis in high-income countries, 1975-2015. Data collected from 32 publications. ○ EOS at 2 days of age, ○ < 3 days of age, ● < 5 days of age, ● < 6 days of age, ● < 7 days of age.
FIgure adapted from Benitz and Achten, *ECinicalMedicine* (2020) [17], references for sources listed in Supplemental Appendix 1.

to mothers with chorioamnionitis [22]. Practices vary widely between [23], and even within countries [24, 25]. In Europe, studies report that between 2 and 16% of all newborns are started on empiric antibiotics for suspected EOS [26–29]. As a result, for each case of EOS, up to 82 newborns without EOS are treated with empiric antibiotics. This often leads to unnecessary separation of mother and child, prolonged hospital stay, and more financial costs. Moreover, the use of empiric antibiotics shortly after birth is associated with long-term sequalae for the child, such as alteration of the microbiome, and increased risks of auto-immune diseases and obesity [30, 31]. The extensive overtreatment with empiric antibiotics in newborns due to suspected EOS also contributes to the increasing issue of antibiotic resistance.

EOS calculator

Recognizing the problem of antibiotic overtreatment and the limitations of guidelines based on categorical risk factors, the group of Puopolo and Escobar from Kaiser Permanente in Northern California, developed and validated a risk prediction tool based on a regression analysis of large birth cohort dataset [4, 32]. The tool provides a quantitative indication of the risk of EOS, individually calculated for a specific newborn, derived from objective clinical measurements for that particular newborn (Figure 2). The calculated result is accompanied by a recommendation for clinical management: to start or strongly consider empirical antibiotics, to routinely check the newborns vital signs for signs of infection, or to proceed without additional care. This tool is known as the (neonatal) 'EOS calculator' and has been made publicly available as an online web tool since 2014 (Figure 3) [33]. Users

Figure 2. Schematic representation of stratification of newborns into risk groups using individual risk estimation by the EOS calculator. Risk factors are depicted as blocks (intrapartum antibiotics as medicine pill, maternal intrapartum temperature as thermometer, duration of ruptured membranes as timer, gestational age as calendar, and maternal group B Streptoccus carrier status without icon) with block size corresponding to their relative importance (based on data from Escobar et al [32]). Risk factors are combined with clinical status to calculate an individual risk score, which is used to assign a risk group and a corresponding clinical recommendation.

can easily enter the clinical information in it using a computer or smartphone (Figure 4), and it is being accessed across the world [34].

Aim of the thesis

This thesis aims to evaluate risk stratification using the EOS calculator in guiding the clinical decision on whether to start or withhold empiric antibiotics for suspected EOS, in newborns born after at least 34 weeks of gestation. The thesis will focus on the effects of EOS calculator implementation in clinical practice, and compare these with conventional diagnostic and management strategies, including recent clinical guidelines. Furthermore, this thesis will include examination of the methodology and inner workings of the tool, with implications for practice and future use of the EOS calculator.

Outline of the thesis

In the first published study on potential effects of the EOS calculator outside the United States, Kerste et al. conducted a retrospective chart analysis of all newborns born at least 34 weeks of gestational age in a single year Tergooi hospital [26]. The study concluded that the EOS calculator holds potential for significant reduction in use of empiric

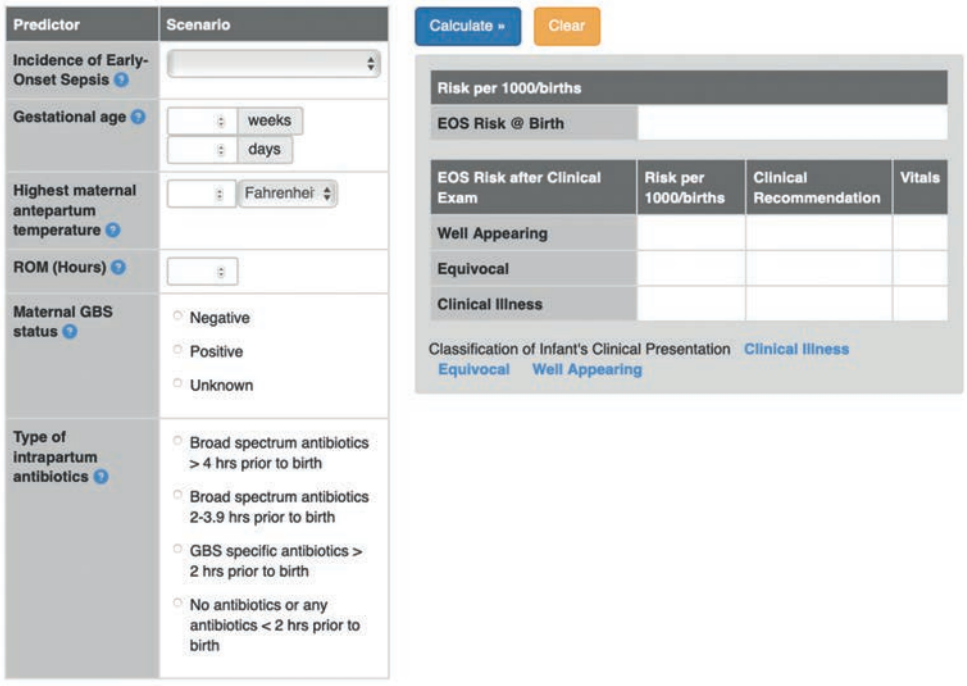

Figure 3. Screenshot of web form of the online EOS calculator tool [33]. As 'Incidence of Early-Onset Sepsis', 0.6 per 1000 live births is most appropiate (see Chapter 6 for a detailed discussion).

Figure 4. Scannable QR code linking to the online EOS calculator tool.

antibiotics for suspected EOS in Tergooi hospital, advocating prospective evaluation. In **Chapter 2** we describe the implementation of the EOS calculator with the clinical workflow of Tergooi hospital. The chapter contains a single-center before-after analysis and evaluates adherence to the EOS calculator recommendations.

Chapter 3 takes a wider approach. We systematically searched literature database to find any studies evaluating use of the EOS calculator in either hypothetical database analysis, or real-world implementation efforts. Results are synthesized and data from before-after implementation studies are meta-analyzed. This analysis provides us with high-level evidence for efficacy of use of the EOS calculator studies, and allows for evaluation of safety outcomes in spite of low EOS incidence.

The EOS calculator uses the presence of *Streptoccus agalactiae* (Group B Streptoccus [GBS]) in the maternal urogenital and/or rectal tract as a risk factor to estimate the risk of EOS in the newborn [32]. Maternal screening strategies for GBS differ between The Netherlands and the United States, where the EOS calculator was developed. **Chapter 4** uses a post-hoc analysis to evaluate the difference in availability of GBS due to the Dutch screening strategy and to what extent this difference affects EOS calculator recommendation.

In 2019, a theoretical analysis computed a high probability of financial benefit of implementation of the EOS calculator [35]. In order to verify this finding using real-world data, **Chapter 5** evaluates the association of implementation of the EOS calculator with the amount of health care utilization and financial costs related to suspected EOS.

To ensure appropriate use, clinicians should understand what the EOS calculator does, what its limitations are, and how these things affect the use in clinical practice. **Chapter 6** provides an in-depth explanation of the workings of the EOS calculator, how its results should be interpreted, and the implications of these matters for clinical practice. As the EOS calculator finds its way into clinical practice, clinicians will wonder how its results compare and complement traditional biomarkers used to identify EOS and other neonatal infections. **Chapter 7** provides insight by exploring associations between the estimated EOS risk and levels of traditional serum EOS biomarkers.

Whereas reports on EOS calculator use [36], and endorsements by authoritative bodies [37], reflect increasing uptake of the EOS calculator in the United States, reports on adoption in other parts of the world remain scarce. As the EOS calculator provides an alternative to existing guidelines, more comparative studies are necessary. To further compare the EOS calculator existing guidelines, **Chapter 8** and **Chapter 9** present findings of a multicenter observational study in seven Dutch hospitals. Adherence to and implications of current national guidelines are reported, and compared, as well as a comparison between recommendations for antibiotic treatment as per current national guidelines and those as generated by the EOS calculator.

Chapter 10 presents a general discussion of the findings from the research in this thesis, placing the results in context of wider early onset sepsis literature, as well as outlining directions for future research. Finally, **Chapter 11** presents summaries of the thesis in Dutch and English.

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2

Sepsis Calculator Implementation Reduces Empiric Antibiotics for Suspected Early-Onset Sepsis

Abstract

Significant overtreatment with antibiotics for suspected early onset sepsis (EOS) constitutes a persisting clinical problem, generating unnecessary risks, harms, and costs for many newborns. We aimed to study feasibility and impact of a sepsis calculator to help guide antibiotic for suspected EOS in a European setting. In this single-center study, the sepsis calculator was implemented as an addition to and in accordance with existing protocols. One thousand eight hundred seventy-seven newborns ≥ 35 weeks of gestational age were prospectively evaluated; an analogous retrospective control group (n = 2076) was used for impact analysis. We found that empirical treatment with intravenous antibiotics for suspected EOS was reduced from 4.8 to 2.7% after sepsis calculator implementation (relative risk reduction 44% (95% confidence interval 21.4–59.5%)). No evidence for changes in time to treatment start, treatment duration, or proven sepsis rates was found. Adherence to sepsis calculator recommendation was 91%.

Conclusion

Pragmatic and feasible implementation of the sepsis calculator yields a 44% reduction of empirical use of antibiotics for EOS, without signs of delay or prolongation of treatment. These findings warrant a multicenter, nation-wide, randomized study evaluating systematic use of the sepsis calculator prediction model and its effects in clinical practice outside of the USA.

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European Journal of Pediatrics, 2018;177(5): 741-746

Introduction

Early-onset sepsis (EOS), defined as an infection that manifests within 72 hours after birth and proven by a positive culture in blood or cerebrospinal fluid, is an important cause of neonatal morbidity and mortality [1]. In Europe, the incidence of EOS is estimated to be around 0.5-1 per 1000 livebirths [2, 3]. Both clinical symptoms and laboratory investigations of developing EOS in a newborn are nonspecific and discriminate insufficient between EOS and, for example neonatal extra-uterine adaptation [4]. Consequently, these limitations result in significant overtreatment with antibiotics, such as in 395,000 European term newborns (almost 8%) yearly. This overtreatment results in the risk of antibiotic resistance, interference with mother-child interaction, and significant health care costs [2, 5, 6].

Recognizing the pressing need for a way to reduce the empiric use of antibiotics for suspected EOS without missing EOS cases, Escobar et al. developed the 'newborn sepsis calculator' [7, 8]. This is a clinical prediction model that estimates EOS risk based on the combination of maternal risk factors and the evolving clinical condition of the newborn. Validation studies have shown significant potential for reduction in antibiotic treatment for suspected EOS [9–13]. Similarly, retrospective application of the sepsis calculator in our setting demonstrated a potential reduction of over 50%, without missing EOS cases [9]. Implementation of the sepsis calculator in the United States has resulted in a significant decrease in invasive diagnostics and empirical antibiotic treatment, without apparent adverse events [10]. As of yet, use of the sepsis calculator has not been evaluated prospectively outside of the United States.

Therefore, the aim of this study was to prospectively evaluate the feasibility and impact of using the sepsis calculator to help guide antibiotic use in children born ≥35 weeks of gestational age at risk for EOS in a Dutch teaching hospital. We hypothesized that antibiotic use can be significantly reduced compared to a historical birth cohort. Secondary outcomes included adherence to sepsis calculator recommendation and timing of start of antibiotic treatment for EOS.

Methods

Study design and population

This was a single center prospective study conducted from April 1, 2016 through March 31, 2017. Neonates born ≥35 weeks of gestational age with either elevated maternal EOS risk and/or possible EOS based on clinical presentation within 72 hours after birth were included. Elevated maternal EOS risk was defined as one or more of the following: maternal fever (≥ 38°C) during labor, positive maternal group B streptococcus (GBS) status, rupture of membranes 24 hours before birth, or presumed chorioamnionitis with or without adequate intra-partum antibiotic prophylaxis. Clinical EOS possibility was defined as any case considered a potential EOS case by the attending physician after clinical examination. Exclusion criteria were (suspected) gross anomalies, including chromosomal anomalies, and birth outside of Tergooi hospital.

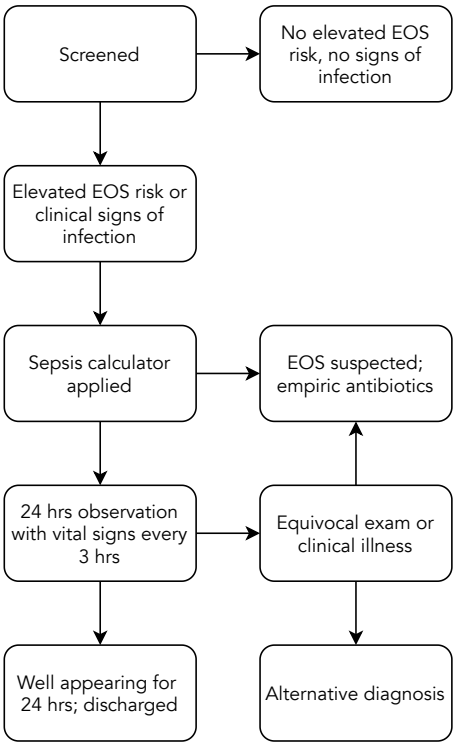

Figure 1. Study protocol

Study protocol

Each birth in Tergooi hospital was evaluated for elevated EOS risk according to the study protocol (Figure 1). In case one or more criteria for elevated maternal EOS risk were met, clinical evaluation of the newborn by a pediatric resident or pediatrician followed within 4 hours after birth. Using the online sepsis calculator (http://www.newbornsepsiscalculator.com), maternal EOS risk factors combined with the results of physical examination were used to assign a risk category and accompanying clinical recommendation based on estimated EOS incidence (low: <0.65; intermediate: 0.65–1.54; high: >1.54 per 1000 livebirths) for each at risk newborn. A priori sepsis incidence was set at 0.6 per 1000 livebirths. Physical examination included objective neonatal clinical findings, including vital signs, respiratory distress and need for respiratory support, as described in published sepsis calculator stratification strategies [7]. Sepsis calculator results were used to assist clinical management decisions on performing either a diagnostic work-up and start of empiric intravenous antibiotics for (suspected) EOS, or a conservative approach with routine controls of vital parameters (heart rate, respiratory rate, and temperature every 3 hours) by the nurse. In case of routine controls, re-evaluation of physical appearance by a pediatric physician followed 24 hours postpartum. In case antibiotics were started, the need for further treatment was assessed after 72 hours of treatment depending on

blood culture results, infection parameters, and clinical condition of the newborn. At any point in time, attending physicians were free to opt for clinical management different from sepsis calculator recommendations and/or study protocol, with deviations being noted.

Follow-up

During follow-up, data on use and timing of antibiotics as well as microbiology results from included infants were recorded from electronic hospital and pharmacy records and collected in a study database. Furthermore, we used pharmacy records to identify eligible newborns treated with antibiotics for suspected EOS without inclusion in EOS protocol. For these patients, we retrospectively collected clinical data on maternal and neonatal risk factors, estimated EOS risk, and follow-up data according to methods described in a preceding retrospective study [9].

Antibiotics before and after implementation of sepsis calculator

A previously described, retrospective cohort of newborns treated empirically for suspected EOS using the existing protocol without sepsis calculator was used to facilitate comparison before and after implementation of the sepsis calculator [9]. This retrospective cohort was established by collecting data on maternal and neonatal risk factors, retrospectively established estimated EOS risk using the sepsis calculator, and antibiotic treatment, using hospital records. In order to match the inclusion criteria of the prospective cohort, the retrospective control group was limited to the subset of newborns born at ≥35 weeks of gestational age (n=100). Both study periods consisted of a single calendar year. We compared median estimated EOS risk at start of antibiotics, number of cases treated with antibiotics for suspected EOS, median age at start of antibiotics, mean duration of antibiotics and EOS incidence before and after sepsis calculator implementation.

Statistical analysis

Statistical analyses were performed using SPSS 24 (Chicago, IL). Differences between groups were analyzed using an independent t-test for normally distributed data and the non-parametric Mann-Whitney U test for ordinal and non-normal data. The level of significance was set at $P \leq 0.05$.

Results

Inclusions

From April 1, 2016 to March 31, 2017, 1877 children were born at ≥35 weeks of gestational age in Tergooi hospital. During prospective data collection 208 (11.1%) of these children were included based on EOS risk factors, of which 34 cases were treated with antibiotics. Full details regarding baseline characteristics, presenting risk factors and antibiotic treatment are detailed in table 1.

Using electronic pharmacy records, we identified 17 additional eligible newborns treated with antibiotics for suspected EOS during the study period, for which we

retrospectively collected data from electronic hospital and pharmacy records according to methods previously described [9]. Together with 34 cases prospectively included through EOS protocol, this resulted in a total of 51 cases treated during the prospective one-year study period. For the retrospective control group we included all 100 eligible cases treated with antibiotics for suspected EOS, among 2076 eligible births from January 1, through December 31, 2014.

Antibiotics before and after implementation of sepsis calculator

After implementation of the sepsis calculator, there was significantly reduced use of antibiotics for suspected EOS (2.7% vs. 4.8%, P<0.001, relative risk reduction 44% (95% CI 21.4–59.5%)) (table 2). This reduction was most prominent in the low EOS risk category (11 vs. 41 newborns, relative risk reduction 70% (95% CI 42.4–84.7)), resulting in relatively more of the treated newborns being categorized as high-risk compared to before sepsis calculator implementation (P=0.008). Correspondingly, estimated EOS risk at start of antibiotic treatment was significantly higher after sepsis calculator implementation (3.38 vs. 1.38 per 1000 livebirths, P=0.03). We found no significant difference in duration of antibiotic treatment, time to treatment start, median gestational age, or gender

Table 1. Baseline characteristics, EOS risk, and use of antibiotics among infants prospectively evaluated using sepsis calculator through EOS study protocol

	Low risk	Intermediate risk	High risk	Overall
N (%)	141 (67.8)	38 (18.3)	28 (13.5)	208 (100)
Weeks of gestational age – median (IQR)	39 (36.9–40.0)	39.1 (37–40.6)	40.1 (37.9–41.6)	39.1 (37.0–40.4)
Male (%)	80 (56.7)	17 (44.7)	20 (71.4)	100 (54.6)
Risk factor presence (%)				
PROM	61 (43.3)	17 (44.7)	12 (42.9)	91 (43.8)
Maternal fever	32 (22.7)	15 (39.5)	15 (53.6)	62 (29.8)
Late preterm birth	33 (23.4)	8 (21.1)	2 (7.1)	43 (20.7)
GBS+ mother	17 (12.1)	2 (5.3)	2 (7.1)	21 (10.1)
Clinical infection symptoms	8 (4.7)	3 (7.9)	12 (42.9)	23 (11.1)
EOS risk[a] – median (IQR)	0.24 (0.11–0.45)	0.97 (0.82–1.12)	7.04 (3.47–24.33)	0.46 (0.18–0.88)
Antibiotics for EOS (%)				
Started	10 (7.4)	3 (7.9)	22 (78.6)	34 (16.3)
Continued ≥7 days	4 (2.8)	2 (5.3%)	17 (60.7)	22 (10.6)

[a] Estimated EOS cases per 1000 livebirth

Abbreviations: GBS, group B streptococcus; IQR, interquartile range; PROM; prolonged rupture of membranes

distribution. Actual EOS incidence as proven by positive blood culture was comparable (2 (0.11%) vs. 2 (0.10%)).

Among the 208 newborns evaluated according to the study protocol, antibiotics were started in 34 (16%) and continued for 7 days in 22 (11%) newborns. This resulted in 65% (22/34) of cases completing 7 days or more of antibiotics if included in EOS protocol, similar to before sepsis calculator implementation (60%, 60/100).

Adherence to sepsis calculator recommendation

We evaluated adherence to sepsis calculator recommendation, comparing actual treatment decision with the recommendation provided by the calculator (Figure 2). Antibiotics were only recommended in only 25 of 208 (12%) cases evaluated using the sepsis calculator according to study protocol. Among cases of suspected EOS in which the sepsis calculator was used, adherence to model recommendation was 91%. Antibiotics were not advised but nonetheless started in 21 cases (74% of deviations from protocol). In 5 cases (16% of

Table 2. Baseline characteristics, EOS risk distribution and treatment aspects before and after implementation of sepsis calculator.

	Retrospective cohort	Prospective cohort	P value
Cases treated with antibiotics for suspected EOS	100 (4.8%)[b]	51 (2.7%)[b]	<0.001
Weeks of gestation age – median, (IQR)	39.9 (37.6–41.0)	40.1 (38.9–41.6)	0.07
Male	64(64%)	39 (77%)	0.14
Neonatal EOS risk group among suspected EOS (%)			0.012
Low	41 (41.0)	11 (20.0)	
Intermediate	9 (9.0)	9 (16.4)	
High	47 (47.0)	34 (61.8)	
Undetermined	3 (3.0)	2 (3.6)	
AB days – mean (SD)	5.49	5.80	0.34
Age (hrs) at start of AB treatment – median (IQR)	7.0 (3.0–7.0)	5.25 (3.0–7.0)	0.45
AB started within 12 hours[c]	59 (59%)	31 (69%)	0.28
EOS risk at start AB – per 1000 livebirths, median (IQR)	1.38 (0.19–12.17)	3.38 (0.93–9.18)	0.03

[b] Percentage based on total births in respective study period (2076 in retrospective cohort, 1877 in prospective cohort).

[c] 6 cases with missing data omitted from analysis.

Abbreviations: AB, antibiotics; hrs, hours; IQR, interquartile range

deviations), antibiotics were not started despite a sepsis calculator recommendation to do so. Notably, sepsis calculator use was recorded per study protocol for 67% (34/51) of all newborns treated with antibiotics in the prospective study period. The 17 infants without prospective EOS calculator use had relative high EOS risk when evaluated retrospectively (median EOS risk 3.17 per 1000 livebirths) and sepsis calculator would have recommended start of antibiotics in 69% of these newborns.

Discussion

The objective of this study was to examine the feasibility and impact of the use of the sepsis calculator to guide the use of antibiotics in newborns suspect for EOS. We found a relative reduction of 44% in antibiotic use for suspected EOS after implementation of the sepsis calculator compared to a historical birth cohort with similar infection rates in the same hospital during an analogous study period. This is a prospective confirmation of the results of our preceding retrospective study [9]. In addition, we found that newborns treated with antibiotics had higher estimated EOS risk, indicating better allocation of antibiotics for suspected EOS. These findings indicate that a significant reduction of antibiotic treatment for suspected EOS is possible without increase in delayed treatment for EOS cases through improved treatment allocation.

To our knowledge, this is the first prospective evaluation of the use of the sepsis calculator outside of the United States. The absolute reduction in antibiotics from 4.8% to 2.7% aligns with the results of our preceding retrospective study, and with results from the prospective analysis by the developers of the sepsis calculator [9, 10]. However,

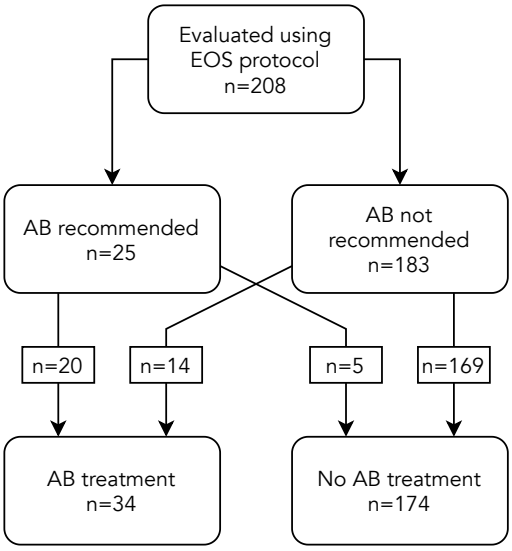

Figure 2. Adherence to sepsis calculator recommendation among newborns evaluated using EOS protocol

considering limited and elective implementation in a different population alongside existing protocols, it is still a remarkable result. The stratification according to EOS risk as proposed by Escobar identified an important low-risk subset of 11% of newborns with either equivocal physical sign but few maternal risk factors or with maternal risk factors but good clinical appearance at physical examination, in which an observe-and-evaluate strategy can replace empiric antibiotics. Our findings confirm this subgroup as particular suitable for reducing use of antibiotics, as the reduction we found was mostly due to the reduction in antibiotics in newborns classified as low-risk by the sepsis calculator. Differentiating low-risk from high-risk infants, the sepsis calculator appears to effectively decrease the use of empiric antibiotics by recommending not starting treatment in 88% of cases evaluated using the calculator. As this reduction occurred in our setting with already modest use of antibiotics for suspected EOS (4.8% compared to up to 8% of (near-)term newborns in Europe) [2], it represents a major opportunity to improve antibiotic stewardship in high-income settings.

Adherence to sepsis calculator recommendation was generally high, but it should be noted that in 33% of cases treated with antibiotics, use of sepsis calculator was not prospectively documented. The sepsis calculator may have been used but undocumented, or clinicians may have had profound or pressing reasons to start antibiotic treatment and therefore consider application of the sepsis calculator not useful or too time-consuming. Indeed, for this group without documented sepsis calculator use, retrospective analysis shows that the sepsis calculator would have classified the newborn as high-risk, recommending start of antibiotics in the majority (69%) of cases. This suggests that more exhaustive use of the sepsis calculator would entail only limited potential for even further reduction of empiric antibiotics.

Strengths of this study include the prospective design of sepsis calculator implementation, the pragmatic approach which allowed for use of a prediction model as an addition to existing guidelines, the comparison with a preceding birth cohort, and the use of comprehensive electronic hospital record data on use of antibiotics and blood culture results. The historical nature of the 2014 cohort used as control group is a limitation, since factors other than use of the sepsis calculator may theoretically have contributed to the reduction in antibiotics. However, this before-after design is a recommended alternative for expensive and time-consuming randomized impact trials [14]. In addition, given a similar setting and analogous study periods, similar rates of proven EOS during study periods, and our standardized methodology to establish outcomes, we believe our historic cohort is a well-designed control group. Other limitations include occasional missing data and incomplete uptake of prospective sepsis calculator use among suspected EOS cases (documented use in only 67% cases treated with antibiotics). Since prediction model impact is known to increase with higher uptake and better implementation, this may have led to an underestimation of the impact of the sepsis calculator [15].

Already, it is acknowledged that the sepsis calculator strategy aligns with current guidelines [16]. Our findings show that implementation of the sepsis calculator in daily

clinical decision-making in a Dutch teaching hospital is feasible in conjunction with existing protocols. The sepsis calculator provides pragmatic and evidence-based assistance in the clinical problem of management of EOS, thereby resulting in important reduction of intravenous antibiotic treatment and hospitalization. In contrast to many other strategies aimed at achieving this, this method is non-invasive and provided at virtually no extra cost. Notably, the current era of electronic patient records provides opportunities for more embedded and widespread implementation of such clinical decision tools, improving their effectiveness [14].

In conclusion, these findings provide ratio and incentive for multicenter, nationwide, randomized validation and implementation studies of systematic use of the sepsis calculator prediction model to further evaluate its effect in clinical practice in places other than the United States. In addition, more research is necessary evaluating how sepsis calculator results should be interpreted in conjunction with new and existing laboratory infection parameters, to further guide and possibly improve the EOS clinical decision process.

Author's contributions

NBA performed data collection, data analysis and writing of the manuscript. WD and PL assisted in data collection and reviewed the manuscript. MB co-designed the study, helped in data collection and reviewed the manuscript. FP designed the study and supervised in data collection, data analysis and writing of the manuscript.

Compliance with ethical statements

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors. The study was approved by the Scientific Review Committee of Tergooi Hospitals (study number 15.58; letter reference kV/15.69).

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

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Informed consent

The Scientific Review Committee of Tergooi Hospitals judged that the study did not fall under the Medical Research Involving Human Subjects Act, so that informed consent by patients and caregivers was not required.

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Association of Use of the Neonatal Early-Onset Sepsis Calculator with Reduction in Antibiotic Therapy and Safety
A Systematic Review and Meta-analysis

Abstract

Importance

The neonatal early-onset sepsis (EOS) calculator is a clinical risk stratification tool increasingly used to guide the use of empirical antibiotics for newborns. Evidence on the effectiveness and safety of the EOS calculator is essential to inform clinicians considering implementation.

Objective

To assess the association between management of neonatal EOS guided by the neonatal EOS calculator (compared with conventional management strategies) and reduction in antibiotic therapy for newborns.

Data Sources

Electronic searches in MEDLINE, Embase, Web of Science, and Google Scholar were conducted from 2011 (introduction of the EOS calculator model) through January 31, 2019.

Study Selection

All studies with original data that compared management guided by the EOS calculator with conventional management strategies for allocating antibiotic therapy to newborns suspected to have EOS were included.

Data Extraction and Synthesis

Following PRISMA-P guidelines, relevant data were extracted from full-text articles and supplements. CHARMS (Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies) and GRADE (Grades of Recommendation, Assessment, Development and Evaluation) tools were used to assess the risk of bias and quality of evidence. Meta-analysis using a random-effects model was conducted for studies with separate cohorts for EOS calculator and conventional management strategies.

Main Outcomes and Measures

The difference in percentage of newborns treated with empirical antibiotics for suspected or proven EOS between management guided by the EOS calculator and conventional

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management strategies. Safety-related outcomes involved missed cases of EOS, readmissions, treatment delay, morbidity, and mortality.

Results

Thirteen relevant studies analyzing a total of 175 752 newborns were included. All studies found a substantially lower relative risk (range, 3%-60%) for empirical antibiotic therapy, favoring the EOS calculator. Meta-analysis revealed a relative risk of antibiotic use of 56% (95% CI, 53%-59%) in before-after studies including newborns regardless of exposure to chorioamnionitis. Evidence on safety was limited, but proportions of missed cases of EOS were comparable between management guided by the EOS calculator (5 of 18 [28%]) and conventional management strategies (8 of 28 [29%]) (pooled odds ratio, 0.96; 95% CI, 0.26-3.52; $P = .95$).

Conclusions and Relevance

Use of the neonatal EOS calculator is associated with a substantial reduction in the use of empirical antibiotics for suspected EOS. Available evidence regarding safety of the use of the EOS calculator is limited, but shows no indication of inferiority compared with conventional management strategies

Introduction

Empiric therapy of newborns at risk for or with suspected early-onset sepsis (EOS) represents the main contributor to the use of antibiotics in early life [1]. The reported number of newborns receiving antibiotic therapy for one episode of culture-proven EOS ranges from 18 to 118 in high-risk infants, and up to 1400 in well-appearing newborns born to mothers with chorioamnionitis [2–4]. Thus, for each case of culture-proven EOS a substantial number of newborns are exposed to potential harms related to empirical antibiotic therapy. Use of antibiotics in newborns is associated with early adverse consequences such as increased risk of necrotizing enterocolitis, fungal infections and death in preterm infants [5, 6]. Moreover, antibiotics increase antibiotic resistance, mother-child separation and healthcare costs [7, 8]. Early life antibiotic-induced microbiome alterations, with downstream effects on the developing immune system [9, 10], are also associated with increased risks of allergic diseases, obesity and auto-immune diseases later in life [6, 11, 12].

The neonatal EOS calculator is designed to improve the accuracy of empirical antibiotic administration in newborns with suspected EOS. It is based on a predictive risk model developed using a nested case-control design in a cohort of 608 014 newborns ≥ 34 weeks' gestation born at 14 hospitals in the United States (US), and further advanced using logistic regression and recursive partitioning [13, 14]. The EOS calculator (kp.org/eoscalc) estimates the EOS risk based on 5 objective maternal and 4 clinical neonatal risk factors. It stratifies newborns into 3 levels of risk with a corresponding recommendation on management, including to start or withhold empirical antibiotic therapy. Implementation of the EOS calculator at Kaiser Permanente Northern California hospitals almost halved the rates of antibiotic administration (from 5.0% to 2.6%) among term and late preterm infants in the first 24 hours postpartum [15].

The EOS calculator prediction model is based on a selected US population, and differences between health care settings may impede generalizability. For example, EOS incidence rates, maternal group B streptococcus (GBS) screening policy, intrapartum antibiotic administration, and/or observation time-in-hospital may differ between the US and other countries. In view of the need to reduce unnecessary antibiotic usage early in life, and the increasing use of the EOS calculator in many settings [3], there is urgency to summarize best available evidence on the EOS calculator to guide policy-making and further research [16–18].

The purpose of the current systematic review and meta-analysis was to identify, critically appraise, and synthesize evidence from studies comparing management guided by the EOS calculator to conventional management strategies, and reporting the rates of empirical antibiotic therapy for suspected EOS. The second objective was to summarize available safety data regarding use of the EOS calculator.

Methods

We used a PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) review protocol for data collection, analysis and reporting (eAppendix 1 in Supplement, contains full methodological details). We registered the review in advance (CRD42018116188, PROSPERO database) [19, 20].

Study eligibility criteria

We pre-specified eligibility criteria as follows: any study design with original data, comparing management guided by the EOS calculator to conventional management strategies, and reporting the rates of empirical antibiotic therapy for suspected EOS as an outcome. No eligibility criteria regarding safety data were set, and all eligible studies were screened for all safety outcomes. To ensure independence of outcome estimates, we excluded datasets that were used to develop the EOS calculator.

Information sources and search strategy

We performed a systematic search of all available literature describing the EOS calculator in Cochrane, EMBASE and PubMed/MEDLINE databases, last updated on the 31st of January 2019. We searched in all search fields for 'EOS calculator', 'eos calculator' or 'sepsis risk calculator'. In title/abstract fields we used 'predictive', 'risk', 'quantitative' or 'stratification', combined with 'model' or 'algorithm', and 'early onset sepsis', 'early onset neonatal sepsis' or 'EOS'. Exact search engine strings are detailed in the review protocol (available in Supplemental Material). We limited our search results to peer-reviewed articles published in 2011 or later, since the multivariate model forming the basis of the EOS calculator was published in 2011 [13]. No other limits were applied. We examined reference lists of included studies and relevant reviews to identify additional eligible studies. We also reviewed all titles and abstracts of all papers citing original EOS calculator publications, identified through Google Scholar and/or Scopus/Web of Science search engines. All citations were combined and duplicates were manually excluded.

Study Selection and Data Extraction

Search results were independently screened by 2 reviewers (N.A., R.B.) who assessed each potentially eligible full-text paper according to predetermined inclusion and exclusion criteria. In case of disagreement, a third researcher (F.P.) had the decisive vote. One author (N.A.) extracted relevant data from papers as well as any available supplements. Two other authors (R.B. and W.B.) verified data-extraction for completeness and accuracy. The following general data were extracted; author, year and country; study design, populations and inclusion criteria. We extracted data on the rates of newborns treated with empirical antibiotics for suspected or proven EOS within ≤72 hours after birth, both for management based on the EOS calculator and conventional management strategies. For these, we calculated the absolute and relative differences with 95% confidence interval

(CI). We extracted data on the following safety outcomes: missed EOS cases (defined as newborns with culture-proven EOS not allocated antibiotic therapy within 24 hours postpartum), changes in EOS incidence, EOS morbidity and mortality, readmissions for neonatal sepsis, and timing of antibiotics, after EOS calculator implementation. We also noted any adverse events specifically reported by the authors. If multiple papers reported data from the same source study, results were combined to avoid overlap among results. For studies eligible for meta-analysis, we retrieved supplementary data from original authors if exact data on antibiotic use within 72 hours postpartum was not present in the original publication. In addition, we surveyed original authors for updates on their data, and retrieved these when available.

Assessment of Methodological Quality

We assessed the risk of bias of individual studies using 8 applicable items of a dedicated checklist for assessment of studies evaluating prediction models (checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies) [21]. Risk of bias for each item, including an overall risk of bias-score, was classified as 'high', 'low' or 'unclear'; disagreements were resolved through a third author (F.P.).

We used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) tool to estimate the quality of evidence, from very low to high [22, 23]. This was done separately for the use of empirical antibiotics for EOS and for safety of EOS calculator usage.

Synthesis of Results and Analysis

We classified studies according to their study design; studies evaluating cohorts before and after actual implementation of the EOS calculator, and studies performing hypothetical analysis of newborn databases. We pooled data from actual implementation studies with comparable homogeneous data before and after implementation, and calculated combined effect estimates. Subgroup analysis was performed for studies including newborns regardless of chorioamnionitis-exposure and for studies restricted to chorioamnionitis-exposed newborns. We quantified inconsistencies between the results of the studies by using the I^2 test. Results were interpreted as representing either absence (I^2 below 25%), low (I^2 25 to 50%), moderate (I^2 50 to 75 %), or high heterogeneity (I^2 75% or higher) [24]. Data entry and meta-analysis were performed using RevMan version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). We calculated relative risk (RR) with 95% confidence intervals. We present the effect-estimates by using the random-effect model due to assumption of clinical and methodological diversity among the studies, subsequently often leading to statistical heterogeneity. To compare proportions of missed EOS cases, we used the Cochran-Mantel-Haenszel method to test for significance (alpha level $P<0.05$), performed using R, version 3.5.0 (R Foundation) [25].

Results

Characteristics and participants of included studies

After reviewing 354 identified publications for study eligibility, we selected and evaluated 56 full-text articles (Figure 1). Thirteen studies were included (Table 1) [15, 26–38]. For 1 study, we used recently added data obtained through surveying authors for updated data [29, 39]. No randomized-controlled studies were found. Six studies evaluated implementation of the EOS calculator in clinical practice using before-after analysis and were therefore eligible for meta-analysis [15, 26, 30, 35–37]. Seven studies estimated effects of the EOS calculator by hypothetical analysis of newborn databases [27, 28, 32–34, 38, 39]. Studies used a retrospective (n=7) [27, 28, 32–34, 36, 39], prospective (n=3) [15, 26, 38], or combined approach (n=3) [30, 35, 37]. Ten of 13 studies were performed in the US [15, 27–30, 32, 33, 36–38].

The 13 included studies involved a total of 175 752 newborns. Of these, 172 385 were included in studies comparing cohorts before (66 949) and after (105 436) EOS

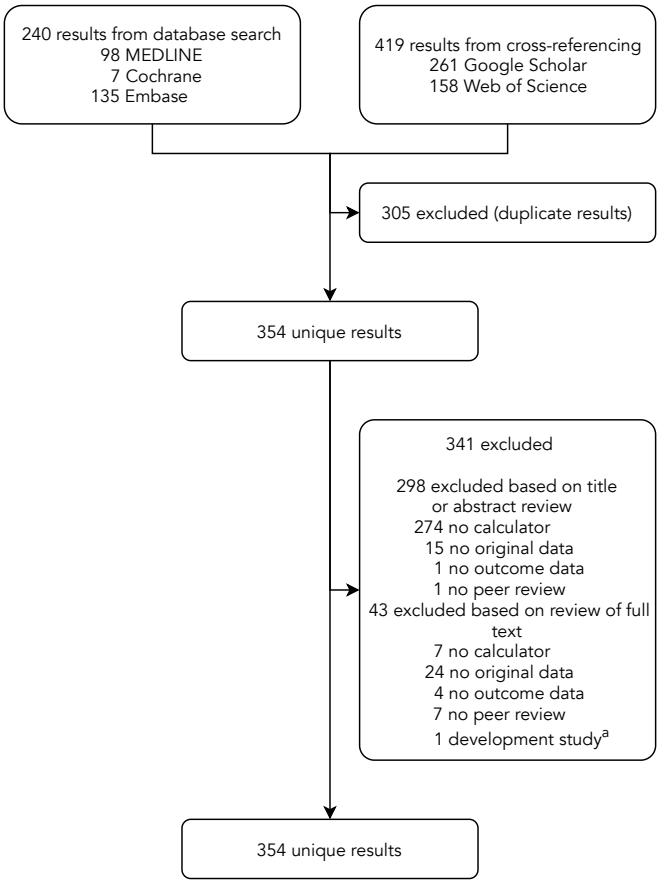

Figure 1. Study selection process

calculator implementation, and 3367 in studies performing hypothetical database analysis. Inclusion criteria differed among studies. The minimal gestational age ranged from 34 to 36 weeks. Three studies were confined to well-appearing newborns, the other 10 studies also included symptomatic newborns. Inclusion was limited to newborns with a diagnosis of maternal chorioamnionitis in 6 studies, and limited to newborns treated with antibiotics in 2 studies.

Risk of Bias and Quality of Evidence

The overall risk of bias was judged as high for 9 studies, low for 2 and unclear for 2 studies (eTable 1 in Supplement). We graded the overall quality of evidence for the primary outcome of reduction in empirical antibiotics as moderate, due to inclusion of very large observational studies that had large effect sizes and the consistency of results. We graded the quality of evidence regarding safety of use of the EOS calculator as very low, mainly due to small number of events across all studies.

Reduction in use of empirical antibiotics when using the EOS calculator

All 13 included studies compared management guided by the EOS calculator to conventional management strategies and used the rate of empirical antibiotics prescribed for suspected EOS as a main outcome. All studies found an RR in antibiotic use favoring use of the EOS calculator (Table 1). Studies evaluating the EOS calculator in newborns born to mothers with the risk factor chorioamnionitis reported stronger reductions (RR ranging from 3% to 39%) compared to studies not limited to chorioamnionitis (RR ranging from 25% to 60%), respectively.

Meta-analysis results of data from before and after EOS calculator implementation favored use of the EOS calculator, with an overall RR of antibiotic use of 45% (95% CI 35-57%) among all 6 studies (Figure 2). We found an RR in antibiotic use of 56% (95% CI; 53-59%) in the 4 studies including all newborns regardless of exposure to chorioamnionitis. We found no heterogeneity among results of these studies, of which 2 were from the US [15, 30], 1 from Australia [26] and 1 from the Netherland [35]. For the 2 studies restricted to chorioamnionitis-exposed newborns [36, 37], the RR in antibiotic use was lower (20%) , but with a large 95% CI (4-91%) and high heterogeneity (I^2 96%) due to large differences between the effect estimates.

Safety when using the EOS calculator

Three studies were specifically designed to evaluate the safety of the EOS calculator as a study objective or by calculating model performance, using before-after analysis [15, 26, 30]. One or more safety outcomes were discussed in 12 of 13 included studies (eTable 2). Across all studies, we found no indication of an increase in the EOS incidence, readmissions, antibiotic use between 24 and 72 hours after birth, or proportion of newborns requiring intensive care or even mortality related to use of the EOS calculator.

Source	EOS calculator No. of Events	EOS calculator Total No.	Conventional management No. of Events	Conventional management Total No.	Risk Ratio (95% CI)	Weight, %
All newborns at risk						
Kuzniewicz et al [15], 2017	1698	56 261	522	95 543	0.55 (0.52-0.58)	20.7
Achten et al [26], 2018	51	1877	100	2076	0.56 (0.40-0.79)	15.0
Dhudasia et al [27], 2018	222	6090	356	5692	0.58 (0.49-0.69)	19.1
Strunk et al [28], 2018	201	2502	235	1732	0.59 (0.50-0.71)	18.8
Subtotal		66 730		105 043	0.56 (0.53-0.59)	73.5
Total events	2172		5917			
Heterogeneity: τ^2=0.00, χ^2_3=0.87; P=.83; I^2 =0%						
Test for overall effect: z = 23.58; P<.001						
Newborns exposed to chorioamnionitis						
Gievers et al [29], 2018	13	143	203	213	0.10 (0.06-0.16)	10.6
Beavers et al [30], 2018	28	76	168	179	0.39 (0.29-0.53)	15.9
		219		392	0.20 (0.04-0.91)	26.5
Total events	41		371			
Heterogeneity: τ^2=1.17, χ^2_1=26.19; P <.001; I^2 =96%						
Test for overall effect: z = 2.09; P=.04						
Total	2213	66949	6288	105435	0.45 (0.35-0.57)	100.0
Heterogeneity: τ^2=0.07, χ^2_5=49.94; P <.001; I^2 =90%						
Test for overall effect: z = 6.55; P<.001						
Test for subgroup differences: χ^2_5=1.79; P=.18; I^2 =44.1%						

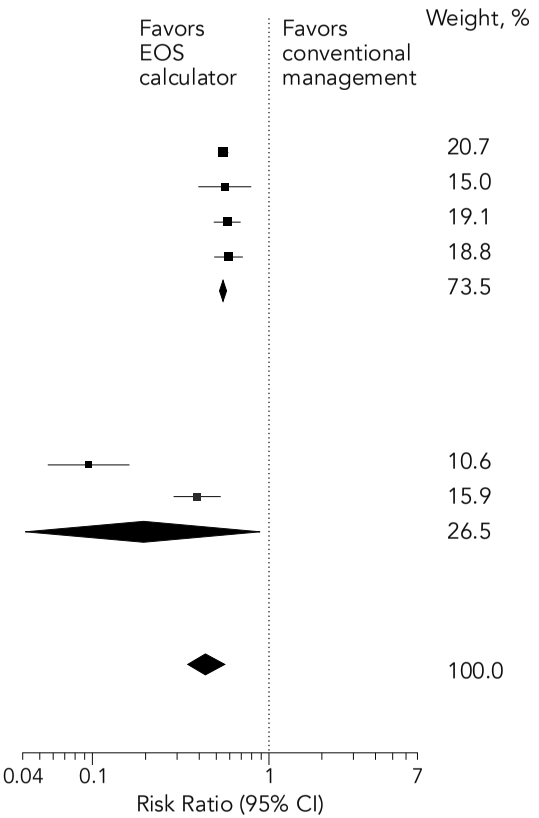

Figure 2. Study selection process. Data presented for before-after studies included in the meta-analysis. Data were pooled under the assumption of a random-effects Mantel-Haenszel model. EOS indicates early-onset sepsis.

Table 1. Characteristics and use of empirical antibiotics in included studies

	Study and location	Setting	Design	Births	Included	EOS calculator	
						n	Empiric AB, n (%)
Before-after analysis	Kuzniewicz 2017, US [15]	Mixed	Prospective	204 485	GA ≥ 35 w	56 261	1698 (3.0)
	Achten 2018, Netherlands [35]	Regional	Retro- and prospective	3953	GA ≥ 35 w	1877	51 (2.7)
	Dhudasia 2018, US [30]	Tertiary	Retro- and prospective	11 782	GA ≥ 36 w	6090	222 (3.6)
	Strunk 2018, Australia [26]	Tertiary	Prospective	4233	GA ≥ 35 w	2502	206 (8.2)
	Gievers 2018, US [37]	Tertiary	Retro- and prospective	9039	Chorioamnionitis, GA ≥ 35 w	143	13 (9.1)
	Beavers 2018, US [36]	Tertiary	Retrospective	NR	Chorioamnionitis GA ≥ 35 w	76	28 (36.8)
Hypothetical database analysis	Shakib 2015, US [32]	Tertiary	Retrospective	20 262	Chorioamnionitis, well-appearing, GA ≥ 34 w	698	39-86 (5.6-12.3) [a]
	Kerste 2016, Netherlands [34]	Regional	Retrospective	2094	AB for suspected EOS, GA ≥ 34 w	108	51 (47.2)
	Warren 2017, US [27]	Tertiary	Retrospective	NR	AB for suspected EOS, GA ≥ 34 w	202	47 (23.3)
	Money 2017, US [28]	Tertiary	Retrospective	19 525	Chorioamnionitis well-appearing for 24 hours [c], GA ≥ 35 w	362	9 (2.5)
	Carola 2017, US [33]	Tertiary	Retrospective	17 908	Chorioamnionitis, GA ≥ 35 w	896	209 (23.3)
	Joshi 2019, US [39]	Tertiary	Retrospective	10 002	Chorioamnionitis, well-appearing at birth, GA ≥ 34 w	596	53 (8.9)
	Klingaman 2018, US [38]	Tertiary	Prospective	505	GA ≥35 w	505	2 (0.4)

Abbreviations: AAP: American Academy of Pediatrics; AB: antibiotics; CDC: Centers for Disease Control and Prevention; CFN: Committee on the Fetus and Newborn; GA: gestational age; n/a: not applicable; NR: not reported; w: weeks

Definitions; 'births': number of births in total study period in the eligible GA range; 'included': inclusion criteria used to select study population. 'chorioamnionitis': newborns with a mother diagnosed with chorioamnionitis;

'N – included'; number of newborns used for EOS calculator application; 'reduction in AB': (hypothetical) reduction in empirical AB for EOS achieved by using the EOS calculator.

Footnotes

[a] Reduction range reported (precluding calculation of meaningful CI), as depending on outcome of newborns in observe-and-evaluate category.

Conventional strategy			Reduction in empirical AB	
Strategy	n	Empiric AB, n (%)	Absolute %	Relative risk, % (95% CI)
CDC informed	95 543	5226 (5.5)	2.5	55.2 (52-58)
National guideline informed	2076	100 (4.8)	2.1	56.4 (40-79)
CDC/AAP informed	5692	356 (6.3)	2.6	58.3 (49-69)
Adaptation AAP guideline	1732	237 (13.7)	5.5	60.2 (50-72)
CDC informed	213	203 (95.3)	86.2	9.5 (6-16)
Pre-implementation	180	168 (93.3)	57.0	39.3 (29-53)
Actual practice (CDC/CFN informed)	n/a	430 (61.6)	49.3–56.0 [a]	9.1–20.0 [a]
Actual practice (national guideline informed)	n/a	108 (100)	52.8 [b]	47.2 (39-58) [b]
CDC guideline	n/a	188 (93.1)	69.8 [c]	25.0 (19-32) [c]
Current protocol (CDC/AAP informed)	n/a	361 (99.7) [c]	97.2 [c]	2.5 (1-5) [c]
Actual practice (AB if chorioamnionitis)	n/a	896 (100)	76.7	23.3 (21-27)
Institutional practice (AB if chorioamnionitis)	n/a	596 (100)	91.1	8.9 (3-11)
CDC informed	n/a	9 (17.8)	1.4	22.2 (5-102)

[b] Studies limited to AB treated infants; reported results represent estimations of maximum potential reduction of empirical AB by EOS calculator use.

[c] Sampling of study excluded n=41 infants who were symptomatic at birth and n=38 infants developing symptoms after initial exam, resulting in an estimated reduction which does not reflect a potential implementation scenario. Use of AB in current protocol inconsistently reported (362/362, and 97.7%).

We reviewed all EOS cases reported in the 13 included studies. Among before-after implementation studies, we found 5/18 (28%) missed EOS cases in cohorts with EOS calculator-based management, compared to 8/28 (29%) in cohorts with conventional management strategies (pooled odds ratio 0.96, 95% CI; 0.26-3.52; *P*=.95) (Table 2). Missed EOS cases were started on antibiotics after 24 hours postpartum in all cases. Among studies performing only database analysis, we found 5/12 (42%) missed EOS cases by hypothetical EOS-calculator application (Table 3). Among all studies, almost half of missed EOS cases remained asymptomatic, regardless of management strategy (eTable 3 in Supplement).

Discussion

Reduction of antibiotic overtreatment in neonates is of paramount importance to avoid early and late adverse effects. In this systematic review and meta-analysis of all studies reporting the results of actual or hypothetical implementation of the EOS calculator including over 175 000 newborns, we found that use of the EOS calculator is associated with a marked reduction in empirical antibiotic therapy compared to conventional management strategies. Studies restricted to chorioamnionitis-exposed newborns indicate an even larger potential for reduction in antibiotic use in such newborns. Data on safety were very limited due to rarity of safety outcomes. However, when scrutinizing available data, we found no indications that EOS calculator use leads to an increase in missed EOS cases, overall EOS incidence, readmissions, delay in antibiotic therapy, or EOS-related morbidity or mortality.

Safety is of critical importance and risk of missing EOS cases is a major concern in the evaluation of management strategies for newborns at risk for or with suspected EOS. EOS risk management strategies need to balance the risk of a missed EOS case against the harm of unnecessary antibiotics on a population level [5, 15]. Even well-appearing newborns without any risk factors can develop EOS. Thus, not every case of EOS is predictable, and clinical judgment and safety-netting continue to be an essential part in early diagnosis [40]. This is reflected in the observation period included in management guided by the EOS calculator, as well as in promising alternatives such as serial physical examinations after birth [29, 40–42]. For many EOS risk management strategies, the risk of missing EOS is largely unknown. In contrast, the EOS calculator provides an individual EOS risk-estimate for each newborn, and our review summarizes the current real-world evidence on this outcome in clinical practice. Depending on setting and strategies used, the EOS calculator can also serve as a safety-net by flagging at-risk newborns overseen by conventional management strategies, which are more categorical in their recommendation [43, 44]. Altogether, although evidence of safety of management guided by the EOS calculator is very limited, it shows no indication of inferiority compared to conventional management strategies thus far.

Table 2. Management of EOS cases using the EOS calculator and conventional management strategies in before-after studies

	Management guided by EOS calculator				Conventional management strategy				
Source	Births	EOS cases	AB <24h	AB >24h (missed)	Births	EOS cases	AB <24h	AB >24h (missed)	P value
Kuzniewicz et al [15], 2017	56 261	12	8	4	95 543	24	18	6	NA
Achten et al [25], 2018	1877	2	2	0	2076	2	0	2	NA
Dhudasia et al [27], 2018	6090	3	2	1	5692	2	0	2	NA
Strunk et al [28], 2018	2502	1	1	0	1731	1	1	0	NA
Total, No. (%)	67 019	18	13 (72)	5 (28)	105 365	28	20 (71)	8 (29)	

Abbreviations: AB, antibiotics; EOS, early-onset sepsis; NA, not applicable.

Table 3. Cases of EOS in database studies and hypothetical management using the EOS calculator

Source	Included population	EOS cases, No.	AB <24h	AB >24h (missed)
Shakib et al [31], 2015	GA ≥34 weeks, chorioamnionitis	1	1	0
Money et al [34], 2017	GA ≥37 weeks, chorioamnionitis	1	0	1
Carola et al [35], 2018	GA ≥35 weeks, chorioamnionitis	5	3	2
Joshi et al [36], 2019	GA ≥34 weeks,	5	3	2
Total, No. (%)	NA	12	7 (58)	5 (42)

Abbreviations: AB, antibiotics; EOS, early-onset sepsis; GA, gestational age; NA, not applicable.

Strengths of our systematic review include an exhaustive search strategy, systematic data extraction and analysis following an *a priori* specified and registered protocol, and surveying of authors of included studies to ensure data completeness. It provides a synthesis of a novel tool in area of great current clinical interest and concern. Our review carries some limitations. Meta-analysis was restricted to before-after implementation studies, but included a large number of newborns. The use of 24 hour postpartum as cut-off to design a missed EOS case is arbitrary, but it reflects a common timeframe

for monitoring of at-risk newborns [3, 15, 29, 45]. Finally, due to a limited scope, this review did not investigate potential secondary benefits of the EOS calculator, such as reductions in laboratory investigations, neonatal ward admissions, or related healthcare costs [15, 26, 37, 46].

Careful interpretation of the results from this systematic review and in particular consideration to local circumstances is warranted. Included studies were unrandomized, inducing high risk of bias and limiting the quality of the evidence [47]. Studies were conducted over a time span in which adjustments to the EOS calculator were made, which may skew results from contemporary effects of the EOS calculator [3]. Furthermore, studies were predominantly performed with newborns born at 35 weeks' gestation or later, in tertiary settings, and conducted within the US. Because other settings and populations can carry differences that can possibly affect the performance of the model, this can limit the generalizability of findings in several ways.

First, the EOS calculator was derived from and validated within the setting of a US health care system, with an EOS incidence rate of 0.6 per 1000 live births, while EOS incidence rates vary across the world and setting [48, 49]. In this review, we observed very similar effects of management by the EOS calculator in studies outside of the US.[26, 35] Furthermore, baseline EOS incidence rates reported in included studies varied between 0.2 and 1.0 per 1000 live births, and selecting at-risk populations resulted in significantly higher a priori EOS risk [33]. To accommodate for this, the EOS calculator allows for a wide range in a priori sepsis risk (up to 4 cases per 1000 live births) to be used, since 2018 [50]. This allows for customization of this aspect according to setting and populations, although this feature is controversial and has thus far not been validated [50, 51].

Second, profound differences are seen in current strategies of empirical antibiotic therapy for suspected EOS. Marked differences exist among guidelines as well as between practices under the similar guidelines [1, 52, 53]. On average, around ~5% of term newborns in the US are treated with empirical antibiotics [54], while percentages vary between 2.3 and 7.9% across Europe [55, 56]. In settings with a high ratio of treated infants to confirmed EOS cases, the opportunity for a reduction using the EOS calculator is likely larger than in settings where use of antibiotics is already limited. Our finding of relatively large reductions associated with management guided EOS calculator in chorioamnionitis-exposed populations illustrates this. Although use of the EOS calculator in these populations is controversial [33, 50, 51], epidemiological data supports the safety of limited use of empirical antibiotics [55, 57]. Notably, 1 study included in this review reported an RR of 22.2% even though use of antibiotics without the EOS calculator would have been relatively low, at 1.8% [38].

Finally, significant variation is seen among strategies for testing maternal GBS status. In the US, routine GBS screening during pregnancy was implemented in 2002 [44], whereas some other countries use strategies based on risk factors [58]. However, the derivation cohort included a significant proportion of newborns born before implementation of routine maternal GBS screening [13]. As such, the EOS calculator allows for 'unknown' as

a valid value for the GBS-variable of the prediction model, allowing for a calculated EOS risk estimate even when GBS status is unavailable. In addition, the relative contribution of GBS as a predictor in the EOS calculator is only 2.3%, and therefore, changes in setting related to GBS-status will by definition have a limited impact on the model [13]. Thus, differences in maternal GBS testing strategies are unlikely to impede EOS calculator implementation.

It is important to emphasize that the EOS calculator was developed and validated using EOS defined as a positive (uncontaminated) blood culture within the first 72 hours of life [13], However, sepsis can occur even when physicians are unable to isolate a pathogen, and antenatal antibiotics may decrease the likelihood of successful pathogen isolation at birth. Critically, a consensus definition of neonatal sepsis is also lacking. Up to 16 times more often than culture-confirmed EOS, physicians label a case as 'presumed', 'suspected' or 'culture-negative' sepsis, often resulting in 5 or 7 days of intravenous antibiotics [59, 60]. Concerns regarding such cases and the EOS calculator include the theory that antenatal antibiotics may interfere with blood culture results creating false negative blood cultures, and that reducing empirical antibiotics may allow for more EOS to develop into severe disease [15, 32]. However, as we found no indications of increased EOS incidence or severity after reduction of empirical antibiotic usage in EOS calculator implementation studies, our findings correspond with the observation that concerns for false-negative blood cultures are largely based on fallacies [59, 61].

Our review shows that the results of the EOS calculator are promising and underscores the worldwide interest in applicability in clinical practice. However, use of a predictive model as an algorithm to allocate treatment strategies to newborns represents a large deviation from conventional protocols, and implementation efforts report on hesitation and concerns among current practitioners [33, 37, 62]. Ideally, implementation of a prediction model in a different setting is preceded by validation in that setting [63]. For the EOS calculator, this is impractical due to the large number of newborns needed to validate for rare outcomes like proven EOS. However, well-designed prospective studies can be used to overcome research gaps and ensure careful implementation of the EOS calculator. Before-after studies such as by Kuzniewicz et al carry an inherent risk of historical bias [15]. A multi-national cluster-randomized trial comparing conventional practices and/or guidelines to the EOS calculator however, possibly using a stepped-wedge design, would represent the ideal design to investigate the question [14, 15, 64, 65]. This would allow for randomization and comparison of results among institutions and countries, while preventing contamination of EOS calculator experience within institutions. The results of such a study can also provide feedback usable for setting-specific adjustments for the use of the EOS calculator, such as a priori EOS risk. This is likely to further improve EOS calculator use and related outcomes. Finally, future research should best evaluate the EOS calculator not isolated, but combined with methods like serial physical examinations [39, 41], and laboratory marker candidates [60, 66].

Conclusions

Our systematic review and meta-analysis demonstrate that the use of the EOS calculator is associated with a substantial reduction in empirical antibiotics for suspected EOS. Evidence regarding safety of use of the EOS calculator is limited, but we found no indication of inferiority compared to conventional management strategies. A risk of missing EOS cases or delaying antibiotics exists, but should be weighed against relatively large reductions in unnecessary empirical antibiotics. Large prospective intervention studies outside of the US, preferably cluster-randomized, will be paramount in comparing the EOS calculator to current and alternative strategies, and in implementing the EOS calculator as a tool to safely reduce unnecessary antibiotics in newborns.

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3b

Neonatal Early-Onset Sepsis Calculator and Antibiotic Therapy – Reply

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We thank Zhang, Niu, and Aghai, for their interest in our systematic review of use of the Early Onset Sepsis (EOS) calculator.

Zhang and Niu worry about study heterogeneity and publication bias. We carefully assessed all 13 included studies, and found it appropriate to meta-analyze the 6 studies reporting data before and after EOS calculator implementation with comparable settings in both epochs [1]. We grouped these studies based on their inclusion criteria; 4 studies including all newborns and 2 studies only including newborns exposed to maternal chorioamnionitis. We found no evidence of heterogeneity within studies including newborns regardless of exposure to chorioamnionitis (I^2 = 0%, Figure 2). Heterogeneity in the chorioamnionitis-exposed subgroup was transparent, because it contained only 2 studies.

Different methods to assess risk of publication bias exist. After assessment using GRADE methodology [2], we included 6 studies in the meta-analysis, whereas a rule-of-thumb requires at least 10 for meaningful funnel plots [3]. Another method involves analysis of results from non-peer-reviewed sources ('gray literature') [4]. Our search revealed 15 'gray literature' reports [1]. Five contained otherwise eligible results (data not shown). Results were largely congruent with the studies included in our systematic review, which supports a low risk of publication bias. We acknowledge that included studies are of western origin, but this likely reflects limited research on this particular topic conducted in other regions, rather than publication bias. However, this also limits generalizability of our findings and we encourage further research, especially in non-western countries.

Aghai questions why we did not include 39 EOS cases from the study by Kuzniewicz et al[5] in the meta-analysis, and that conclusion on non-inferiority of safety of the EOS calculator would be different if more cases would be included. This before-after study reported 51 EOS cases (eTable 1). Of these, 36 were included in our meta-analysis (12 post-implementation cases in the EOS calculator group, 24 pre-implementation cases in the conventional management group) (Table 2) [1]. We excluded 15 cases (not 39), because they were treated in the 'learning period' and could not be assigned to either group. No other cases were excluded. Hence, in contrast to Aghai's comment, the total of 46 included cases from all studies exceeds the number of 15 excluded cases.

Studies using hypothetical databases were not included in the meta-analysis, but included in the review [1], and their results regarding EOS cases are summarized in Table 2. We could have performed hypothetical application of the EOS calculator on the EOS cases from before-after studies. However, except the aforementioned 15 cases from the learning period of the Kuzniewicz study, these cases would then be analyzed twice and thus be overrepresented in the review. Retrospective hypothetical application of the EOS calculator indeed sometimes does not recommend antibiotics to an EOS case. However, all current risk assessment strategies are imperfect [6]. We cautiously concluded that "Available evidence regarding safety of the use of the EOS calculator is limited, but shows no indication of inferiority compared with conventional management strategies" and we do not believe Aghai's comments alter this conclusion.

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4

Risk-based Maternal Group B Streptococcus Screening Strategy is compatible with Neonatal Early Onset Sepsis Calculator Implementation

Abstract

Background

The early onset sepsis (EOS) calculator was developed and validated in a setting with routine-based Group B Streptococcus (GBS) screening.

Purpose

The aim was to evaluate to what extent a risk-based GBS screening influences management recommendations by the EOS calculator.

Methods

All newborns with a gestational age of more than 35 weeks were screened for EOS risk factors in a Dutch regional teaching hospital, which uses a risk-based GBS screening strategy. For each included infant we calculated the EOS risk at birth and we stratified newborn infants into 3 levels of risk (low: <0.65; intermediate: 0.65-1.54; high:> 1.54 per 1000 live newborns) with a corresponding recommendation on management. Thereafter, we recalculated the EOS risk and recommendation for those newborn infants in whose mothers the GBS culturing results were unavailable at time of birth.

Results

In one year, 1877 eligible births occurred and 206 infants were included. Maternal GBS status was available for 28/206 (14%) infants at birth. A definitive GBS status was later available for 162/206 (79%) newborn infants. Median EOS risk was slightly lower after definitive GBS status (0.41 vs 0.46 per 1000 live births, P=0.004). In 199/206 (97%) of newborn infants, the EOS calculator recommendation remained unchanged after the mostly unknown GBS results at birth were updated to the definitive GBS status later. Use of the GBS status, as known at time of birth, did not withhold antibiotic treatment in any newborn infant compared to use of the definitive GBS status.

Conclusions

The use of risk-based GBS screening is compatible with implementation of the EOS calculator. Larger studies are needed to address the best way of combining GBS screening with use of the EOS calculator.

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Accepted for publication

Introduction

Maternal colonisation with Group B Streptococcus (GBS) is a risk factor for neonatal sepsis, as vertical transmission in utero or during labour can result in a life-threatening early-onset sepsis (EOS) in the newborn infant [1]. In the United States, GBS colonisation is therefore extensively determined among pregnant women, with screening rates at 85% or higher [2]. This universal routine-based screening strategy contrasts with the heterogeneous practice worldwide. For example, in Europe various guidelines advocate risk-based GBS screening depending on obstetric history [3–6], whereas in Korea guidelines for the screening of pregnant women for GBS still need to be established [7, 8]. A recent study found a GBS colonization rate of 11.6% among pregnant Korean women and recommended GBS screening and the administration of intrapartum antibiotic prophylaxis in pregnant Korean women [8]. The status of maternal vaginal or rectal GBS colonisation needs to be available in labour to allow timely administration of intrapartum antibiotic prophylaxis (IAP) to prevent EOS [3]. Partly attributed to IAP, a decline in the incidence of EOS to less than 0.5 in 1000 live births has been observed among term infants [9]. However, the reported number of infants receiving empiric antibiotic therapy for suspected EOS is much higher [10].

To improve the accuracy of empirical antibiotic administration in newborn infants at risk for EOS, the neonatal EOS calculator was designed and validated in the United States. It has proven to be effective in limiting antibiotic treatment in suspected EOS in term and near-term infants without apparent adverse effects [11–16]. The sepsis calculator uses maternal GBS status at birth as one of five maternal risk factors. The EOS calculator allows 'positive', 'negative' and 'unknown' as input for maternal GBS status in the algorithm. In contrast to a routine-based GBS screening, risk-based GBS screening carries the possibility that maternal GBS colonisation information is unavailable at time of birth. Often, the GBS culture results become later available after birth. As the EOS calculator is being evaluated for implementation in European and Asian practice, it is important to know whether implementation is compatible with risk-based GBS screening.

The aim of this study was to evaluate to what extent a risk-based GBS screening influences management recommendations by the EOS calculator. If our results indicate that antibiotic recommendation are not influenced by this strategy then the sepsis calculator may also be implemented in countries with a risk-based GBS screening policy.

Methods

Study population

We used data from our EOS calculator implementation study in a Dutch regional teaching hospital (Tergooi hospital) [16]. Briefly, we prospectively screened during a single year (April 2016 through March 2017) all newborn infants born at a gestational age of 35 weeks or more, for risk factors or clinical signs of EOS. EOS risk factors included prematurity, maternal fever (≥ 38°C), positive maternal GBS status, rupture of membranes for more

than 24 hours before birth, and presumed chorioamnionitis with or without IAP. Newborn infants were included if either one or more maternal risk factors for EOS and/or clinical signs of EOS were present. All data regarding maternal risk factors and the results of the physical examination of the newborn infant were collected through a case report form by the attending physician. Exclusion criteria were birth outside Tergooi hospital. This study was approved by the Scientific Review Committee of Tergooi Hospitals (study number 15.58; letter reference kV/15.69).

GBS screening protocol

According to Dutch national guidelines, maternal GBS screening was performed depending on obstetric history (risk-based GBS screening). Screening was performed in case of prematurity, defined as a gestational age less than 37 weeks, rupture of membranes for more than 18 hours, maternal fever higher than 38°C during delivery, or a history of

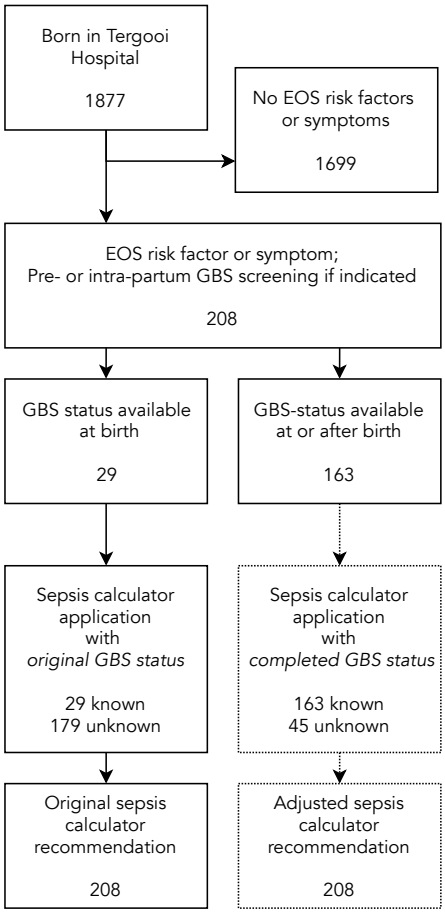

Figure 1. Study design and inclusions. Numbers denote the number of newborns for each step.

a previous child with GBS-related disease [17]. The Dutch guidelines advise IAP in case of a GBS positive urine culture to prevent GBS-disease [5].

EOS calculator

The EOS calculator is a multivariate risk assessment based on 5 maternal objective risk factors and the newborn infant's clinical condition to estimate each infant's risk of EOS. The 5 maternal risk factors are gestational age, duration of rupture of membranes, highest intrapartum maternal temperature, use of intrapartum antibiotics (considered adequate prophylaxis if administered more than 4 hours before birth), and maternal GBS-status. The EOS calculator allows 'positive', 'negative' and 'unknown' as input for maternal GBS status in the algorithm. We used 'unknown' in cases where GBS test results were unavailable at time of EOS calculator application. To assess the clinical condition attending physicians were trained to define the newborn infant's clinical appearance status ('well-appearing', 'equivocal exam', or 'clinical illness') according to definitions published along with the EOS calculator [18, 19]. For each included infant we calculated the EOS risk at birth, using a prior EOS probability of 0.6 per 1000 livebirths, and we stratified newborn infants into 3 levels of risk (low: <0.65; intermediate: 0.65-1.54; high:> 1.54 per 1000 live newborns) with a corresponding recommendation on management. This recommendation consisted of standard care, monitoring of vital signs every 3 hours, or the start of empirical antibiotic therapy, respectively.

Data analysis

For this study, we retrospectively collected the results of all maternal blood, urine, genital and anorectal cultures performed at any time during pregnancy or delivery. We calculated EOS risk and recommendation for each included newborn infant after birth (Figure 1). We recalculated the EOS risk and recommendation for those newborn infants in whose mothers the GBS culturing results were unavailable at time of birth. This was defined as definitive GBS status. We compared EOS risk and recommendation at birth and after completing the definitive GBS status. We used Wilcoxon's Signed Rank test with an alpha-level set at $p<0.05$ to determine statistical significance. Data were analyzed using SPSS 25 (Chicago, IL).

Results

Patients

During the study period, 1877 eligible births occurred. Among these, 208 newborn infants fulfilled the inclusion criteria and 206 had sufficient data to be included in the analysis. Inclusion was due to the presence of one or more maternal risk factors in 183/206 (89%), the presence of clinical symptoms in the newborn infant in 13/206 (6%), or a combination of both in 11/206 (5%). Newborn infants were predominantly male (57%), median gestational age was 39 weeks (interquartile range 37-40 weeks).

Maternal GBS status was available for 28/206 (14%) of included newborn infants at birth, mainly from cultures performed during pregnancy (original GBS status). A final GBS status was determined for 162/206 (79%) newborn infants (Table 1). Twelve of these included a positive urine culture, of which 6 (50%) were adequately treated with intrapartum antibiotics.

GBS status and EOS calculator results

We compared EOS risk and recommendation as generated by the EOS calculator at birth and after completing a definitive GBS status (Table 1). Median EOS risk was slightly lower using the definitive GBS status (0.41 vs 0.46 per 1000 live births, P=0.004). EOS calculator recommendation changed in 7/206 (3%) of newborn infants. Three were assigned a recommendation for clinical observation using vital signs, instead of 'no additional care'; this was the opposite for another 3 infants. Use of the definitive GBS status did not lead to additional recommendations for empirical antibiotic therapy; in 1 case the recommendation changed from antibiotic treatment to clinical observation (Figure 2).

Discussion

As use of the EOS calculator spreads to areas without universal screening for GBS, it is important to consider how use of other screening strategies may impact recommendations by the EOS calculator. In particular, it is important to address whether the lack of universal GBS screening may lead to fewer recommendations of antibiotic therapy. We found that in 97% of newborn infants at risk for EOS in a single Dutch centre, the EOS calculator recommendation remained unchanged after we recalculated the EOS risk using the definitive

Table 1. GBS test results and EOS calculator results in newborns before and after completing maternal GBS status

GBS status and EOS calculator results		Original GBS status (N=206)	Final GBS status (N=206)	P-value
GBS status	Positive	19	33	N/A
	Negative	9	129	
	Unknown	178	44	
EOS risk, median (IQR)		0.46 (0.19–0.89)	0.41 (0.17–0.85)	0.004
Recommendation	NAC	141	142	0.655
	Vitals every 3 hours	38	37	
	Start empiric antibiotics	27	27	

IQR; interquartile range; NAC: no additional care; N/A: not applicable.

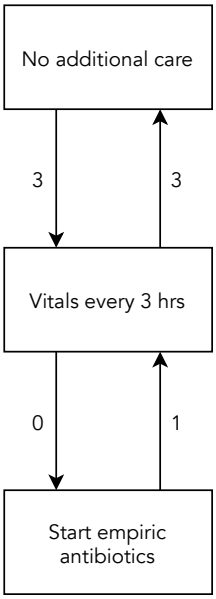

Figure 2. EOS calculator recommendation changes resulting from definitive GBS information Changes in EOS calculator recommendation after adjusting for definitive GBS carrier information, which was not available at birth when using risk-based GBS screening. Numbers denote each number of newborns for related category change.

GBS results, which were not yet available at birth. Median EOS-risk was slightly lower after recalculation using the definitive GBS screening results. Most importantly, additional knowledge on the GBS status did not increase the total number of recommendations for antibiotic treatment in newborn infants with a GBS positive mother. In other words, the risk-based screening method did not withhold antibiotic treatment in infants at risk for EOS. These observations together indicate that use of a risk-based screening method only marginally influences EOS calculator management recommendations.

These findings correspond with the modest contribution of the GBS status as a risk factor to the total predictive value in the multivariate EOS calculator model [19]. They are further explained by the finding that definitive GBS results were mostly negative, thus decreasing EOS risk. In our study population, GBS-status was available at birth in only few cases, whereas a definitive GBS status was determined in the vast majority of cases. This indicates that GBS screening shortly prior to birth is common with a risk-based screening strategy, limiting the opportunity to timely administer IAP. A definitive GBS status was not determined in the remaining fifth of our study population, most likely because of absence of indications for testing in obstetric history. Importantly, a substantial part of GBS-related EOS disease occurs despite negative GBS status,[20] reflecting that other factors and clinical signs should be taken into account at all times.

Maternal GBS status can mediate the calculated EOS risk and management guided by the EOS calculator indirectly through IAP, which is widely used to decrease GBS-related EOS [21]. Notable differences across guidelines and in practice exist, [5, 22], but Dutch guidelines recommend IAP in case of a positive urine culture [5]. We found that in our population only 6% of tested mothers qualified for IAP as a result of a GBS-positive urine culture. Only half of these mothers received adequate intrapartum antibiotics, possibly due to late availability of results of maternal GBS screening.

As use of the EOS calculator spreads to areas with various approaches regarding prevention of GBS neonatal sepsis, this development should be accompanied with thoughtful evaluation of GBS screening strategies. Our findings indicate that use of risk-based GBS screening only marginally impacts EOS calculator antibiotic management recommendation in the newborn infant. However, GBS screening strategies may be most – if not only – helpful when results are provided timely enough for administration of IAP and for use in the EOS calculator. The new generation of rapid intrapartum tests based on polymerase-chain-reactions is a promising opportunity in this matter [23, 24]. Rapid availability of results will be more suitable for guiding decisions on timely IAP and for direct use in the EOS calculator at birth.

Among the strengths of our study is its thorough data collection on maternal GBS status. Also, to our knowledge, this is the first study to evaluate the important difference in GBS screening strategies in the context of the increasingly adopted EOS calculator. Limitations include the single-centre study design, which means that results may be different in settings with different risk-based screening strategies. It was conducted in a high-risk population subset with limited sample size, selected on presence of maternal EOS risk factors or neonatal clinical EOS symptoms. The results therefore cannot be generalized to the general newborn infant population without precautions. However, the remaining population of the newborn infants in our hospital had no known EOS risk factors or clinical EOS symptoms. It is therefore at low risk for EOS, and thus unlikely to receive an EOS calculator recommendation for empiric antibiotic therapy, irrespective of maternal GBS status. Hence, we are confident that our design included the vast majority of relevant births where GBS status could have a significant role in decisions regarding empiric antibiotic therapy, making the results indicative for the larger population. Finally, although these results are supportive of the applicability of the EOS calculator in settings with a risk-based screening strategy, this study does not validate the EOS calculator itself for such settings.

Conclusion

We found very similar results in management recommendations by the EOS calculator when using a risk-based GBS screening method compared with a routine-based GBS screening scenario. This indicates that use of risk-based GBS screening is compatible with use of the EOS calculator. Larger studies are needed to address the best way of combining GBS screening with use of the EOS calculator.

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Disclosure of interest

The authors report no conflict of interest.

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5

Early Onset Sepsis Calculator Implementation is associated with Reduced Health Care Utilization and Financial Costs in Late Preterm and Term Newborns

Abstract

The neonatal early onset sepsis (EOS) calculator is a novel tool for antibiotic stewardship in newborns, associated with a reduction of empiric antibiotic treatment for suspected EOS. We studied if implementation of the EOS calculator results in less health care utilization and lower financial costs of suspected EOS. For this, we compared two single-year cohorts of hospitalizations within 3 days after birth in a Dutch non-academic teaching hospital; before and after implementation of the EOS calculator. All admitted newborns born at or after 35 weeks of gestation were eligible for inclusion. We analyzed data from 881 newborns pre-implementation and 827 newborns post-implementation. We found significant reductions in EOS-related laboratory tests performed and antibiotic days, associated with implementation of the EOS calculator. Mean length of hospital stay was shorter and EOS-related financial costs were lower after implementation among term, but not among preterm newborns.

Conclusion

In addition to the well-known positive impact on antibiotic stewardship, implementation of the EOS calculator is also clearly associated with reductions in healthcare utilization related to suspected EOS in late preterm and term newborns, and with a reduction in associated financial costs among those born term.

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Introduction

The neonatal early onset sepsis (EOS) calculator is a novel tool for antibiotic stewardship in newborns [1]. The EOS calculator estimates the EOS risk based on five maternal and four neonatal objective clinical risk factors. It stratifies newborns into 3 levels of risk with corresponding recommendations for management: (1) no additional care, (2) obtaining a blood culture and monitor vital signs for at least 24 hours, or (3) start treatment with empiric antibiotic therapy after obtaining a blood culture [1, 2]. This approach is associated with a reduction of empiric antibiotic treatment for suspected EOS between 41 and 45% compared with conventional strategies [2–4].

Studies evaluating the EOS calculator have provided evidence of secondary benefits associated with EOS calculator implementation, such as reductions in the number of laboratory tests and blood cultures taken [2], and the rate of admissions to neonatal intensive care [5, 6]. These findings, together with the reduction in empiric antibiotic treatment, suggest that use of the EOS calculator may lead to a reduction in overall health care utilization and associated health care costs. This hypothesis is further supported by a recent theoretical cost-benefit analysis, which estimated a net monetary benefit of $3998 per infant with a 60% likelihood of net benefit in a United States setting [7]. To our knowledge, despite signs of significant uptake [8], and multiple reports on adoption of the EOS calculator [3, 9, 10], no real-world evidence of the effect of EOS calculator use on financial costs associated with health care for suspected EOS has been published.

We conducted a retrospective before-after analysis in a Dutch non-academic teaching hospital [3], to compare health care use and associated costs of suspected EOS before and after implementation of the EOS calculator. As we demonstrate a reduction of 44% in the empiric use of antibiotics [3], we hypothesize a significant reduction in health care utilization and overall financial costs in the post-implementation cohort versus the cohort before implementation.

Methods

Study setting, design and patients

This single-centre before-after EOS calculator implementation study was conducted in a Dutch non-academic teaching hospital with a mother-child unit and a neonatal ward. The hospital provides care up to Level II special care for stable or moderately ill newborns,[11] and admits newborns for various reasons. Our study compared two single-year birth cohorts. We screened all newborns born in our hospital from January 1, 2014 through December 31, 2014 (pre-implementation cohort), and from April 1, 2016 through March 31, 2017 (post-implementation cohort) (Figure 1). We evaluated all births at or after 35 weeks of gestation and included newborns admitted for pediatric care within 3 days after birth. The current study is a post-hoc analysis of our implementation study, which focused on the rate of empiric antibiotic treatment in the entire birth cohort [3]. For the current analysis, we focused on admitted newborns, because it is the population susceptible to EOS care utilization and associated costs.

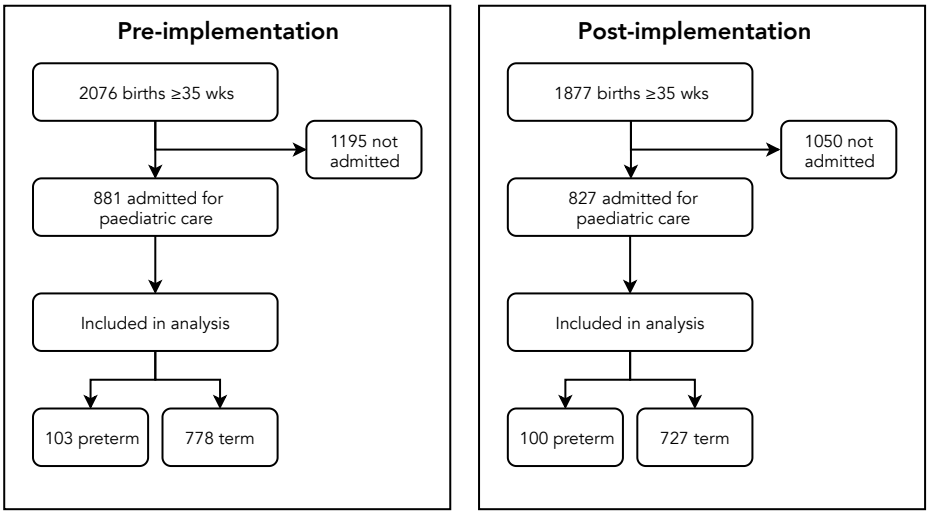

Figure 1. Flowchart of study inclusion process.

Clinical practice before and after implementation of the sepsis calculator

Before implementation, newborns born at our hospital were screened for maternal risk factors and clinical symptoms by the attending staff from the mother-child unit. Maternal EOS risk factors warranting pediatric evaluation included prolonged rupture of membranes (more than 18 hours), maternal fever (38°C or higher), prematurity, and positive maternal GBS status. Newborns requiring evaluation or care by pediatric staff for any reason were admitted for hospital care, either at the mother-child unit or neonatal ward. Newborns not admitted for hospital care, accompanied mother in the mother-child unit or were discharged home.

Before implementation, a newborn at risk for EOS was assigned observation on vital signs, or treatment with empiric antibiotics. This arbitrary decision was made by the attending physician, based on the combination of maternal EOS risk factors, physical examination and/or results of complete blood count (CBC) and C-Reactive Protein (CRP). Within the study population, prematurity was defined as birth at 35 to 37 weeks' gestation. If born between 35 weeks and 35 weeks and 6 days of gestation, newborns were always admitted to the neonatal ward. Without other risk factors or clinical symptoms, prematurity alone was not a reason to start empiric antibiotic treatment per se. If default empiric antibiotic therapy was started, it consisted of intravenous gentamicin and amoxicillin, followed by intravenous amoxicillin/clavulanic acid after 72 hours if not discontinued. Before the start of antibiotic treatment, blood was drawn for a CBC, CRP, and blood culture. A gentamicin serum concentration was determined, and repeated if necessary. CBC and CRP were repeated after 48-72 hours of antibiotic treatment. In case of a negative blood culture after three days of treatment, antibiotic treatment was either stopped, or continued for clinical reasons, per discretion of the attending physician. In case of a positive blood

culture, antibiotic treatment was continued for at least 7 days from start. If continued despite a negative culture, treatment was continued for 7 days.

After implementation of the EOS calculator, each birth was screened for maternal EOS risk factors and clinical symptoms, as before implementation. In case of 1 or more maternal EOS risk factors, or if the newborn showed any clinical signs of EOS, prompt clinical evaluation of the newborn followed, using the EOS calculator. Based on the EOS risk calculation, in our hospital two options were possible; either start empiric antibiotics at the neonatal ward or perform routine control of vital parameters every 3 hours at the maternal-child or neonatal ward for at least 24 hours. The EOS sepsis calculator recommendation obtaining a blood culture without starting antibiotic treatment was incongruent with our practice and this recommendation was therefore followed by the second option. In case of antibiotic treatment, treatment protocol was equal to before implementation, as described above. Treating physicians were free to deviate from the recommendation by the calculator.

Data collection and outcomes

Data were obtained electronically from the clinical, pharmaceutical and financial hospital registration and billing systems. For the first outcome, EOS-related health care utilization, we included three groups of clinical outcomes; outcomes related to hospital length of stay, outcomes related to relevant laboratory tests (blood cultures; complete or partial blood counts; CRP; gentamicin serum concentration), and outcomes regarding (empiric) antibiotic treatment for EOS (start of antibiotic treatment, number of antibiotic days). For the second outcome, defined as financial costs related to EOS health care, we retrieved for each group of clinical outcomes the related costs from the hospital billing administration, and calculated the combined financial cost. Costs associated with EOS-related antibiotics were calculated using costs for antibiotics in the protocol for suspected EOS described above. Because in-house billing costs were not different between the mother-child unit and the neonatal ward, these costs were not separated. To insulate our analysis from temporal cost changes during the study timeframe, we used 2017 in-house billing costs throughout analysis for both cohorts. Costs in this study represent actual cost of care, rather than final billing charges.

Statistical Analysis

Data from newborns hospitalized before implementation were compared with data from newborns hospitalized after implementation. Subgroup analyses were performed for term and preterm newborns. We also compared newborns with and without antibiotic treatment. Categorical variables were reported as (relative) frequencies with and compared with Chi-square analysis. Continuous variables were reported as means with standard deviation (SD) to provide meaningful outcome measures, and compared using Welch two-sample t-test, which is appropriate for skewed distributions[12–14]. All analyses were performed using R version 3.5.2 (R Foundation, Vienna, Austria).

Results

Inclusions

The year after implementation involved 1877 births at or after 35 weeks of gestation of which 827 (44.1%) were admitted for pediatric care in the first three days after birth, compared with 2076 births and 881 (42.4%) admissions before implementation. All admitted newborns were included in the analysis. Fifty of 827 (6.0%) admitted newborns were started on empiric antibiotics for suspected EOS after implementation, compared with 100 of 881 (11.4%) before implementation (P<0.001). The rate of prematurity was comparable in both cohorts (12.1% after versus 11.7% before implementation, P=0.798).

EOS healthcare utilization

Healthcare utilization was assessed for three clinical outcome groups (Table 1 and Figure 1). Mean length of stay did not differ significantly between the two cohorts in the overall study sample, but was 0.37 days shorter after implementation among term newborns specifically, (P=0.005). We found a significant reduction in mean number of EOS-related laboratory tests per newborn after implementation (P<0.001, Table 1), including fewer blood cultures, blood counts, CRP, and gentamicin serum concentration tests (P≤0.001). Use of antibiotic treatment was significantly lower after implementation (number of antibiotic days, P=0.009). Start of empiric antibiotics in at-risk newborns, independent of implementation, was associated with significant more EOS healthcare utilization (Table 2).

EOS care financial costs

Mean costs related to length of stay did not differ significantly between cohorts in the overall population, but were significantly lower after implementation in the subpopulation of term newborns (Table 1 and Figure 2). Mean costs associated with EOS related laboratory tests and use of empiric antibiotics were significantly lower after implementation (36.8€ vs 24.9€; P<0.001 and 1.54€ vs 0.96€; P=0.008, respectively). Mean combined cost associated with

EOS-related care per included newborn did not differ between cohorts in the overall population, but were significantly lower after implementation among term newborns specifically (2248€ vs 2041€; P=0.020). Combined mean costs were dominated by costs related to length of stay, which accounted for 98.5% of combined costs after implementation and 99.0% before implementation.

A total of four culture-confirmed EOS cases occurred during the study period; two before and two after implementation. The mean combined costs associated with EOS related care for these cases were €7415 per newborn. Culture-confirmed EOS represented 0.7% of total cost associated with EOS related care in the entire study period.

Table 1. EOS healthcare utilization and associated costs before and after EOS calculator implementation

	Before implementation N, group / N, total (%)	After implementation N, group / N, total (%)	P*
Overall	881 (100.0)	827 (100.0)	
Term newborns	778 (88.3)	727 (87.9)	0.798
Preterm newborns	103 (11.7)	100 (12.1)	
Healthcare utilization related to suspected EOS			
Empiric antibiotics			
Overall	100/881 (11.4)	50/827(6.0)	<0.001
Term newborns	85/778 (10.9)	46/727 (6.3)	0.001
Preterm newborns	15/103 (14.6)	4/100 (4.0)	0.009
	Mean (SD)	Mean (SD)	
Length of stay in days			
Overall	3.48 (4.16)	3.27 (3.78)	0.281
Term newborns	2.95 (2.97)	2.58 (1.96)	0.005
Preterm newborns	7.48 (7.98)	8.27 (7.88)	0.475
EOS-related laboratory tests			
Overall	2.34 (4.77)	1.63 (3.62)	<0.001
Term newborns	2.08 (4.28)	1.42 (3.42)	<0.001
Preterm newborns	4.32 (7.24)	3.16 (4.57)	0.173
Antibiotic days for suspected EOS			
Overall	0.57 (1.84)	0.36 (1.47)	0.009
Term newborns	0.57 (1.85)	0.37 (1.85)	0.023
Preterm newborns	0.55 (1.77)	0.24 (1.23)	0.144
Financial costs related to suspected EOS			
Costs associated with length of stay, in €			
Overall	2614 (3034)	2516 (2737)	0.481
Term newborns	2215 (2141)	2019 (1444)	0.036
Preterm newborns	5629 (5842)	6128 (5676)	0.537
Costs associated with EOS-related laboratory tests, in €			
Overall	36.8 (89.5)	24.9 (59.2)	<0.001
Term newborns	31.4 (75.6)	21.0 (54.7)	0.002
Preterm newborns	77.7 (154)	52.7 (79.8)	0.147
Cost associated with antibiotic treatment, in €			
Overall	1.54 (5.13)	0.96 (3.99)	0.008
Term newborns	1.56 (5.17)	1.00 (4.08)	0.020
Preterm newborns	1.45 (4.80)	0.64 (3.23)	0.164
Combined costs, in €			
Overall	2653 (3092)	2542 (2772)	0.434
Term newborns	2248 (2190)	2041 (1480)	0.020
Preterm newborns	5708 (5940)	6181 (5731)	0.564

* Welch two-sample t-test

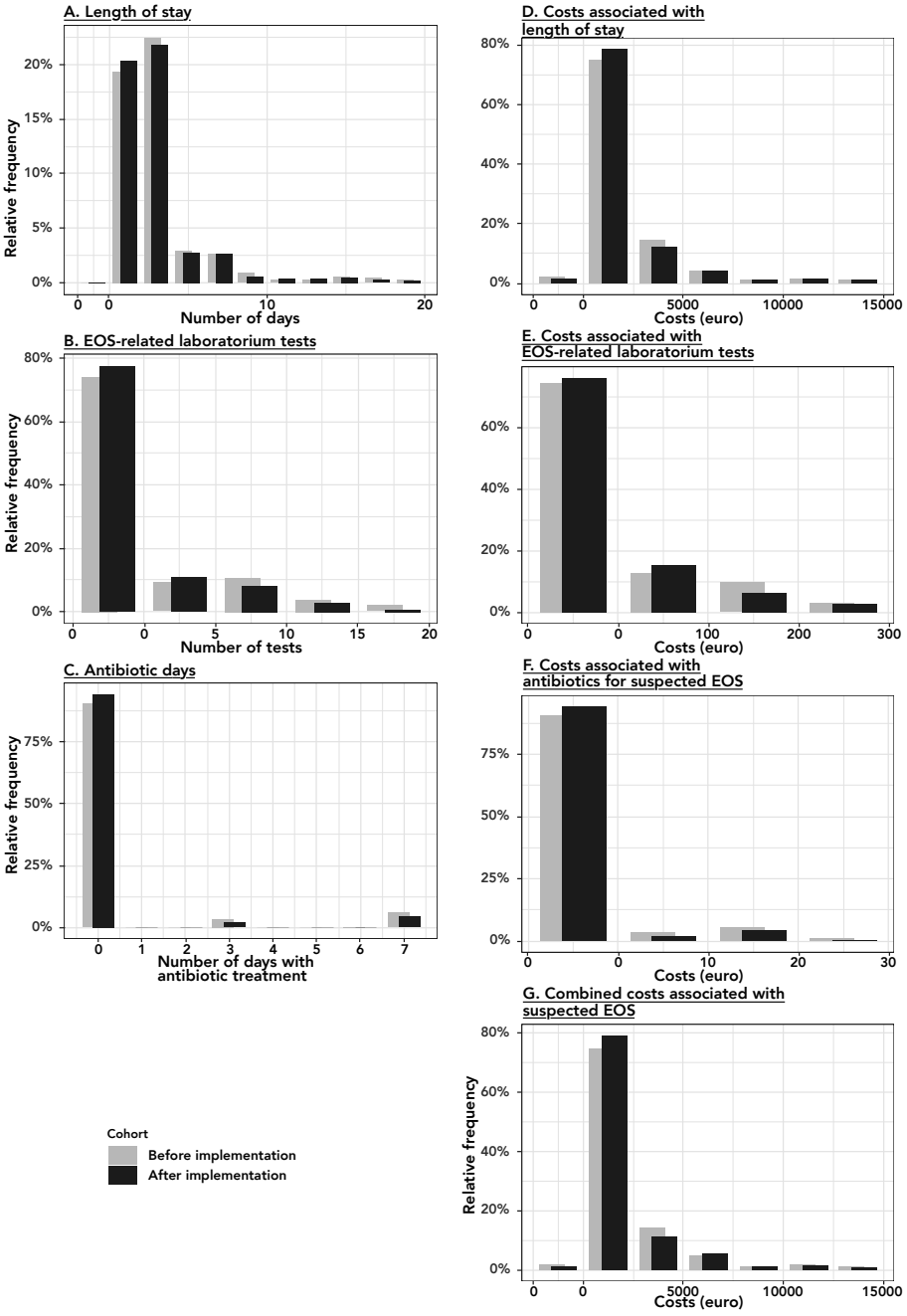

Figure 2. EOS-related health care utilization and associated costs before and after implementation of the EOS calculator. Distributions of the frequencies of clinical outcomes (panels A, B, and C) and associated costs (panels D through G), for cohorts before and after implementation. Frequency of zero as a value displayed as the first bin in continuous variables (panels A, B, and D through G). Outliers omitted from panels (A, n=23; B, n=9; C, n=3; D, n=20; E, n=25, F, n=1; G, n=24) for optical clarity; no outliers were removed from analysis.

Table 2. EOS care utilization and associated costs in at-risk newborns with or without empirical antibiotics for suspected EOS

	Treated with AB (n=150) Mean (SD)	Not treated with AB (n=1558) Mean (SD)	P*
Length of stay, in days	7.37 (4.88)	2.99 (3.66)	<0.001
Number of EOS related laboratory tests	11.2 (4.71)	1.11 (2.99)	<0.001
No. of days with AB for suspected EOS	5.29 (2.54)	0.00 (0.00)	<0.001
Costs associated with duration of hospital stay	5492 (3587)	2285 (2655)	<0.001
Costs associated with EOS related laboratory tests	194 (117)	15.3 (47.9)	<0.001
Cost associated with antibiotic treatment for suspected EOS	14.3 (7.46)	0.00 (0.00)	<0.001
Combined costs	5700 (3639)	2300 (2684)	<0.001

* Welch two-sample t-test

Discussion

This before-after study evaluated the effect of implementation of the EOS calculator on EOS related health care utilization and the related financial costs in late preterm and term newborns. Implementation of the EOS calculator was associated with a significant reduction in laboratory investigations for suspected EOS and lower costs associated with these tests. In addition, we found that significant reductions in length of stay or overall EOS-related hospital costs associated with implementation of the EOS calculator were limited to the term newborn population.

Implementation of the EOS calculator was associated with fewer antibiotic days. Fewer newborns were started on antibiotics, but the duration of an antibiotic course was similar after implementation [3]. Therefore, observation of fewer antibiotic days is most likely due to fewer cases of 'rule out sepsis' rather than fewer extended courses of antibiotics. Because each instant of blood collection and insertion of peripheral catheter for administration of antibiotics entails a painful procedure and a risk of infection, the reductions and antibiotic days and EOS-related laboratory tests imply a reduction in clinical burden and hazards. This effect may be emphasized downstream, as investigations like repeated CRP for suspected EOS lead to further investigations and longer treatment [15].

Our study shows that length of stay is the primary driver for costs in this at-risk population, and that newborns treated with antibiotics have more than two-fold higher EOS-related costs than those not treated (Table 2). Despite a clear reduction in antibiotic treatment in both term and preterm newborns after EOS calculator implementation,

reductions in length of stay and costs after EOS calculator implementation, were limited to term newborns. We suggest two explanations for the lack of clear reductions in length of stay of preterm newborns. First, the number of preterm newborns was relatively small, limiting statistical power to detect reductions in length of stay in this subgroup. Second, both prematurity in itself and related neonatal problems such as feeding difficulties warrant hospital stay, regardless of the decision to treat for EOS.

Our findings of reduced economic costs in term newborns align with a recent theoretical study by Gong et al, predicting significant costs reductions due to EOS calculator implementation [7]. For acute medical care, the model by Gong et al predicted estimated cost savings of 1930$, equaling a relative reduction of 52%. Mean cost reduction for term newborns in our study was significantly smaller, at 207€ or a relative reduction of 9%. This may be explained by several factors. First, Gong et al used a fictious relative reduction of 67% in empiric antibiotic treatment by implementation of the EOS calculator, which is significantly above real-world evidence in the literature [4]. Second, the predicted cost savings were based on American health care costs, which are relatively high compared with European countries [16]. Finally, earlier studies reporting significant reductions in hospitalizations and other secondary benefits were performed in populations with relative high rates of neonatal ward hospitalization among well-appearing newborns and use of blood cultures without start of empiric antibiotic treatment [2]. Both of these practices are uncommon in European settings, including ours [17–19].

Strengths of this novel study include the use of robust data from electronic hospital registration systems for clinical and economical outcomes and for an unbiased determination of eligibility of patients. We included data from all admitted newborns to avoid selection bias when selecting at-risk newborns. Because EOS calculator was applied only when a newborn was considered at-risk based on maternal risk factors or clinical symptoms, this means our results may underestimate cost reductions on the patient level associated with the EOS calculator. Although the study is inherently limited by its retrospective and temporal nature, our results are corrected for temporal cost changes and data were available for all included newborns. Finally, our study used real-world billing costs for cost calculations, specific for our center. Different applicable costs in other centers and countries will impact the size of cost reductions associated with EOS calculator implementation.

To our knowledge, this is the first study to evaluate the effects of implementation of the EOS calculator on health care utilization and financial costs using non-hypothetical data from implementing the calculator in daily clinical practice. Its findings suggest that the benefits of the EOS calculator are predominantly clinical, including decreased unnecessary treatment and fewer laboratory tests. In addition, we found significant reductions in duration of hospital admission and economic costs for term newborns at risk for EOS, further reducing the burden of suspected EOS. The economic benefits will depend on health care tariffs and clinical protocols of a particular settings. However,

the clinical benefits may very well justify implementation of the EOS calculator, even if economic benefits are modest.

Conclusion

In addition to the well-known positive impact on antibiotic stewardship, implementation of the EOS calculator is also clearly associated with reductions in the healthcare utilization related to suspected EOS in late preterm and term newborns, and with a reduction in associated financial costs among those born term.

Compliance with ethical standards

Funding

No funding was provided for this study. There were no sponsors involved in this study.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors. This study was approved by the Scientific Review Committee of Tergooi Hospitals (study number 15.58; letter reference kV/15.69).

Informed consent

Informed consent by patients and caregivers was not required.

Authors contribution

NBA and FBP designed the study. All authors helped to draft the manuscript. All authors read and approved the final manuscript.

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6

Technical Assessment of the Neonatal Early-Onset Sepsis Risk Calculator

Abstract

The Neonatal Sepsis Risk Calculator developed by Kaiser Permanente Northern California is coming into increasing use for management of late preterm and term newborn infants at risk for early-onset sepsis. The Calculator is based on a robust logistic regression model that provides quantitative individualized estimates of early-onset sepsis risk. Low sensitivity for prediction of sepsis at birth demonstrates that traditional perinatal risk factors alone are insufficient for ascertainment of early-onset neonatal sepsis. Performance is enhanced by addition of physical examination findings at birth, but the sensitivity of combined findings remains limited. The current implementation of the Calculator integrates risk factors and examination findings. A methodological error in adapting the regression for application in the population (rather than the development sample) and several subsequent modifications compromise accuracy of quantitative predictions of absolute sepsis risk, but are not likely to seriously undermine the utility of the Calculator for risk stratification. While the Calculator has served as an instrument of change away from previously recommended categorical risk ascertainment strategies, and its implementation reduces diagnostic testing and empiric antibiotic treatment without apparent ill effects, it should not be relied upon for accurate estimates of individual absolute risk of early-onset sepsis in newborn infants.

William E. Benitz, Niek B. Achten

In revision

Introduction

Over the past half-decade, the Neonatal Early-Onset Sepsis Calculator provided by the Kaiser Permanente Division of Research [1] has come into increasing use [2]. Endorsement of management strategies based on individualized risk estimation for late-preterm and term neonates at risk for early-onset sepsis (EOS) in recent *Clinical Reports* from the American Academy of Pediatrics [3,4] may accelerate further adoption. As with any diagnostic tool, users should understand what it does, its limitations, and its results. The foundation of the Calculator is a quantitative risk estimation model, but it incorporates other components (Figure 1). We undertook this technical assessment to evaluate the contributions of each component and of modifications introduced in the fully implemented online Calculator [2].

The Risk Factor-Based Logistic Regression Model

In response to concerns that previously recommended strategies [5] resulted in treatment of too many uninfected neonates [6], Puopolo and colleagues re-evaluated strategies for identifying infants at high risk for EOS [7]. Drawing upon data from 608,014 neonates born at two Boston hospitals and 12 Kaiser Permanente Northern California (KPNC) hospitals between 1993 and 2007, a data set consisting of all 350 observed EOS cases and 1063 randomly chosen controls was assembled.

For this analysis, EOS was defined "a positive blood or cerebrospinal fluid culture result for a pathogenic bacteria obtained before 72 hours of age"; nonpathogenic species (e.g., coagulase-negative *Staphylococcus*) were excluded unless antibiotic treatment was provided for ≥ 5 days or until neonatal death. This definition of EOS has the advantages of simplicity, clarity, and objectivity, but may lead to either over- or underestimation of the rate of serious bacterial infection in the first 3 days after birth. For example, nearly one-third of the EOS cases in the development set (113 of 350) did not meet criteria for designation as "clinically ill" for at least 12 hours after birth [8]. In a more recent report from the KPNC system, 9 of 51 neonates with positive blood cultures were treated only in response to the positive culture and either never had clinical signs of illness (6) or had a negative blood culture before treatment (4, including all 3 with signs of illness); none had a positive follow-up culture [9]. Six additional cases received early empirical treatment and never had clinical signs of illness. Many (or all) of these infants may have had transient bacteremia [9,10] and might have done well without diagnostic testing or antibiotic treatment. These observations suggest that 20-30% of neonates with early positive blood cultures may have transient bacteremia, potentially leading to overestimation of sepsis risk by the regression model. On the other hand, some neonates with early serious bacterial infection are not bacteremic [11-13]. Blood cultures as routinely performed may be insensitive (particularly if an inadequate volume of blood is cultured) [14] and may underestimate the risk of bacterial infection. These uncertainties reflect the difficult nosology of neonatal sepsis [15-17], for which a positive blood culture is hitherto the best available proxy. Because

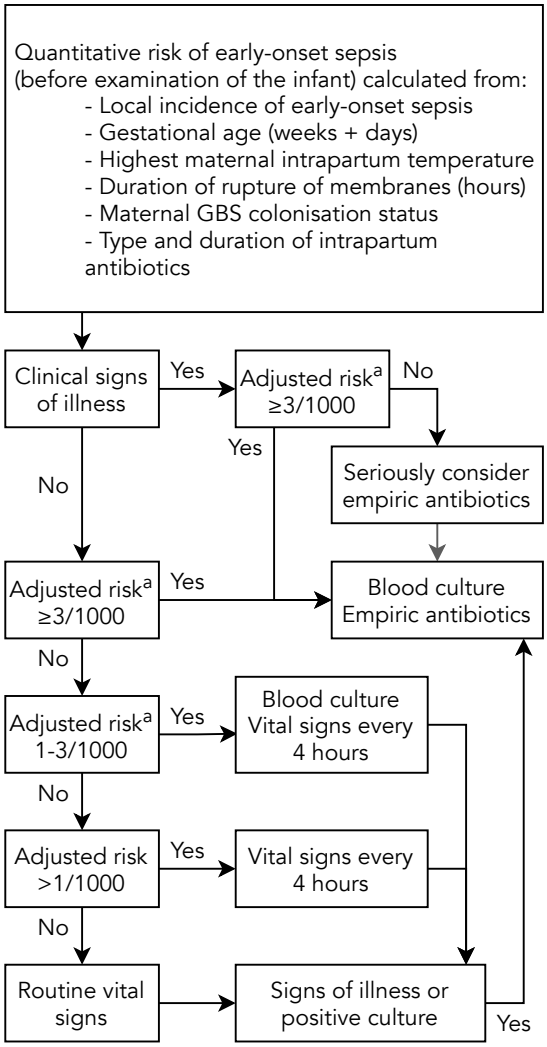

Figure 1. Decision diagram for Early-Onset Sepsis Calculator. Dimmed arrow indicates progression suggested but not mandated by algorithm. [a] Clinical signs as defined in Kuzniewicz et al [2]. [b] Adjusted risk after incorporation of examination findings [2].

the analysis focused on prediction of culture-confirmed bacteremia or meningitis, there is unavoidable uncertainty with respect to inferred rates of bacterial infection requiring treatment.

In the development sample, individual traditional risk factors (maternal fever, duration of rupture of membranes, intrapartum antibiotic use) were poor predictors of neonatal bacteremia [7]. The best of these, highest intrapartum temperature > 100.4°F, observed in nearly 5% of the population, identified only 30% of the infected neonates. Fewer than half (47%) of infants with EOS had one or more of these findings. Hypothesizing that

synthesis of risk indicators into an integrated quantitative estimate of risk might improve diagnostic performance, Puopolo *et al* developed a logistic regression model based on 4 maternal factors (gestational age, maximum antepartum temperature, duration of rupture of membranes, and group B *Streptococcus* [GBS] colonization) and intrapartum antibiotic use (stratified by spectrum and duration) [7]. The clinical diagnosis of chorioamnionitis, which is difficult to integrate into practice paradigms [18] and is poorly predictive of EOS in late preterm and term infants [19-21] was not used. Regression coefficients for these variables are shown in Table 1 [22, 23] The largest predictive contributions came from highest maternal temperature (58%), gestational age (17%), and duration of ruptured membranes (13%). When applied to the development data, the model performed well by standard statistical measures (area under the receiver-operator characteristic curve 0.800, Hosmer-Lemeshow goodness-of-fit $P = 0.142$) [24]. A cutoff risk estimate of 0.5 per 1000 live births stratified the study population (attack rate [AR] 0.58/1000 live births) into a small group (6% of infants) at substantially higher risk for EOS (4.2/1000, including only 45% of the EOS cases) and a much larger group (94% of infants) at low risk (0.34/1000). A major implication of these observations is that traditional risk factors alone are not adequate to guide management of neonates at risk for EOS, even when their information content is rigorously extracted.

Adjustment for Oversampling of Cases

Logistic regression models are useful for predictive modeling of rare events such as EOS because they allow utilization of data from all instances of the event of interest (oversampling cases), while sampling a much smaller proportion of instances in which that event did not occur (undersampling controls). This greatly reduces the burdens of data compilation and computational complexity. Estimation of absolute risk for individuals from the underlying population requires adjustment of the intercept term (β_0) in the resulting regression equation, so that the total predicted event incidence for the underlying population will match that observed (in this case, 0.576 per 1000). An apparent error in calculating this adjustment (see Table 1, footnote *c*) leads to initial risk estimates (before incorporation of examination findings) that are less than half of the correct values (see Table 2). This compromises the accuracy of these absolute risk estimates, but is less likely to compromise their utility for stratifying risk across individuals or groups.

Updating the Model for Other Populations

Similar intercept adjustments are sometimes used to update models for use in populations for which the original model is poorly calibrated (i.e., predicted probabilities are systematically too high or too low) [25]. The observation that the event rate in the new population is different is not sufficient to justify adjustment, because that may result simply from different prevalences of risk predictors [25]. Lower EOS rates [21, 26-28] resulting from low rates of maternal GBS colonization or changing obstetrical practices

Table 1. Changes in Sepsis Risk Calculator: Origins to Current Implementation[a]

Model Elements	Original Source		Current Implementation	
Risk factor β coefficients [7,9]	Gestational age	-6.9325	Unchanged	
	(Gestational age)^2	0.0877		
	Temperature (°F)	0.8680		
	Ruptured membranes (hrs)[b]	1.2256		
	GBS +	0.5771		
	GBS unknown	0.0427		
	Broad antibiotics ≥ 4 hrs	-1.1861		
	Broad antibiotics < 4 hrs	-1.0488		
	GBS antibiotics	-1.0488		
Intrapartum treatment strata definitions and associated regression coefficients [7,9]	No value No antibiotics	0	No value No antibiotics GBS antibiotics < 2 hrs Broad antibiotics < 2 hrs	0
	Some value GBS antibiotics Broad antibiotics < 4 hrs	-1.0488	Some value GBS antibiotics > 2 hrs Broad antibiotics 2-4 hrs	-1.0488
	Full value Broad antibiotics > 4 hrs	-1.186	Full value Broad antibiotics > 4 hrs	-1.1861
Intercept adjustment for oversampling [7,9]	β_0 = 47.8398 adjusted to 40.712 for AR 0.576/1000 live births[c]		*Adjusted β_0 for AR 0.6/1000 live births*	40.7489
Differences in secular attack rates between populations [9]	Adjusted β_0 = 40.712 (reflecting index population AR = 0.576/1000 live births)		Current version allows adjustment for AR ranging from 0.1 to 4.0/1000 live births.	
Examination findings likelihood ratios [2, 33]	Well-appearing	0.36	*Well-appearing*[f]	0.41
	Equivocal[e]	3.75	*Equivocal*	5.00
	Ill	14.5	*Ill*	21.2
Categorical override for clinical illness [2]	—		*Strong consideration of treatment* if clinically ill, despite risk estimate < 3/1000	

(e.g., increased use of intrapartum antibiotics or measures to limit duration of rupture of membranes) or higher attack rates in selected subgroups (e.g., neonates born to mothers with chorioamnionitis) are predicted by and accounted for in the model. It is not appropriate to adjust for such differences a second time by also adjusting the intercept. Such adjustments should be applied only after demonstration of poor calibration in the new population [29], ascertainment that predictive variables in the new population have prevalences comparable to those in the development data [30], and confirmation

Table 1. (continued)

Model Elements	Original Source	Current Implementation
Management recommendation strata and criteria [2, 33]	Well, prior risk < 0.65/1000: Continued observation Well, prior risk 0.65-1.54/1000, or equivocal, prior risk < 0.65/1000: Observe and evaluate All others: Treat empirically	*Posterior risk < 1/1000*: No culture, no antibiotics, routine vital signs *Posterior risk 1-3/1000, well or equivocal exam*: Blood culture, vital signs every 4 hours *Posterior risk < 3/1000 but ill*: Strongly consider starting empiric antibiotics, vital signs per NICU *Posterior risk > 3/1000*: Empiric antibiotics, vital signs per NICU *Frequent vital signs* for infants with prior risk > 1/1000, exam-adjusted risk < 1/1000

[a] *Italicized text* denotes model characteristics that differ between the original regression model and the current online Calculator.

[b] Entered into the regression as the transformed value $(ROM + 0.05)^{0.2}$.

[c] All β0 values used in the Calculator were calculated using a nonstandard method, in which the intercept estimate was adjusted to make the predicted EOS rate in the regression sample (n = 1413) equal to the stipulated rate in the underlying population (0.1 to 4 per 1000) [18]. Standard formulas [22,23] adjust β0 to make the predicted EOS rate in the population (n = 608,014) equal to the observed rate in the underlying population (0.576/1000). EOS odds calculated using the value for β0 (41.4913) obtained using standard methods exceed those obtained from the published regression equation by a factor of 2.18 ($e^{[41.4913-40.712]} = e^{0.7793}$) and those from the Calculator using an EOS incidence of 0.6/1000 by a factor of 2.10 ($e^{[41.4913-40.7489]} = e^{0.7424}$).

[d] Approximate values inferred from multiple applications of the online Calculator.

[e] The value for this likelihood ratio recalculated from original data is 3.65, not 3.75 as originally reported;[33] the confidence interval is correct.

[f] The likelihood ratios for examination findings used in the Calculator are not the point estimates for the population-based likelihood ratios, but rather their upper 95% confidence limits.

that calibration is improved by the adjustment [31-32]. In that event, it is plausible that poor calibration is caused by factors not represented in the model, and recalibration for a new environment may be appropriate. Poor calibration may be institution-specific, even for institutions included in the original development dataset. Model recalibration or even rederivation may be necessary as outcomes, prevalences of independent variates in the model, and influences of factors not reflected in the model may change over time or differ among venues. For this reason, application of the Calculator in fundamentally different environments – low income countries where the prevalence of EOS is much higher, causative organisms different, and risk predictors less certain, for example – should await validation in those settings.

No publications report fulfillment of the aforementioned requirements for recalibrating the Calculator's prediction model. Therefore, adjustments to account for EOS incidences ranging from 0.1 to 4 per 1000 live births, as provided for in the online Calculator [9], are

Table 2. Calculator Components Impacting Accuracy of Absolute Risk Estimates

Factor	Impact on EOS Risk Estimates
Use of blood culture results as a surrogate for invasive bacterial infection in regression model	Uncertain; over- or underestimation both possible
Methodology for adjustment of regression intercept to account for oversampling	Underestimation of EOS odds by approximately 55%[a]
Recalibration of model for use in different settings/populations	Overestimation (e.g., in subpopulation with chorioamnionitis) or underestimation (e.g., in setting with EOS rates) Not justified in subgroups defined by variable(s) included model (fever, GBS colonization) Not justified for external applications *unless* poor calibration demonstrated and remedied by intercept adjustment
Integration of examination findings as unadjusted likelihood ratios	Uncertain; over- or underestimation both possible Simple inclusion as additional regression term assumes no covariance with other variates
Use of upper 95% confidence limits for exam finding likelihood ratios	Overestimation of EOS odds by 14%, 37%, and 46%, for well, equivocal, and ill neonates, respectively[b]
Recategorizing intrapartum treatments	Overestimation of EOS odds for infants who received intrapartum antibiotics for < 2 hours before birth (approximately 3-fold)[c]; no impact on estimation of EOS odds for other infants

[a] Due to an error in the initial calculation of the regression intercept (β_0; see footnote *c* in Table 1).
[b] Resulting from use of likelihood ratios of 0.41, 5.00, or 21.2, rather than 0.36, 3.75, or 12.5 for infants who are well-appearing, equivocal, or clinical ill, respectively (ignoring potential effects of covariance of examination findings with other independent variables in the model).
[c] Reassignment of infants born to women who received intrapartum antibiotics for < 2 hours before birth to the "No value" category increases their regression β value by 1.0488, resulting in an increase in estimated odds by a factor of $e^{1.0488} = 2.85$.

not justified. The only valid value for this term would be the correctly adjusted intercept based on the observed population attack rate (see above). None of the options for EOS incidence offered in the online Calculator produces accurate risk estimates.

Incorporating Examination Findings into Management

Recognizing inadequacy of traditional risk factors, Escobar *et al* built on the regression model in two steps [33]. First, recursive partitioning defined three strata of sepsis risk based on maternal risk factors: < 0.65, 0.65-1.54, and ≥ 1.54 cases per 1000 live births. Second, neonates in each stratum were classified according to physical examination

findings as appearing *well*, *equivocal*, or clinically *ill*, producing a 3-by-3 risk allocation matrix (Figure 2). Specific objective criteria (provided in the original publication [33] and the online Calculator [1]) were established, demonstrating feasibility and utility of objective stratification based on examination findings. Three risk clusters were defined, based on expected EOS attack rates in each category (Figure 2). With this grouping, the 4.1% of the population identified as high risk included 60.8% of the neonates with EOS [33] – a substantial improvement over previous strategies. In the highest risk group, 118 neonates would be treated for each one with culture-proven EOS, so many babies would still be treated unnecessarily, and nearly 40% of the cases still are not identified as high-risk at birth.

This first-stage adaptation of the Calculator to incorporate each baby's clinical status was semi-categorical [33]. To move towards quantitative estimates of individual risk, likelihood ratios (LR) for each category of clinical findings were estimated from development data (well-appearing, LR 0.36 [95% CI 0.31–0.41]; equivocal, 3.75 [2.83–5.00], and clinically ill, 14.5 [10.2–21.2]). In the Calculator, the prior probability (pre-examination risk based on risk factors) is converted to prior odds, multiplied by the upper 95% confidence limit of the LR to produce posterior odds, which are finally converted to posterior probability [2]. Multiplying prior odds by an LR is exactly equivalent to converting the LR to a β coefficient and adding it as a new term in the regression equation. That is analogous to combining coefficients from univariate regressions into a single putatively multivariate equation, which is not valid, as it ignores covariance [34]. Furthermore, use of upper 95% confidence limits rather than LR point estimates systematically skews risk predictions to higher values (increasing odds by 14%, 37%, and 46% compared to those predicted using point estimates for well, equivocal, and ill neonates, respectively). Rigorous incorporation of examination findings into quantitative risk estimation would require recalculation of the regression, including examination findings as independent variables in the multivariate analysis.

Categorizing Intrapartum Antibiotic Treatment

In the original model, intrapartum treatments were categorized as "no value" (no intrapartum antibiotics), "some value" (any GBS-specific antibiotics or broad-spectrum antibiotics given < 4 hours before delivery), or "full value" (broad-spectrum antibiotics given ≥ 4 hours before delivery). In the current implementation, antibiotic prophylaxis for < 2 hours before delivery is considered to have "no value", on the grounds that shorter duration of intrapartum treatment may compromise efficacy [35]. Recent reports have questioned this assumption [36, 37], so this redefinition may no longer be justified. The effects of redefinition of treatment categories on risk estimates is uncertain, but may not be inconsequential. In the development data, 7.4% of neonates received antibiotics < 4 hours before birth.[24] The proportion treated < 2 hours before birth is probably small (≈3-4% of the population), limiting population-level effects of redefinition. However,

Clinical Presentation	Sepsis Risk at Birth Estimated from Maternal Risk Factors (cases per 1000 live births)		
	< 0.65	0.65 – 1.54	≥ 1.54
Well appearing	84.7% of neonates 15.7% of cases 0.11 cases/1000	4.7% of neonates 8.9% of cases 1.08 cases/1000	0.7%of neonates 7.7% of cases 6.70 cases/1000
Equivocal findings	6.4% of neonates 14.6% of cases 1.31 cases/1000	0.2% of neonates 4.9% of cases 14.65 cases/1000	0.4% of neonates 6.0% of cases 9.10 cases/1000
Clinical illness	2.6% of neonates 24.6% of cases 5.54 cases/1000	0.2% of neonates 9.4% of cases 28.06 cases/1000	0.2% of neonates 6.3% of cases 24.74 cases/1000

Consolidated Risk Groups		
Low	Intermediate	High
84.7% of neonates 15.7% of cases 0.11 cases/1000	11.1% of neonates 23.4% of cases 1.21cases/1000	4.1% of neonates 60.8% of cases 8.40 cases/1000

Figure 2. Distribution of infants and those with EOS in the development population, with expected EOS rates for each category. Adapted from Table 2 and Supplemental Table 8 of Escobar 2014 [8,33]. Each cell in the matrix presents the proportions of all infants and of those with EOS, along with the expected EOS rate, in the indicated category. These categories can be consolidated into three risk strata, based on the expected EOS rates: low (white; risk < 1/1000), intermediate (light gray; risk 1-3/1000), and high (dark gray; risk > 3/1000).

reassignment of infants whose mothers received prophylaxis < 2 hours before delivery increases their predicted odds of sepsis by nearly 3-fold. Mitigation of effects of this *post hoc* redefinition of variables would require recalculation of the regression model using the redefined variables.

Thresholds for Management Recommendations

In the first step towards integration of quantitative risk estimates with examination findings, three strata of *pre-examination* risk estimates were defined by recursive partitioning and combined with the three categories of examination findings; the resulting 9 strata were consolidated into three risk groups (Figure 2) [33]. The fully implemented Calculator quantitatively incorporates examination findings into *post-examination* risk estimates [9]. There is no simple correspondence between semi-categorical strata and quantitative post-examination estimates, so action thresholds based on the latter must be separately established. The Calculator recommends treatment for infants with risk estimates > 3/1000, frequent vital signs and screening blood cultures for those with intermediate risk (1-3/1000), and more frequent vital signs for well-appearing neonates with low *post*-examination risk estimates (< 1/1000) if pre-examination risk is > 1/1000 live births (Figure 1). These thresholds are conservative by intent, but arbitrary, having been reached by consensus [2]. The threshold for treatment (3/1000) is higher than those evaluated in the original

model derivation (1.5/1000) [7] or stratification based on examination findings (1.54/1000) [33], which were insensitive (detecting 18% and 20% of EOS cases, respectively), and led to treatment of 142 infants for each infant with confirmed bacteremia [9]. Optimal action thresholds could be established by receiver-operator characteristic analysis or a new recursive partitioning, preferably using an independent data set [38, 39].

For infants with an adjusted risk estimate between 1 and 3 per 1000, the Calculator recommends blood culture and more frequent vital signs (Figure 1). Postimplementation data from KPNC suggest that the yield of such blood cultures is very low [9]. Of 1259 blood cultures performed in the first 24 hours after birth without initiation of treatment, only one yielded a pathogenic organism. The infant remained well and repeat cultures of blood and cerebrospinal fluid were sterile, suggesting that this was a case of transient bacteremia rather than sepsis. The utility of this limb of the decision tree is therefore questionable.

The Calculator also recommends more frequent vital signs for infants with a low (< 1/1000) post-examination risk but higher (> 1/1000) pre-examination risk (i.e., well neonates with pre-examination risk < 2.44/1000). Neither the number of neonates who fall into this category nor the impact of this recommendation have been formally evaluated. Among the 51 early-onset bacteremia cases in the KPNC system between 2010 and 2016, only 2 of the 30 infants with EOS despite post-examination risk estimates < 1/1000 had pre-examination risk estimates > 1/1000 [9].

Override for Clinical Illness

Because they "did not want physicians to withhold antibiotics in an infant with clinical illness, even if his or her posterior probability was below the consensus threshold" [2], the developers of the Calculator included a recommendation to "strongly consider treatment" in neonates who appear ill but have low predicted risk (< 3/1000). This very reasonable modification is a deviation from the objective of a strictly quantitative strategy, in which decisions are guided by "information on an individual infant's risk rather than [placement] in categories with a wide range of risk" [3]. It likely will almost always lead to evaluation and treatment of such infants. With this provision, recommendations based on quantitative risk estimation effectively apply only to infants who are not initially ill. KPNC data suggest that high quantitative risk estimates are rarely the basis of ascertainment of EOS in such babies (2 of 35) [9]. The utility of risk-factor-based quantitative risk estimation for infants who initially do not appear ill has not been validated in more current or demographically distinct populations.

Summary

The Early-Onset Sepsis Risk Calculator combines a logistic regression model for predicting bacteremia with a pragmatic clinical algorithm to provide a paradigm for risk ascertainment and management of suspected EOS in late-preterm and term infants. Development of the Calculator has produced key insights into EOS ascertainment. It revealed that

information available in maternal risk factors alone is insufficient to guide management decisions [7]. Incorporation of examination findings demonstrated feasibility of standardization of examination-based criteria and their utility in stratification of risk [33]. Modifications to the Calculator in the course of its development have amended variable definitions, incorporated examination findings, reformulated thresholds for diagnostic testing and treatment, and standardized management recommendations. The latest iteration provides a range of adjustments to account for different EOS incidences, a practice justified only if preceded by demonstration of poor calibration and improvement with intercept revision. The resulting estimates of absolute EOS risk by the Calculator are precise but inaccurate, yet effects on risk stratification or ranking across the population are less problematic, so results still have validity as an index (if not a reliable absolute measure) of risk. Therefore, selection of appropriate thresholds of this index for intervention may obviate concerns about inaccuracy of the Calculator's estimates of absolute risk for EOS.

The separate contributions of each component of the overall Calculator paradigm remain to be elucidated, but much of its utility apparently follows from recognition of clinical signs of illness. The large proportion of EOS cases not identified by either calculated risk or clinical illness at birth indicates that ongoing vigilance for developing signs of illness is essential. No strategy can promise perfect case ascertainment, and failure to recognize at birth an infant who goes on to develop EOS does not constitute evidence of negligence. Only a few babies with EOS who were not ill at birth have been reported, so continued surveillance of large populations is needed to better define best practices.

The accuracy of estimates of absolute risk for EOS provided by the Sepsis Risk Calculator is substantially compromised by several technical issues (Table 2). These predicted risks cannot be relied upon as accurate estimates for an individual infant or for quantitative population analyses, such as estimation of the number of babies treated per confirmed EOS case or cost-benefit studies. Nonetheless, risk estimates remain useful for risk stratification and careful selection of action thresholds can offset effects of inaccurate predictions on clinical utility. Post-implementation surveillance has shown that adoption of the Calculator paradigm allows substantial reductions in diagnostic testing and empiric treatment rates (improving antimicrobial stewardship), without apparent safety concerns [9, 40]. The Calculator provides an alternative to previously recommended categorical approaches, promoting consideration and adoption of innovative strategies for ascertainment of EOS. The contributions of the Calculator or its components to early ascertainment of newborn infants with early-onset sepsis will be determined as experience with its application in practice accrues.

Contributors

WEB prepared the initial draft of the Personal View. WEB and NBA participated in analysis of the components of the sepsis calculator, evaluated the statistical validity of adaptations for the current clinical implementation, and revised and share responsibility for the final manuscript.

Conflicts of Interest

We declare that we have no conflicts of interest.

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7

Association between Early Onset Sepsis Calculator and Infection Parameters for Newborns with Suspected Early Onset Sepsis

Abstract

Context

Early onset sepsis remains an important clinical problem with significant antibiotic overtreatment as a result of poor clinical and infection parameters. Quantitative risk stratification models such as the EOS calculator are promising, but it is unclear how these models relate to infection parameters in the first 72 hours of life.

Aims

To evaluate the relationship of early EOS calculator results with infection parameters in newborns with suspected EOS.

Subjects and Methods

EOS risk estimates were determined for infants born ≥ 34 weeks of gestation who were started on antibiotic treatment for suspected EOS within 72 hours after birth. These were retrospectively compared to (changes in) available laboratory infection parameters including C-reactive protein (CRP), leukocyte and thrombocyte count.

Statistical analysis used

Spearman's *rho* rank correlations coefficient was used when testing for correlations between continuous parameters. Kruskal-Wallis and Mann-Whitney U tests were applied to differences between stratified risk groups.

Results

EOS risk was not correlated with changes in infection parameters. We found negative correlations between both EOS risk and CRP level and leukocyte count within 6 hours of the start of antibiotics, as well as CRP level between 6-24 hours after start of treatment.

Conclusions

High EOS risk at birth was consistently correlated with lower CRP and leukocyte counts within 24 hours after the start of antibiotics, but not with infection parameters after 24 hours. Further interpretation of infection parameters during sepsis calculator use needs to be elucidated.

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Introduction

Early onset neonatal sepsis (EOS) remains an important clinical problem in neonatal care. Due to poor specificity of clinical findings and limited usability of available infection biomarkers, there is significant over-treatment with antibiotics in the first 72 hours of life of newborns with suspected EOS [1]. In an attempt to overcome this problem a quantitative risk stratification strategy based on objective maternal risk factors and neonatal clinical findings has been developed [2]. This model, hereafter referred to as the EOS calculator, provides a quantitative estimation of EOS risk along with a recommendation on the use of antibiotics, and is available online. Two retrospective studies revealed that application of the sepsis calculator may significantly reduce antibiotic therapy and thus use of the EOS calculator may become more common in clinical practice [3, 4].

Despite this promising potential, it is currently unclear how the EOS calculator estimated risk and recommendations relate to infection parameters in the first 72 hours of life. Serial values in C-reactive protein (CRP) and leukocyte count are still commonly used as arguments for the start and duration of antibiotic therapy.[1, 5] For this study, our aim was to evaluate the hypothesis that higher EOS calculator results are associated with (serial) laboratory infection parameters. As EOS is associated with elevated CRP and a lower leukocyte count [5, 6], we particularly hypothesized high EOS risk estimate to be associated with an increase in CRP within 24-48 hours, and low leukocyte counts.

Subjects and Methods

Study design

Data from a previously established retrospective birth cohort were used for analysis [4]. The study included all newborns born ≥34 weeks of gestation who were started on antibiotic treatment for suspected EOS within 72 hours after birth, in Tergooi Hospitals, Blaricum, The Netherlands, during 2014. Exclusion criteria were major congenital anomalies, including chromosomal, and prophylactic treatment with antibiotics. The study was approved by the Scientific Review Committee of Tergooi Hospitals.

Data collection

Maternal and neonatal clinical data were derived from hospital records. Local protocol required routine infection parameter testing in newborns treated for clinically suspected EOS at start of antibiotic therapy, and follow-up testing at 12-24 hours and/or 24-72 hours after the start of antibiotic treatment. Infection parameter results were derived from electronic laboratory records.

EOS calculator risk estimates and stratification

EOS risk estimates were determined using the online calculator as provided by Escobar et al., through http://newbornsepsiscalculator.org [2, 7]. These estimates represent the estimated incidence of EOS per 1000 live births, and were calculated individually for

each newborn in the study. The resultant sepsis risk was categorized into three levels; <0.65 (low risk), 0.65-1.54 (intermediate risk) and >1.54 (high risk) per 1000 live births, as recommended by Escobar et al. In addition to using EOS calculator risk estimate as continuous variables, we used these groups for stratified analysis.

Delta variables

Since specifically serial values in infection parameters are used to guide clinical decisions [8], we calculated delta variables when serial values were available. For delta variables, we calculated absolute differences between values derived from initial blood draw (0-6 hours after start of treatment) and follow-up values 24 hours after start of treatment. Values derived between 6-24 hours were used as follow-up values if values >24 hours were unavailable.

Statistical analysis

All data were statistically analyzed using R (version 3.2.1) (http://www.r-project.org). Distributions of continuous variables were visualized using kernel density plots. Spearman's *rho* rank correlations coefficient was used when testing for correlations between EOS risk estimates and infection parameters (continuous variables not normally distributed). Kruskal-Wallis and Mann-Whitney U tests were applied to determine significance of differences between EOS stratified risk groups.

Results

After exclusion of three newborns with insufficient clinical information to estimate EOS risk, data from 108 newborns were used for analysis (Table 1).

CRP

We found negative correlations between EOS risk estimations and CRP levels within 6 hours and between 6 and 24 hours after the start of antibiotics (Spearman's rho -0.45 and -0.24, respectively). This was confirmed by EOS stratified group analysis, where the high EOS risk group was associated with lower CRP levels (<1 versus 11.5 mg/l, $p<0.05$, Table 1). EOS risk estimate was not correlated with change in CRP as determined by the delta CRP variable based on serial CRP values.

Leukocytes and thrombocytes

EOS risk estimate was not correlated with changes in serial leukocytes count. Lower leukocyte counts within 6 hours after the start of antibiotics were associated with higher EOS risk estimations (Spearman's rho -0.30). Leukocyte count within 6 hours after start of antibiotics was lower in the high-risk group compared to the intermediate/low risk group ($p<0.05$) (Table 1). There were no correlations between EOS risk and (serial) thrombocyte counts.

Table 1. Infection parameters and correlation results among total and stratified risk group analysis

	EOS risk group					
	Overall (*n*=108)			Stratified risk group analysis, median (IQR)[a]		
Infection parameter	Median (IQR)	*n* (%)	Spear-man's rho	Low (*n*=41)	Intermediate (*n*=10)	High (*n*=57)
CRP (median, mg/L)						
<6 h	<1 (13)	100 (93.6)	−0.45***	11.5 (25)	<1 (8)	<1 (3)***
6–24 h	7 (23)	82 (75.9)	−0.24*	11.5 (25)	2 (8)	5 (20)
>24 h	5.5 (17)	58 (53.7)	−0.01	7 (15)	3 (20)	5 (26)
Delta	4 (19)	96 (88.9)	−0.08	6 (18)	2 (21)	4 (19)
Leukocytes (median, $\times 10^9$ L)						
<6 h	16.4 (9)	102 (94.4)	−0.30**	20.6 (11)	15.3 (20)	15.3 (9)**
6–24 h	16.5 (10)	70 (64.8)	−0.13	16.6 (11)	26.2 (15)	14.4 (10)
>24 h	13.1 (7)	53 (49.1)	−0.19	15.0 (5)	14.3 (16)	11.4 (6)
Delta	3.7 (6)	85 (78.7)	−0.18	4.7 (9)	8.1 (8)	2.9 (5)
Thrombocytes (median, $\times 10^9$ L)						
<6 h	219 (87)	94 (87.0)	0.04	224 (112)	217 (93)	215 (92)
6–24 h	214 (113)	67 (62.0)	0.11	208 (159)	233 (91)	208 (113)
>24 h	245 (106)	49 (45.4)	0.01	241 (169)	280 (80)	243 (105)
Delta	27 (39)	77 (71.3)	0.09	25 (57)	32 (24)	27 (39)

Statistically significant results marked in bold; *P<0.05, **P<0.01, ***P<0.001, [a]Mann–Whitney U-test, high versus low/intermediate risk group. EOS risk; early-onset sepsis risk as calculated with sepsis calculator. EOS – Early-onset neonatal sepsis; IQR – Interquartile range

Discussion

In contrast to our hypothesis, we did not find any correlations between EOS risk and changes in serial CRP or serial leukocyte or thrombocyte counts. We observed negative correlations between EOS risk estimate and CRP level and leukocyte count within 6 hours of start of antibiotics, as well as CRP level between 6-24 hours after start of treatment. Analyzing differences between EOS stratified risk groups, comparable results within 6 hours of start of treatment were found.

In the high-risk group CRP levels were in the normal range at start of antibiotic therapy, which was started shortly after birth. This can be explained by the fact that CRP levels represent endogenous neonatal synthesis, rise above 5 mg/l by 6-8 hours and peak around 24-48 hours [9, 10]. Negative correlation between high EOS risk and CRP levels at the start of antibiotic treatment may be explained by the fact that high-risk newborns started with antibiotic treatment shortly after birth, before endogenous synthesis of CRP occurred.

Furthermore, this may also explain the significant differences of CRP levels of <1 mg/l in high-risk group versus 11.5 mg/l in the low-risk group at the start of antibiotics ($P<0.05$). In contrast to the high-risk group, antibiotic therapy was mostly started 12 hours after birth in the low risk group of our population [4]. Remarkably, CRP levels did not clearly increase in the high-risk group. This differs from various studies that confirmed that the sensitivity of CRP increases substantially with serial determinations of CRP 24-48 h after the onset of symptoms [9].

From a clinical point of view these findings underline the puzzling nature of EOS clinical management, with high EOS risk associated with low CRP levels. In the high-risk group, based on objective maternal factors and newborn clinical evaluation, antibiotic therapy is started and continued for 7 days. In this group, (serial) CRP measurement is not of additional value to discontinue antibiotic therapy in case of negative blood cultures. In the low-risk group, however, serial CRP may serve to discontinue antibiotic treatment after 3 days, given the negative predictive value of serial low CRP levels [10].

The correlation between higher EOS risk estimates and lower leukocyte counts within 6 hours after start of antibiotics corresponds with published findings showing lower leukocyte counts being associated with EOS [6]. It should be noted however, that low leukocyte counts are rare – reflected in a modest difference in absolute leukocyte count between the high-risk group and overall median (15.3 vs 16.4 x10^9/l). Therefore, leukocyte counts are likely to be of limited clinical value in EOS diagnostics. Finally, (changes) in thrombocyte counts were, in line with published literature, not related to EOS risk. Thus, we do not recommend the use of thrombocyte counts to guide clinical decisions regarding antibiotics for EOS, regardless of estimated EOS risk.

Limitations of this study include its retrospective nature and selection bias for determination of infection parameters. However, given the high percentage of available results within 6 hours of start of antibiotics, we think this bias is limited for the correlations we found. Our sample size is limited, but given the consistent results among correlation and stratified group level analysis, we do not expect different results with a larger sample size.

In conclusion, EOS remains an important clinical problem with significant antibiotic overtreatment as a result of poor clinical and infection parameters. In newborns treated for EOS, risk estimates are neither associated with changes in CRP level, nor leukocyte or thrombocyte count. If more widespread use of the sepsis calculator is expected, the interpretation of common infection parameters in the context of EOS risk needs to be further elucidated.

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8

Dutch multicenter study found that adherence to antibiotic recommendations for neonatal early-onset sepsis is low

Abstract

Aim

Our primary aim was to evaluate adherence to the Dutch adaption of the National Institute for Health and Clinical Excellence neonatal early-onset sepsis (EOS) guidelines and its effect on antibiotic recommendations. The secondary aim was to determine the duration of and reasons for prolonged antibiotic treatment of suspected EOS in case of a negative blood culture.

Methods

We performed a multicenter, prospective observational cross-sectional study in seven hospitals in the Netherlands between 1 September 2018 and 1 November 2019. Newborns born at 32 weeks of gestational age or later were eligible in case at least one EOS risk factor or clinical signs of infection were present.

Results

Clinical data of 1024 newborns at risk for EOS were studied. Clinicians adhered to the guidelines in 72.3% of included newborns. The guidelines recommended antibiotic treatment to 42.8%, but it was started in only 18.2% due to non-adherence. Antibiotic treatment was continued for 3 days or longer in 31.5% of treated newborns despite a negative blood culture.

Conclusion

We observed low adherence to the Dutch guidelines for allocating antibiotic treatment leading to less antibiotic treatment than recommended and prolonged use in case of a negative blood culture. Improvement of the guidelines should be considered.

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Submitted

Introduction

Suspected neonatal early-onset sepsis (EOS) can be defined by the suspicion of a systemic infection within the first 72 hours after birth [1], whereas proven EOS is confirmed by a positive blood- or cerebrospinal fluid culture [2–4]. The incidence of proven EOS is approximately 0.5 to two cases per 1000 live newborns (7,8), whereas the incidence of suspected EOS is estimated to be much higher [1]. Difficulties in ascertaining EOS have led to many newborns being exposed to potential harms related to antibiotic treatment, despite not having EOS [5, 6].

Guidelines have been published to provide evidence-based support for prevention, recognition and optimization of diagnosis and treatment of EOS [7–10]. These contain three general approaches to identify newborns at increased risk of EOS: a categorical risk factor assessment, a multivariate risk assessment, and risk assessment primarily based on the newborn's clinical condition [10, 11]. The Dutch guidelines are adapted from the National Institute for Health and Care Excellence (NICE) guidelines [8, 9], and are a simplified version of their categorical assessment. Eight maternal and fifteen neonatal risk factors, each categorized as 'red flag' (major criteria) or as 'non-red flag' (minor criteria), are used to guide the decision to start or withhold antibiotic treatment [8, 9]. In accordance with the NICE guidelines, the Dutch guidelines advocate considering discontinuation of antibiotic treatment after 36 hours in case of a negative blood culture.

Both adherence to and appropriateness of the NICE guidelines in clinical practice are subject to debate [5, 12–14]. We therefore prospectively evaluated the use of the Dutch guidelines in clinical practice. The primary aim was to evaluate the adherence to antibiotic recommendations of the guidelines. The secondary aim was to determine the duration of and reasons for antibiotic treatment in case of a negative blood culture.

Methods

Study design and setting

This was a prospective multicenter observational study. From 1 September 2018 through 1 November 2019 data were collected in seven non-academic hospitals (Dijklander Hospital in Hoorn, Juliana Children's Hospital in The Hague, Isala in Zwolle, Martini Hopsital in Groningen, Spaarne Hospital in Hoofddorp, Tergooi in Blaricum, Zaans Medical Center in Zaandam), all in the Netherlands. Participating centers provide care up to Level II special care for stable or moderately ill newborns [15], with annual birth rates between 1200 and 4000 births per year.

Study participants

Newborns born at 32 weeks of gestational age or later were eligible in case at least one EOS risk factor or clinical signs of infection (suspected of EOS) were present. Risk factors included maternal intrapartum fever, prolonged rupture of membranes, moderate to late prematurity (32-37 weeks), positive maternal group B Streptococcus (GBS) status, and or

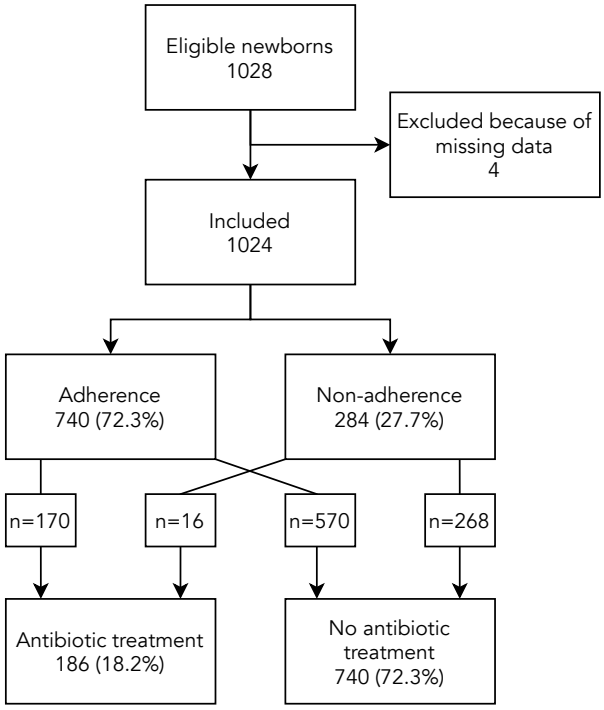

Figure 1. Flowchart of study population. Flowchart of included at-risk newborns, observed rates of antibiotic recommendations by the Dutch guidelines and actual treatment in clinical practice.

prescribed intrapartum antibiotic prophylaxis. Suspected EOS was based on the clinical conditions within the first 72 hours of life, per the clinician's discretion.

Study protocol

Simplifying the NICE guidelines, the Dutch guidelines use eight maternal and fifteen neonatal risk factors, each categorized as either red flag or non-red flag (Table S1) [8, 9]. These criteria guide clinicians on the management in case of suspected EOS. Briefly, antibiotic treatment is recommended in the presence of at least one red flag and/or two or more non-red flags (Supplemental Figure 1). An observation period of at least 12 hours is recommended in the presence of one non-red flag (this could be a maternal risk factor or a clinical symptom of the newborn). Antibiotic treatment is recommended when infection is suspected during this observation. When all possible flags are absent, no antibiotic treatment is recommended and the newborn is discharged after normal maternity care.

Data collection

Data on maternal risk factors were collected by clinicians at time of inclusion, using a clinical report form. Collected data of newborns included data on red flags, and results of a physical examination performed by a pediatric resident or by a pediatrician. After

clinical evaluation, potential management options included discharge of the newborn, clinical observation for at least 12 hours, or start of antibiotic treatment. If antibiotic treatment was started, additional data on use of antibiotics (start and duration) and on results of performed laboratory tests (blood culture, C-reactive protein (CRP) levels) were collected. In case of a negative blood culture, but continuation of antibiotic treatment, the clinician reported the reason for continuing antibiotic treatment. Potential reasons were the clinical condition of the newborn at start of antibiotic treatment, the clinical course of the newborn until the blood culture results, the results of laboratory tests, or the clinical experience of the attending physician. Castor Electronic Data Capture version 1.4 (Ciwit B.V., Amsterdam, the Netherlands) was used to process all clinical report forms.

Data analysis

Adherence to the guidelines was defined as either start of antibiotic treatment in accordance with the guidelines (in case at least one red flag and/or two or more non-red flags were present), or withholding antibiotic treatment in accordance with the guidelines (in case zero red flags and at most one non-red flag were present). Non-adherence to the guidelines was defined as the start of antibiotic treatment against recommendation of the guidelines (without red flags and at most one non-red flag present) or not starting antibiotic treatment against recommendation of the guidelines (in case at least one red flag, and/or two or more non-red flags were present). To avoid interference to the adherence to the guidelines, clinicians were not asked to report themselves as adhering to the guidelines or not. The adherence was retrospectively determined by comparison of reported clinical findings to the guidelines, done by a research fellow independent from the attending physicians.

Statistical methods

For statistical analysis SPSS Statistics, version 26.0 (IBM Corp, New York, USA), was used. Categorical variables were analysed using Pearson's chi-square test or Fisher's exact test when the expected frequencies were low. For all comparisons an alpha value of <0.05 was considered statistically significant.

Ethical standards

The study was approved by the Medical Ethics Review Committee (Zwolle committee, reference number 180220). Informed consent from the patients' caregivers was required. The study was not subject to the Medical Research Involving Human Subjects Act, because no intervention was performed and only data were collected.

Results

During the study period, 1028 eligible newborns were identified and included in the study. Of these, 4 (0.4%) were excluded because of incomplete data to determine adherence

(Figure 1). Clinical characteristics of the study population and data on antibiotic treatment are reported in Table 1.

Adherence regarding start of treatment

Overall, clinicians adhered to the guidelines in 72.3% (740/1024) among included newborns (Figure 1). Dutch guidelines recommended antibiotic treatment for 42.8% (438/1024) of included newborns. Adherence to this recommendation to start antibiotics was 38.8% (170/438). The guidelines advised withholding antibiotics for 57.2% (586/1024) of included newborns. Adherence to this recommendation to withhold antibiotics was 97.3% (570/586).

Within the 438 newborns who qualified for antibiotics according to the guidelines, we compared the adherence group to the non-adherence group (Table 2). Three maternal risk factors were significantly more present in the non-adherence group and seven neonatal risk factors were significantly more present in the adherence group (Table 2).

Duration of antibiotics

In total, 18.2% (186/1024) of all patients received antibiotics. Blood cultures were determined in 97.8% (182/186) of treated newborns, of which 97.8% (178/182) were negative. Prolonged antibiotic treatment (>3 days) despite a negative blood culture was observed in 31.5% (56/178), of which 87.5% (49/56) received ≥7 days of antibiotic treatment. Reasons for continuation were sustained clinical suspected infection in 69.6% (39/56) or increasing CRP levels in 39.3% (22/56). Median CRP levels increased from 2.0 (interquartile range 0.9-23.0) to 20.5 (interquartile range 6.3-50.8).

Discussion

This study showed that the adherence to the Dutch guidelines was low, mainly as a result of withholding antibiotics against recommendation of the guidelines. Once started, antibiotic treatment was continued in one third of the newborns despite a negative blood culture. Strict guideline adherence would lead to much more unnecessary antibiotics.

To our knowledge, this is the first study reporting on adherence to antibiotic recommendations in adapted NICE guidelines for EOS. Surveys have reported on compliance to the NICE guidelines for use of laboratory investigations, suggesting variation in adherence in practice [12, 13]. In the United Kingdom, the NICE guidelines led to treatment of 16% of the entire newborn population, significantly more than other European antibiotic treatment rates (5-8%) [16, 17]. Our results suggest that strict adherence to the Dutch guidelines would also lead to increased rates of antibiotic treatment.

Alternative approaches to the categorical risk factor approach of these guidelines exist, and can lead to less unnecessary use of antibiotics. For example, multivariate risk assessment using the EOS calculator appears to result in significantly less start of antibiotic treatment for EOS in newborns born after at least 34 weeks of gestation, without apparent

Table 1. Clinical characteristics, presence of (non-)red flags and treatment characteristics for study population

Characteristic	Overall (1024)	AB treated (186)	No AB (838)
Baseline characteristics			
Male sex	56.7% (581)	60.2% (112)	56.0% (469)
Gestational age (mean (SD))	38.7 (2.3)	37.6 (3.0)	38.9 (2.1)
Major criteria to start antibiotics			
Maternal risk factors—red flag(s)	2.5% (26)	6.5% (12)	1.7% (14)
Infant clinical indicators—red flag(s)	4.0% (41)	17.7% (33)	1.0% (8)
Both maternal and neonatal red flags	0.3% (3)	1.6% (3)	0% (0)
Minor criteria to start antibiotics			
Two or more maternal non-red flags only (no red flags or clinical non-red flags)	13.0% (133)	11.8% (22)	13.2% (111)
Two or more clinical non-red flags in infant only (no red flags or maternal risk factors)	2.1% (22)	9.1% (17)	0.6% (5)
At least one maternal and one clinical non-red flag (no red flags)	20.8% (213)	44.6% (83)	15.5% (130)
No recommendation to start antibiotics			
One maternal non-red flag only (no red flags or clinical indicators)	50.6% (518)	2.7% (5)	61.2% (513)
One clinical non-red flag in infant only (no red flags or maternal risk factors)	2.6% (27)	4.8% (9)	2.1% (18)
No maternal or clinical red or non-red flags	4.0% (41)	1.1% (2)	4.7% (39)
Blood culture results			
Blood culture obtained	17.8% (182)	97.8% (182)	0% (0)
Blood culture positive	0.4% (4)	2.2% (4)	-
Blood culture negative	17.4% (178)	97.8% (178)	-
Antibiotic treatment			
Any antibiotics	18.2% (186)	100% (186)	0% (0)
Antibiotics <48 hours	0.6% (6)	3.2% (6)	-
Antibiotics 48-72 hours	11.4% (117)	62.9% (117)	-
Antibiotics 4-6 days	0.8% (8)	4.3% (8)	-
Antibiotics ≥7 days	5.4% (55)	29.6% (55)	-
Antibiotics >3 days with a negative blood culture	5.5% (56)	31.5% (56)	-

SD: standard deviation

safety concerns [5, 18]. Data on adherence for the EOS calculator approach is scarce, but one implementation study reported 91% adherence, suggesting better congruence with clinical judgment. Similar to the EOS calculator, the use of serial physical examinations may lead to even lower rates of antibiotic treatment [19, 20], although evidence on safety of such approach is limited.

We observed that antibiotic treatment was continued for more than 2 days in almost all treated newborns, and more than 3 days in nearly a third, despite negative blood

Table 2. Comparison between adherence and non-adherence groups within newborns qualifying for antibiotics according to the guidelines.
Risk factors summarized for clarity; detailed descriptions available in Table S1.

Risk factor	Adherence	Non-adherence	P-value
Total (n)	170	268	N/A
Maternal risk factors			
Parenteral antibiotic treatment	5.3% (9)	4.9% (13)	0.836
(Suspected) infection in sibling multiple pregnancy	3.5% (6)	0.7% (2)	0.060
Invasive GBS in previous neonate	1.8% (3)	2.2% (6)	1.000
GBS colonisation	12.9% (22)	24.6% (66)	**0.003**
Prelabour rupture of membranes for >24 hours in a term birth[a]	23.2% (39)	40.8% (109)	**<0.001**
Preterm birth following spontaneous labour	40.6% (69)	31.3% (84)	**0.048**
Rupture of membranes for > 18 hours in a preterm birth[b]	24.3% (41)	19.8% (53)	0.267
Intrapartum fever > 38°C or (suspected) chorioamnionitis[b]	35.9% (61)	36.7% (98)	0.862
Neonatal risk factors			
Respiratory distress starting more than 4 hours after birth	19.4% (33)	3.0% (8)	**<0.001**
Neonatal epileptic seizures	0% (0)	0% (0)	-
Need for mechanical ventilation in a term neonate	3.5% (6)	0% (0)	**0.003**
Signs of shock	1.2% (2)	0% (0)	0.150
Altered behaviour, -responsiveness or -muscle tone	12.9% (22)	3.0% (8)	**<0.001**
Feeding difficulties	8.2% (14)	4.9% (13)	0.151
Apnoea and bradycardia	8.8% (15)	0.7% (2)	**<0.001**
Signs of respiratory distress	67.6% (115)	32.1% (86)	**<0.001**
Hypoxia	19.4% (33)	3.7% (10)	**<0.001**
Neonatal encephalopathy	0% (0)	0.4% (1)	1.000
Need for cardio-pulmonary resuscitation	1.8% (3)	0.4% (1)	0.304
Need for mechanical ventilation in a preterm neonate	3.5% (6)	0% (0)	**0.003**
Persistent pulmonary hypertension	0.6% (1)	0% (0)	0.388
Unexplained temperature abnormality	18.8% (32)	17.9% (48)	0.810
Local signs of infection	0.6% (1)	0.7% (2)	1.000

[a]Three missing. [b]One missing.

cultures and reassuring CRP levels. This contrasts with the recommendations of the Dutch guidelines. Prolonged antibiotic treatment is a common problem in low-risk EOS situations [21, 22]. Various reasons contribute to continued antibiotic treatment despite negative cultures, such as concern about sensitivity of blood cultures [23]. We found that CRP levels were a common argument. This can be considered a fallacy, because the positive predictive value of serial CRP levels is still very low. In the future, other biomarkers such as procalcitonin may be helpful in early discontinuation of antibiotic treatment [24].

The Dutch guidelines contains 23 risk factors (Supplemental Table 1), of which 6 hardly occurred in clinical practise in this cohort. This raises the question to what extent these

risk factors have added value. We found that the presence of three objective maternal risk factors (known positive GBS colonisation, prolonged rupture of membranes (>24 hours) and preterm birth) were significantly more associated with non-adherence, while the presence of more subjective neonatal risk factors were significantly more associated with adherence. This suggests that clinicians depend mostly on clinical assessment. These findings, along with poor adherence, signal important discrepancies between the current Dutch guidelines and clinical judgment or intuition.

We acknowledge the limitations of our study. First, inclusion and data collection by attending physicians may have resulted in selection bias. It is possible that patients were more likely to be included if they had more symptoms or risk factors, and this may have affected our estimate for adherence. Second, although this was purely an observational study, the systematic data collection and comparison with guidelines may have increased the physicians' adherence to the guidelines, leading to an overestimation of adherence in a non-research context. Finally, this study observed the use of an adaption and not the original version of the NICE guidelines, limiting generalization of our findings. Overall, despite these limitations, this study provides the first large, multicenter analysis of adherence to management based on the NICE guidelines, providing essential data to help answer current calls for more re-evaluation and better tailored consensus guidelines for the use of antibiotics for suspected EOS [25].

Conclusion

We observed low adherence to the Dutch guidelines for allocating antibiotic treatment leading to less antibiotic treatment than recommended and prolonged use in case of a negative blood culture. Strict adherence to the guidelines would result in more newborn infants being exposed to antibiotic treatment. In order to prevent unnecessary antibiotic treatment, improvement of the guidelines should be considered.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Neonatal early-onset sepsis calculator recommends significantly less empiric antibiotic treatment than current Dutch guidelines

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Submitted

Suspected early-onset sepsis (EOS) remains a significant challenge for clinicians and often requires a balance between efficient sepsis care and antimicrobial stewardship. Low EOS incidence rates with widespread antibiotic use currently result in widespread overtreatment. Strategies for identifying newborns who are at high risk of EOS include categorical risk factor assessment, multivariate risk assessment, and risk assessment primarily based on the newborn clinical condition. In the Netherlands, guidelines were renewed in 2017, adapted from work by the National Institute for Health and Care Excellence (NICE) institute. This categorical assessment includes eight maternal and fifteen neonatal risk factors, each categorized as 'red flag' or 'non-red flag', to guide clinicians on the need to start antibiotic treatment. Prospective evaluation of these guidelines in this issue of the journal showed that strict adherence leads to empiric antibiotic recommendation in as much as 42.8% of newborns at risk for EOS.

As an alternative to categorical methods, the 'EOS calculator' has been introduced in the United States [1]. For this clinical decision aiding tool, Escobar et al. developed a multivariate predictive model based on maternal intrapartum risk factors and neonatal clinical risk factors to estimate the probability of EOS. This model was modified into an interactive EOS calculator, combining individual EOS risk assessment with clinical recommendations for management of the newborn [1]. A recent meta-analysis and systematic review concluded that use of the EOS calculator is associated with a substantial reduction in the use of empirical antibiotics for suspected EOS [2]. Although in this study the evidence regarding safety of EOS calculator use was limited, it showed no indication of inferiority compared with conventional management strategies. It is currently unknown if the EOS calculator would result in less empiric antibiotic recommendations compared to the recent Dutch guidelines for the Dutch population.

The aim of this study is to compare the national Dutch guidelines and the EOS calculator on antibiotic recommendation in newborns born at least 34 weeks of gestation at risk for EOS. This was a planned sub-study of a prospective multicenter observational study that enrolled 1024 infants at risk for EOS. Data were collected in seven participating hospitals in The Netherlands from 1 September 2018 through 31 October 2019. The study was approved by the Medical Ethics Review Committee (Zwolle committee, reference number 180220). Informed consent from the patients' caregivers was obtained. It was not subject to the Medical Research Involving Human Subjects Act. For this sub-analysis, we included the subset of newborns with a gestational age of 34 weeks or more, because the EOS calculator is developed for this age group. We included newborns with risk of EOS, defined as presence of one or more of the following criteria: maternal intrapartum fever higher than 38.0°C, ruptured membranes for 18 hours or longer, prematurity (gestational age less than 37 weeks), positive Group B Streptococcus status of mother, intrapartum antibiotic prophylaxis, and/or clinical EOS suspicion based on the clinical conditions within the first 72 hours of life. Clinical maternal and neonatal data were prospectively collected by clinicians including data needed to evaluate the national Dutch guidelines as well as to use the EOS calculator. Clinical appearance was categorized into 'well-appearing',

'equivocal', or 'clinical illness' assisted by EOS calculator instructions [1]. The baseline EOS incidence used for the EOS calculator was set at 0.6 per 1000 live births. The advice of starting antibiotic treatment according to the EOS calculator was compared to the advice according to the national Dutch guidelines. These comparisons were made in retrospect and did not determine or change the clinical decisions. Antibiotic recommendation rates were reported as relative frequencies and compared using Chi-square test. We used SPSS 26 (IBM Corp, New York, USA), as statistical software. An alpha level of 0.05 was used to determine statistical significance.

A total of 976 newborns of ≥34 weeks gestational age were eligible. Sufficient data to determine both recommendations was available for 890/976 (91.2%), all of which were included in the analysis. Demographic data, maternal and neonatal risk factors, (non)-red flag presence and antibiotic recommendations are presented in Table 1. Antibiotic treatment was recommended by Dutch national guidelines for 363/890 (40.8%) newborns, versus for 101/890 (11.3%) by the EOS calculator ($p<0.01$). The two included newborns with positive blood cultures were recommended antibiotic treatment by both strategies.

The findings of this study echo the results of several retrospective and prospective studies, which also studied the use and impact of the EOS calculator [2]. All of them found a decrease in the use of empiric antibiotics us, but most compared the EOS calculator to American guidelines. Only one British study compared antibiotic use recommended by the NICE guideline to the EOS calculator, indicating the EOS calculator has potential to reduce antibiotic treatment by 74% among all late preterm and term newborns [3]. This study is the first to compare the EOS calculator with the Dutch adaptions of the NICE guidelines. The nearly four-fold difference in antibiotic treatment underscores the need to move away from categorical risk factor assessment to more precise methods. More research is necessary to determine the best methods and ways of implementation, but multivariate risk assessment using the EOS calculator appears a valid alternative to the current (adapted) NICE guidelines. Although the NICE guidelines are evidence-based, there is a lack of data on adherence in clinical practice, as well as a lack of evaluation on the impact on patient outcomes. In contrast, implementation of the EOS calculator has been associated with good adherence, significant reduction in empiric antibiotic treatment and significant reduction in EOS related health care utilization and costs [2, 4, 5].

We advocate not just the adoption of better strategies to allocate empiric antibiotics for suspected EOS in new guidelines, but also periodical monitoring, validation and evaluation of the effects of these strategies and guidelines.

Table 1. Patient characteristics, presence of risk factors, and antibiotic treatment recommendation for the Dutch guidelines and EOS calculator

		Dutch guidelines recommendation		EOS calculator recommendation	
	Total cohort	AB	No AB	AB	No AB
N	890	363 (40.8%)	527 (59.2%)	101 (11.3%)	789 (88.7%)
Infant sex (male)	512 (57.5%)	226 (62.3%)	286 (54.3%)	67 (66.3%)	445 (56.4%)
Gestational age, mean (SD)	38.9 (2.0)	38.5 (2.2)	39.1 (1.8)	38.4 (2.5)	39.0 (1.9)
Risk factors					
Maternal fever	223 (25.1%)	145 (39.9%)	78 (14.8%)	51 (50.5%)	172 (21.8%)
PROM	72 (8.1%)	71 (19.6%)	1 (0.2%)	17 (16.8%)	55 (7.0%)
Clinical appearance					
Well-appearing	782 (87.9%)	268 (73.8%)	514 (97.5%)	14 (13.9%)	768 (97.3%)
Equivocal	76 (8.5%)	65 (17.9%)	11 (2.1%)	55 (54.5%)	21 (2.7%)
Clinically Ill	32 (3.6%)	30 (8.3%)	2 (0.4%)	32 (31.7%)	0 (0%)
Positive blood culture	2 (0,2%)	2 (0.55%)	0 (0%)	2 (1.98%)	0 (0%)
Red flags (number of flags, combined total)	55	55	0	20	35
Non red-flags (number of flags, combined total)	1353	863	290	272	1081

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General Discussion

This thesis revolves around the EOS calculator, a tool based on a clinical prediction model. The EOS calculator uses the prediction model to provide a risk estimation specific for each newborn to guide use of empiric antibiotics for that particular newborn. As we enter the era of breakthroughs in personalized medicine and 'big data', these developments should be accompanied with thoughtful evaluation. Clinical research is needed to determine the proper and effective ways of implementing tools that guide management on an individual risk basis. This thesis analyzes the EOS calculator and its effects in practice from several angles, providing clinicians with a comprehensive overview of a tool that is likely to gain widespread use in the near future.

EOS and use of antibiotics

Pre-antibiotic accounts of neonatal sepsis depict the dangerous and fast trajectory of invasive bacterial infection in the neonatal phase, with close to 90% mortality [1]. Wide-spectrum, empiric antibiotic therapy is now the cornerstone of treating early EOS. Recognizing the importance of early treatment and potential to overlook subtle signs and symptoms, clinicians resolved to treating newborns based on categorical risk factors. This approach is present in many guidelines used today [2–4]. However, as EOS incidence rates dropped dramatically, this approach has led to excessive use of antibiotics, with wide variation. In Europe, up to 8-16% of all newborns are treated with antibiotics for suspected EOS [5, 6]. For each case of culture-confirmed EOS, now up to 96 newborns are started on antibiotic treatment [6]. In **Chapter 2**, we describe antibiotic use for suspected EOS in a Dutch cohort of 2076 births at 35 or more weeks of gestational age in Tergooi hospital. One hundred (4.8%) newborns were treated with empirical antibiotics, of which two had a positive culture. Including births at 34 weeks of gestational age showed even more antibiotic overtreatment (5.3% of births, or 56 treated newborns per case of EOS) [7].

The awareness on antibiotic overtreatment due to suspected EOS has been on the rise, but the issue has become more urgent with emerging evidence of adverse effects and worrisome correlations of early antibiotics with long-term sequelae. Short term adverse effects include mother-child separation with interference of breastfeeding, and increased healthcare expenditure [8, 9]. In preterm newborns, antibiotics have been associated with increased risk of necrotizing enterocolitis, fungal infections and death [10, 11]. Early antibiotics induce microbiome alterations, effecting the developing immune system [12, 13]. Culminating evidence reports associations with increased risks of allergic diseases, obesity and auto-immune diseases later in life [11, 14–16].

The combination of a dangerous but increasingly rare disease with severe overtreatment has led to a quest for a way to reduce empiric antibiotics in a safe way. This requires better methods to distinguish newborns in need of antibiotic treatment from those in which clinicians can safely await clinical course.

EOS calculator and use of antibiotics in practice

Since 2014, a web-based tool, commonly known as the neonatal early-onset sepsis calculator, or EOS calculator has been available freely online [17, 18]. Based on individual data, the tool provides a quantitative estimation of EOS risk. It also provides recommendation on the start of empiric antibiotics, determined by risk thresholds that were based on consensus [18].

The study presenting the EOS calculator calculated that it identifies 4% of newborns after at least 34 weeks of gestational age as 'high-risk' for EOS, recommending antibiotics for this group [17]. After some modifications to the calculator [18], Kuzniewicz et al performed the first implementation study in 14 hospitals in the United States [19]. In a prospective analysis of 204485 infants born at 35 weeks of gestation, use of the EOS calculator reduced the proportion of newborns receiving empirical antibiotic treatment, from 5.5% to 3.0%, without apparent adverse effects. In **Chapter 2**, we described the first published implementation of the EOS calculator outside the United States. The EOS calculator was introduced in accordance with existing protocols, and used for newborns considered at risk for EOS. We found a reduction from 4.8% to 2.7% after EOS calculator implementation in all newborns born after at least 35 weeks of gestation (relative reduction 44%). The results are in line with the comparable Australian study by Strunk et al, in which the proportion of newborns treated with antibiotics decreased from 12.0% to 7.6% after EOS calculator implementation, a relative reduction of 47%.

Because of increasing interest in and uptake of the EOS calculator [18, 20], we performed a systematic review and meta-analysis of all studies comparing EOS calculator use with conventional management strategies, detailed in **Chapter 3** [21]. We included 13 studies, 6 before-after implementation studies and 7 hypothetical database analysis studies. We found significant less use of antibiotics when using the EOS calculator, compared to conventional management. Meta-analysis indicated that EOS calculator use is associated with 44% less newborns started on antibiotics for suspected EOS (relative risk of 56% (95% confidence interval (CI) of 53%-59%). We found a wide range in calculated relative reductions in antibiotics among all studies, from 40 to 97% (relative risk 3-60%). This underscores that effects of implementing the calculator will greatly depend on local circumstances, including the prevalence of EOS and EOS risk factors in the population, pre-implementation policy for allocating antibiotics, and exact clinical algorithms for use of the EOS calculator. The issue of differences in GBS screening is an example of a local condition hypothesized to potentially compromise the applicability of the EOS calculator in European settings [6]. **Chapter 4** contains a post-hoc analysis evaluating the impact of different GBS screening strategies on the results of the EOS calculator. With risk-based screening, maternal GBS status was only known for a small proportion of newborns. Yet, EOS calculator recommendation results were equal to a routine-based GBS screening scenario in 97% of newborns, and risk-based screening did not result in fewer recommendations for antibiotic treatment. Although the numbers in this analysis

do not permit validation of the EOS calculator for risk-based screening settings, these findings present real-world evidence underscoring the theoretically limited contribution of GBS status to the EOS calculator prediction model, with a relative prediction weight of only 2.3% [17, 22].

Recent publications since our findings have further confirmed the association between EOS calculator and reduced antibiotics for suspected EOS, both in populations limited and not limited to exposure to maternal chorioamnionitis [6, 23–29].

Adherence to EOS calculator and guidelines

Both traditional guidelines and the EOS calculator method provide clinicians with a recommendation on the start of empiric antibiotics, but clinicians may deviate from these recommendations, for different reasons. The study in **Chapter 2** is unique in capturing adherence to the EOS calculator. We found over 90% adherence to the recommendation of the calculator, indicating clinicians only rarely felt the EOS calculator recommendation was against their clinical judgment. **Chapter 8** provides context to this finding by evaluating adherence to the current Dutch national guidelines [3], introduced in 2017 as adaptions of the British NICE guidelines [4]. We found that in more in the majority of newborns at risk for EOS that were eligible for empiric antibiotics by the Dutch guidelines, clinicians decided against the guideline and did not start antibiotics. This indicates that clinicians feel that the threshold for empiric antibiotics in the guidelines is too low, and implies that better adherence would lead to an increase in empiric antibiotics. Similar concerns about compliance and effects of the NICE guidelines have been reported in the United Kingdom [6, 30, 31].

EOS calculator and identifying EOS cases

A quintessential worry of clinicians caring for newborns is discharging a newborn that later proves to be suffering from EOS. Although it is recognized even perfectly well-appearing newborns without maternal risk factors can develop EOS, there is a strong focus on timely start of antibiotics even in these newborns. Fear of 'missing' EOS is a persistent worry among researchers evaluating the EOS calculator [18–20, 32–34].

Essential in **Chapter 3** is the meta-analysis of timely treatment of EOS cases, enabling evaluation of a rare outcome. It demonstrated that proportions of EOS 'missed' (not treated within 24 hours after birth) were comparable between management guided by the EOS calculator (5 of 18 [28%]) and conventional management strategies (8 of 28 [29%]) (pooled odds ratio, 0.96; 95% CI, 0.26-3.52; P = .95). Further analysis did also not indicate inferiority of the EOS calculator compared with conventional management strategies. A recent study by Goel et al confirmed the similar identification of EOS cases by the EOS calculator and existing guidelines [6].

In an editorial published along with **Chapter 3**, the developers of the EOS note that not all cases of EOS are predictable, and suggest to move away from the concept of 'missing

EOS cases', as it implies otherwise [35]. Clinical reality indeed dictates that prediction of EOS is limited, and vigilant observation for signs and symptoms is crucial. However, for clinicians and institutions using the calculator, it is important to be informed on what proportion of EOS cases it identifies, and the probability of EOS cases occurring if not started on antibiotics.

Mechanisms of the EOS calculator

In two subsequent landmark studies, the group of Puopolo and Escobar from Kaiser Permanente Northern California, presented the EOS calculator, a combination of a risk prediction model and a clinical management algorithm [17, 22]. **Chapter 6** presents a detailed evaluation of the methodology of construction of the model as well as the subsequent alterations, and the mechanisms of the paradigm that combines the prediction model and clinical algorithm.

The analysis found that multiple decisions in the development of the prediction model render the estimated risk estimate for a newborn reported by the EOS calculator to deviate from absolute risk. With a β0 coefficient different from standard methodology and post-hoc integration of upper 95%CI boundaries of physical examination risk estimation, the result deviate from what accurate absolute risk estimation by regression analysis would predict. At least in part, these decisions have a well-considered or pragmatic origin during development [18]. **Chapter 6** explains that, because stratification of newborns into the risk categories that determine management recommendation by the calculator depends on ranking rather than absolute estimation, this does not render use of the EOS calculator invalid. However, clinicians should be aware of these limitations, especially when making decisions on implementation in clinical care based on the individual risk estimation.

Since 2018, the EOS calculator presents a wide range of baseline EOS attack rates as input to the calculator use [36]. Attack rates other than 0.6 per 1000 live births have now been used in multiple studies [6, 19, 32, 37], but no studies have performed validation of this approach. **Chapter 6** comments on the controversial use of this unvalidated feature. The use of the standard baseline EOS risk 0.6 per 1000 live births as input best approaches the actual baseline risk. If there is evidence that a different baseline attack rate exists and is *not* due to differences in risk factors accounted for in the calculator, use of a different baseline attack rate can be considered. In that case however, recalibration of the model is strongly recommended to ensure the different baseline attack rate improves actually performance of the model. Although the developers of the EOS calculator use an adjusted attack rate of 0.6 per 1000 live births [19], no calibration efforts have been published for this rate, either.

EOS calculator and secondary benefits

Clinical care for newborns with suspected EOS involves much more than the decision to start or withhold empirical antibiotics. As **Chapters 2 and 3** demonstrate a reduction in

antibiotics associated with EOS calculator use, secondary reductions in EOS care can be hypothesized. Clinicians may wonder whether implementation of the EOS calculator may impact the duration and level of hospital care, rates of mother child-separation, the use of blood cultures and other laboratory investigations. Reductions in antibiotic use and related secondary benefits may in turn decrease health care costs.

To help answer these questions, **Chapter 5** presents a retrospective analysis of healthcare utilization and related economic costs before and after implementation of the EOS calculator in a non-academic Dutch teaching hospital. We found significant fewer EOS-care related laboratory investigations among all admitted newborns. Length of stay and total economic costs were significantly reduced in admitted term newborns, but not in preterm infants. As discussed in the chapter, these results follow the trend of findings by a theoretical approach by Gong et al, but are minor in comparison. The difference may reflect differences in health care costs between the United States and the Netherlands, a general difference between theory and practice, as well as differences in the implementation approach.

The results of **Chapter 5** regarding reductions in health care utilizations align with those of other implementation studies, that found reduced rates of blood cultures [19, 38, 39], other laboratory investigations [19, 39–43], and hospital or NICU admissions [43]. Again, studies report vast differences in magnitude of these effects. This suggests that although secondary benefits are very likely to result from EOS calculator implementation, their magnitude will strongly depend on local circumstances of clinical care policies, health care organization, EOS calculator implementation, and local costs of EOS care. Importantly, there is evidence that reductions in diagnostic testing do not lead to treatment delay [44].

Implications for the individual patient

The introduction of this thesis (**Chapter 1**) was illustrated using the dilemma of whether to start Xander and Yasmin on empiric antibiotic treatment. To many clinicians, they will appear as equally borderline cases; a minor symptom that may represent the normal post-birth transition phase, and few, but not zero risk factors. The EOS calculator can help. It calculates risk estimates of Xander at 0.58 per 1000 live births before examination, and 2.87 per 1000 live births after examination, compared to 4.07 and 20.03 per 1000 live births for Yasmin. These approximately 7-fold differences in risk estimates between the two newborns are clinically relevant: the EOS calculator recommends an observational approach for Xander, but antibiotic treatment for Yasmin. This contrasts with current guidelines, which advocate antibiotic treatment to both or only Xander, depending on the interpretation of the severity of the symptom. If Xander is started on treatment in spite of relatively low risk, he risks harms like unnecessary early-life intravenous antibiotics, a hospital admission instead of early discharge, and potential parental anxiety. Use of the EOS calculator can help prevent such a scenario.

Extrapolation to the Dutch situation

Roughly, about 170.000 children are born each year in the Netherlands, of which about 97% after 35 or more weeks of gestation and 87% occurring in hospitals [45]. **Chapter 2** estimates the use of empiric antibiotics for EOS in this population at roughly 5%, translating into ~7.000 newborns yearly treated with antibiotics. Based on **Chapters 2, 3, 8** and **9**, introduction of the EOS calculator into Dutch clinical practice can lead to a relative decrease in empiric antibiotic use of 41-47%, thus protecting ~3000 newborns from unnecessary antibiotics each year. The results of **Chapter 5** indicate an implementation of the calculator is associated with mean cost-savings of €207 per admitted term newborn. With 95% of Dutch births occurring term or later [45], 85% occurring in-hospital and 43% of those admitted for pediatric care or evaluation (**Chapter 5**), this would translate into estimated total yearly savings of ~€11.5 million per year. These estimations have a high degree of uncertainty, but are likely conservative. For instance, the 5% rate of empiric antibiotic use is based on data collected prior to introduction of the new Dutch guidelines [3], which are adaptions of the British NICE CG149 guidelines [4]. Research from the United Kingdom as well as our findings in **Chapter 8** indicate that strict adherence to these guidelines may result in a two-fold or more increase rate in empiric antibiotics for EOS [6, 30, 31]. In that context, implementation of the EOS calculator would result in even greater reductions in both clinical and financial burdens.

Limitations of this thesis

Although this thesis presents a comprehensive evaluation of the EOS calculator, the findings should be considered in the context of the limitations of the research presented. First, all included studies use a positive blood and/or CSF culture within 72 hours after birth as the 'gold standard' to define EOS. However, sepsis in a newborn is a complex, dynamic and poorly understood systemic condition [46]. Presence of clinical symptoms in absence of a positive blood culture is a recognizable clinical problem and has given rise to poorly defined terminology such as 'rule-out sepsis' or 'culture-negative sepsis' [47, 48]. At the same time, the literature reports on cases of positive blood culture spontaneously followed by negative blood cultures without antibiotic intervention, with and without transient symptoms [19]. Such cases may represent transient bacteremia, in which a pathogen temporarily infects the newborn's bloodstream, but is cleared by the immune system without a septic response [49]. Although these observations highlight the limitations of blood culture as a gold standard and the urgent need for a better, consensus definition [50], it remains the best proxy to date. In practice however, clinicians should keep both unconfirmed sepsis and transient bacteremia in mind as clinical possibilities, especially when using the EOS calculator.

Second, a significant part of the research presented in this paper (**Chapter 2**, **4**, **5** and **7**) took place in a single center, a non-academic Dutch regional teaching hospital. **Chapter 3** contains a rigorous overview of related studies across the world, showing wide variation

in effects of EOS calculator implementation. This is not surprising, given the wide variation in clinical management practices in suspected EOS between and within countries [51–54]. It underscores, however, that results cannot be easily generalized between countries and study centers, as they may be highly dependent on local conditions. A main takeaway of this thesis is therefore that careful consideration of local condition is warranted before and during implementation of EOS calculator, as well as monitoring and evaluation after implementation.

Third, the focus of this thesis on the EOS calculator comes at a cost of the consideration of alternative approaches. Compared to traditional guidelines such as the CDC 2010, NICE CG149, and Dutch national guidelines, the research in this thesis demonstrates superiority in limiting unnecessary antibiotics and suggests non-inferiority in safety outcomes. It does not however, compare the EOS calculator to other recent alternatives to these guidelines. The most promising of these is structured serial physical examinations [55–57].

Conclusions and future directions

The EOS calculator provides a much-needed alternative to categorical guidelines and algorithms in selecting newborns for empiric antibiotic therapy. It is founded on large quantitative data, provides objective assessment of newborns and uses an algorithm adapted to clinical reality and acceptance. Adoption of the EOS calculator allows substantial reductions in diagnostic testing, empiric treatment rates, and financial costs, without apparent safety concerns.

Further evaluation and validation

The EOS calculator is now adopted by the American Academy of Pediatrics as a valid strategy of managing newborns at risk for EOS [58], but a lot remains to be elucidated. Evidence to determine performance of ascertainment of EOS cases in practice is still limited, due to rarity of EOS. In addition, effectiveness of the EOS calculator outside of the United States and especially in countries with low empiric antibiotic use is uncertain. A multinational, multicenter approach could provide more insight in the relative potential gains for specific countries and settings. A cluster-randomized, stepped-wedge design could provide even stronger evidence regarding effectiveness than the before-after analyses conducted to date. Future implementation of the EOS calculator, whether in research context or as general quality improvement initiatives should be accompanied by thorough administration and monitoring of adherence and performance, enabling evaluation and comparison with alternative strategies.

Electronic implementation

In order to avoid subjectivity and variability in the input for the prediction model, the EOS calculator was developed using data nowadays often available in and extractable from electronic medical records. Although the EOS calculator is easily accessible using a desktop

or mobile web interface, this method still requires human input of these data. This step may impede usage and introduces opportunity for error. Integration in the inpatient electronic medical record software may be a solution to this [59]. Such embedding was envisioned by the developers [17], but not detailed in subsequent implementation reports [18, 19].

In a recent study, the group of Shakib studied integration of the EOS calculator in their electronic health record system in the nursery [29]. Discrete data entry elements were integrated into the electronic admission form with a hyperlink to the online EOS calculator, and calculator recommendations were linked to populate the admission, progress, and discharge notes. EOS calculator use subsequently increased by 44%. Integration reduced antibiotic orders from 7% to 1%, without more adverse events.

EOS calculator and biomarkers

In contrast to infections in older populations, traditional biomarkers of infection and inflammation are of little use in EOS [60, 61]. As the EOS calculator paradigm gains track in clinical practice, the best way of combining the EOS calculator with biomarkers will be a new field of interest. Research in this thesis showed little association between the EOS calculator risk estimation and C-reactive protein (CRP) and blood count parameters, suggesting minimal overlap in predictive value (**Chapter 7**). A recent large Chinese study hypothesized increased predictive value of the EOS calculator when used in combination with blood biomarkers, such as procalcitonin [62]. The latter is emerging as potentially useful in early neonatal sepsis, especially to assist in preventing prolonged use of antibiotics [63]. The search for new useful biomarkers for neonatal sepsis is ongoing, revealing promising candidates, such as presepsin [64, 65]. Future EOS calculator research reviewing it not as an isolated tool but in combination with promising biomarkers to further is likely to improve the ascertainment of sepsis and further limit unnecessary use of antibiotics [65].

Extending to different populations

The EOS calculator was developed using data of newborns born after at least 34 weeks of gestational age, and most validation occurred in those born at 35 weeks or later [17, 21, 22]. However, use of empirical antibiotics for suspected EOS is even higher among preterm infants, explained by vulnerability and higher infection rates [66]. However, overtreatment and difficulties in allocation are problems in this population as well, and there is room and rationale for better antibiotic stewardship.

A first step can be performing more studies including those born at 34 weeks of gestational age, which is already being done in retrospective analyses [6, 7]. Databases of even more premature newborns can then be used to determine epidemiology of EOS and EOS risk factors, and subsequently study applicability of the EOS calculator to improve antibiotic allocation. Adaptations to the model or different treatment threshold can be investigated to enhance applicability.

Another population lacking in EOS calculator research are the newborns in low- and middle-income countries. **Chapter 3b** contains a reply letter to comments in *JAMA Pediatrics* by Zhang and Niu in response to our systematic review and meta-analysis of EOS calculator studies [67]. They correctly emphasize that all eligible studies were of western origin. This is despite the fact that most cases of EOS occur in low- and middle income countries, and that these early neonatal infections are far more harmful compared to high-income countries [68]. A recent study in Thailand illustrates the presence of overtreatment and need for more antibiotic stewardship, with almost 300 newborns treated per culture-confirmed case of EOS [69]. The EOS calculator is available at no cost, does not require complicated laboratory equipment and its usage is relatively easy to learn for clinicians, making it an affordable and accessible tool for low-resource settings. Limited availability and inaccurateness of input data, such as gestational age, may create difficulties for applicability and implementation, just like differences in epidemiology. Robust epidemiological data of EOS and risk factors in low-and middle-income countries are therefore needed [70], followed by EOS calculator validation and implementation studies, which may have widespread impact on global neonatal care.

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11

A calculated risk
English summary

Een afgewogen risico
Samenvatting in het Nederlands voor niet-medici

A calculated risk – English summary

Newborn babies are vulnerable, and a bacterial infection entering the blood stream in the first days ('early onset sepsis', EOS) can have severe consequences. Early administration of empiric antibiotic treatment is an effective treatment, but it is very difficult to discern the early symptoms of EOS from normal newborn physiology or other neonatal problems. As a result, large numbers of newborns are treated with antibiotics and exposed to the harmful effects of antibiotics, despite actually not having EOS. This results in negative short- and long-term effects for newborns and parents, and increases costs for society.

This thesis evaluates the EOS calculator, a new method to allocate antibiotics for suspected EOS to newborns. We found a significant reduction in unnecessary antibiotics associated with the EOS calculator in three different studies: a single center implementation, a systematic review and meta-analysis of 13 studies evaluating use of the EOS calculator, and a sub-analysis of an observational multicenter prospective cohort study. We also found that in addition to protecting newborns from unnecessary antibiotics, the EOS calculator may reduce other health care utilization and help bring down health care costs. It appears that recommendations by the EOS calculator may be more in line with clinician intuition than those with current Dutch national guidelines; we found that adherence to those is low.

Implementation and of the EOS calculator should be thoughtful, and with caution. Interpretation should be nuanced and not seen as reflective of or communicated as absolute risk, and use of non-standard parameters should be preceded by recalibrations. We found however, that use of different strategies to determine maternal presence of the dangerous Group B Streptococcus pathogen is unlikely to hinder implementation.

Further research should focus on cautious implementation and good monitoring of the EOS calculator in clinical practice. It should involve comparisons to and potential combinations with other clinical strategies as well as new biomarkers.

Een afgewogen risico – Samenvatting in het Nederlands voor niet-medici

Een pasgeboren mens is kwetsbaar. Het afweersysteem is nog onrijp, en weinig weerbaar tegen infecties. Een bacterie die de bloedbaan binnendringt en verder groeit, kan in een tijdsbestek van uren of dagen een pasgeborene in levensgevaar brengen. Dit fenomeen wordt vroeg-neonatale sepsis genoemd, en vaak afgekort als EOS, naar het Engelse *early-onset sepsis*. Hoewel EOS dus gevaarlijk kan zijn, is het doorgaans goed te behandelen als tijdig gestart wordt met de juiste antibiotica via een infuus.

Bewezen EOS komt maar heel zelden voor; in westerse landen lopen schattingen uiteen van ongeveer 1 per 1000 tot zelfs maar 1 per 5000 pasgeborenen [1–4]. Véél vaker is er sprake van een verdenking op EOS [5]. Symptomen van EOS zijn lastig te onderscheiden van tekenen van normale fysiologische processen na de geboorte, of van symptomen van andere problemen. Zo kan een versnelde ademhaling een tekenen zijn van EOS, maar veel vaker optreden bij nog resterend vocht in de longen van de pasgeborene, of als gevolg van onrijpe longen bij te vroeggeboren kinderen. In tegenstelling tot de diagnostiek van infecties bij oudere kinderen en volwassenen, zijn de klassieke infectiewaarden in het bloed bij pasgeborenen van weinig toegevoegde waarde [6]. Artsen verdenken de aanwezigheid van EOS ook vaak op basis van de aanwezigheid van risicofactoren bij geboorte. Onbegrepen vroeggeboorte, of bijvoorbeeld de verdenking van een infectie bij de moeder, kunnen redenen zijn om aan EOS te denken.

De combinatie van de moeilijkheid om EOS te onderscheiden van andere zaken en het risico op ernstige gevolgen indien niet tijdig gestart wordt met antibiotica, heeft geleid tot het laagdrempelig starten van antibiotica bij pasgeborenen. Dit heeft geresulteerd in drastische overbehandeling: voor één pasgeborene met bewezen EOS worden in Europa naar schatting tot wel 80 pasgeboren behandeld met antibiotica [7–9]. De mate van overbehandeling verschilt sterk tussen landen, en zelfs tussen verschillende ziekenhuis in landen [8, 10]. Overbehandeling leidt tot onnodige ziekenhuisopname, scheiding van ouders en kind, bemoeilijkt borstvoeding, en resulteert in prikken voor bloedafnames en infuustoegang. Daarnaast worden kinderen onnodig blootgesteld aan de langetermijngevolgen van antibiotica, welke zijn geassocieerd met aantasting van de darmflora, overgewicht, en auto-immuunziektes [11–15]. Tenslotte zorgt overbehandeling van pasgeborenen voor hogere zorgkosten.

Traditionele richtlijnen, zoals die van de Verenigde Staten, het Verenigd Koninkrijk en van de Nederlandse vereniging van Kindergeneeskunde, gebruiken risicofactoren en symptomen om categorisch aan te wijzen welke pasgeborenen in aanmerking komen voor antibiotica in verband met mogelijke EOS [16–18]. Sinds 2011 is in de Verenigde Staten een nieuwe methode ontwikkeld om te bepalen bij welke pasgeborenen gestart moet worden met antibiotica, en bij welke eerst kan worden afgewacht [19, 20]. Deze methode, vaak de "EOS calculator" genoemd, gebruikt een combinatie van gedetailleerde informatie over risicofactoren en de aanwezigheid van specifieke symptomen, om voor elke

pasgeborene een individueel risico op EOS te berekenen. In dit proefschrift onderzoeken we de werking en effecten van de EOS calculator en vergelijken we deze methode met de bestaande richtlijn. Het doel is om te onderzoeken of met de EOS calculator het overmatig antibioticagebruik op een verantwoorde wijze kan worden teruggedrongen.

In **hoofdstukken 2**, **3** en **9** vergelijken we antibioticagebruik bij gebruik van de EOS calculator met antibioticagebruik bij gebruik van conventionele richtlijnen. In het Tergooi ziekenhuis in Blaricum zagen we een het antibiotica gebruik na invoering van de EOS calculator bijna halveren (een afname van 44%, om precies te zijn). De resultaten van onderzoek uitgevoerd in 7 verschillende ziekenhuizen in Nederland bevestigden de potentie van de EOS calculator om het antibioticagebruik te beperken. Ook het systematisch analyseren van de gegevens van 13 gepubliceerde onderzoeken toonden dat gebruik van de EOS calculator samengaat met een sterke afname in antibioticagebruik. We zagen in die analyse ook dat de afname nog veel groter is bij groepen pasgeborenen waarbij er bij de moeder ook gedacht werd aan een infectie. In sommige ziekenhuizen krijgen bij deze pasgeborenen allemaal antibiotica als de EOS calculator niet wordt gebruikt. Door het combineren van de gegevens van deze studies tot een grote dataset, konden we ook kijken naar de zeldzame gevallen van EOS. We zagen dat het percentage pasgeborenen met EOS waarbij binnen 24 uur na geboorte met antibiotica gestart werd, niet verschilde tussen gebruik van de EOS calculator of gebruik van conventionele richtlijnen. We zagen ook géén andere verschillen die erop konden wijzen dat de EOS calculator minder veilig was dan conventionele richtlijnen. Meer onderzoek is nodig om daar definitieve conclusies over te kunnen trekken.

In **hoofdstuk 8** tonen we aan dat artsen vaak afwijken van de huidige Nederlandse richtlijn, en ervoor kiezen om géén antibiotica te starten waar dit voor de richtlijnen wel geïndiceerd zou zijn. Dit wijst erop dat de richtlijn ook volgens artsen te laagdrempelig leidt tot antibioticagebruik. Strikt gebruik van de richtlijn zou leiden tot nóg meer antibioticagebruik, en dit wordt ook gezien bij een vergelijkbare richtlijn in het Verenigd Koninkrijk [9]. Vergelijkend met de EOS calculator, vonden we in **hoofdstuk 9** dat de richtlijn voor circa 4 keer zoveel pasgeborenen adviseert als de EOS calculator, en in **hoofdstuk 2** dat artsen zich vaak wél aan de aanbevelingen van de EOS calculator houden.

De meest voorkomende bacterie die EOS veroorzaakt is de Groep B streptokokken-bacterie, die van moeder naar kind kan worden overgedragen rondom de bevalling. Er zijn verschillende strategieën mogelijk om moeders te testen op de aanwezigheid van de bacterie. In Nederland wordt een risico-gebaseerde teststrategie gebruikt, terwijl in bijvoorbeeld de Verenigde Staten, waar de EOS calculator wordt gebruikt, in principe alle zwangeren worden getest. **Hoofdstuk 4** onderzoekt of dit verschil de resultaten van de EOS calculator beïnvloed. We zagen dat de resultaten voor 97% overeenkomen tussen de strategieën, wat erop wijst dat de EOS calculator ook met de Nederlandse strategie goed samen gaat.

In **Hoofdstuk 6** analyseren we gedetailleerd de ontwikkeling van en de werking van de EOS calculator. De EOS calculator is gebaseerd op een voorspellingsmodel dat aan

de hand van risicofactoren de kans op EOS voor een individuele pasgeborene voorspelt. Die kans wordt gekoppeld aan een algoritme dat leidt tot een aanbeveling voor het wel of niet starten van antibiotica. Een aantal aanpassingen aan het model en het algoritme hebben ertoe geleid dat de uiteindelijke voorspelling van de EOS calculator meer een relatieve indicatie van risico is (dus ten opzichte van pasgeborenen), dan een absoluut risico (precieze kans) representeert. We betogen in dit hoofdstuk ook dat de optie om de EOS calculator aan te passen aan de lokale hoeveelheid EOS gevallen eigenlijk niet gebruikt zou moeten worden; hiervoor zou eerst meer lokaal onderzoek moeten gebeuren. Dit zijn belangrijke bevindingen voor artsen en ziekenhuizen die het gebruik van de EOS calculator al hebben ingevoerd of dat overwegen.

Zoals hierboven samengevat, gaat gebruik van de EOS calculator samen met een duidelijke afname in het aantal pasgeborenen waarbij gestart wordt met antibiotica. Logischerwijs wordt aangenomen dat dit leidt tot minder ziekenhuiszorg en minder zorgkosten, maar daarover zijn maar weinig gegevens bekend. **Hoofdstuk 5** onderzoekt het effect van invoering van de EOS calculator op zorggebruik en EOS kosten. We zagen dat invoering van de EOS calculator wel samengaat met significante afnames in zorggebruik bij op tijd geboren kinderen, maar niet bij te vroeggeboren kinderen. Dit laatste is mogelijk te verklaren doordat te vroeg geboren kinderen, ongeacht het starten van antibiotica voor EOS, veel zorg nodig hebben in de eerste levensfase. Binnen de groep op tijd geboren kinderen zagen we minder bloedtesten, een kortere duur van de ziekenhuisopname, en gemiddeld 207 euro kostenbesparing per kind. Als we dat generaliseren naar de algehele Nederlandse populatie, behoort een kostenbesparing van ~€11.5 miljoen per jaar tot de mogelijkheden.

Gebruik van de EOS calculator is niet de enige strategie om antibioticagebruik bij pasgeborenen te verminderen. Er is veel onderzoek gaande naar nieuwe bloedtesten die EOS kunnen helpen aantonen of uitsluiten. Het meten van de stoffen presepsin en procalcitonine lijkt veelbelovend [21–24]. **Hoofdstuk 7** van dit proefschrift geeft aan dat de samenhang tussen EOS calculator en klassieke bloedtesten gering is. Er is in de toekomst vergelijkbaar en meer, groot opgezet onderzoek nodig naar de combinatie van de EOS calculator en bestaande en nieuwe bloedtesten.

Een andere recente ontwikkeling is het invoeren van systematisch herhaaldijk lichamelijk onderzoek van de pasgeborene, en de beslissing met betrekking tot antibiotica daarop te baseren [25–27]. Over de effecten van dergelijke strategieën is nog weinig bekend, met name met betrekking tot de veiligheid. In het vervolg zullen grote onderzoeken nodig zijn om de EOS calculator en andere strategieën te vergelijken, en om combinaties van strategieën te onderzoeken.

Tenslotte is meer onderzoek nodig naar gebruik van EOS calculator in niet-westerse context, en lijkt integratie van de EOS calculator in elektronische patiëntendossiers een veelbelovende ontwikkeling.

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Appendices

Curriculum Vitae

Born in 1990, Niek Achten was raised in Eindhoven, where he completed the Gymnasium at the Augustinianum secondary school in 2008. During medical school at the University Medical Center Utrecht, he worked as a research student at the Wilhelmina Children's Hospital for the Respiratory Syncytial Virus Research Group of professor Louis Bont from 2009 to 2015. It marked the start of a clinical research journey with a focus on infectious diseases and use of prediction modelling in pediatrics. Also interested beyond the field of medicine, Niek obtained a premaster in Political Science at the Vrije Universiteit van Amsterdam, and completed the interdisciplinary Honors Program of Utrecht University. After a research fellowship focused on respiratory pediatric viral infections, supervised by professor Tina Hartert at Vanderbilt University in Nashville, TN, USA, he graduated as MD in 2015.

Niek started clinical work at the pediatrics department of Tergooi hospital. Under supervision of mentor Frans Plötz, he continued his research journey with work on reducing unnecessary antibiotics for early onset sepsis. Interested in global child health, a position for clinical and research work ensued at the Academic Pediatric Center Paramaribo of the Academic Hospital Paramaribo in Suriname. Returning to the Netherlands in 2018, the work on early onset sepsis progressed into a full-time PhD project under supervision of Frans Plötz as co-promotor and professor Hans van Goudoever as promotor. Niek currently works as a junior doctor in pediatrics at the Sophia Children's Hospital/Erasmusmc in Rotterdam, looking to start specialist training in pediatrics in the near future.

Niek serves as the treasurer on the board of his childhood boy scouts association, which he holds dearly. He enjoys sports with a touch of adrenaline like (free)diving, kitesurfing and paragliding, but also futsal with 'FC Drogster'. He lives together with his girlfriend Praew.

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Sepsis Calculator Implementation reduces Empiric Antibiotics for Suspected Early-Onset Sepsis
The author's responsibilities were as follows: Data collection (NA, WD, PvdL, MvB, FP); Data Analysis (NA); Writing manuscript (NA, FBP), Data interpretation and critical review of manuscript (NA, WD-Z, PvdL, MvB, FP)

Association of Use of the Neonatal Early-Onset Sepsis Calculator with Reduction in Antibiotic Therapy and Safety – A Systematic Review and Meta-analysis
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The author's responsibilities were as follows: Data collection (NA); Data Analysis (NA, ET); Writing manuscript (NA, FP); Data interpretation and critical review of manuscript (NA, RZ, ET, FP)

Dutch multicenter study found that adherence to antibiotic recommendations for neonatal early-onset sepsis is low
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2019 - New information technologies for research with Big Data (0.6 ECTS)

2019 - Practical Biostatistics (1.1 ECTS)

Scientific conferences: posters and presentations

3rd Congress of joint European Neonatal Societies (2019) (1 ECTS)
Reduction in antibiotic therapy and safety associated with early-onset neonatal sepsis calculator use

Amsterdams Kindersymposium (2019) (0.75 ECTS)
Maternal risk-based group B streptococcus screening strategy and sepsis calculator implementation

Nederlandse Vereniging voor Kindergeneeskunde, 40e congres (2018) (0.75 ECTS)
Afname in antibioticagebruik voor verdenking vroeg neonatale sepsis na implementatie van de sepsis calculator

ReSViNET, 4th Meeting (2017) (1.25 ECTS)
Derivation of a Clinical Prediction Model for Severe Bronchiolitis Outcomes

American Thoracic Society 2017 International Conference (1.75 ECTS)

- » Interference Between Respiratory Syncytial Virus And Human Rhinovirus Infection In Infancy
- » Derivation Of A Clinical Prediction Model For Severe Bronchiolitis Outcome

Tergooi Wetenschapssymposium (2017) (0.75 ECTS)

Use of antibiotics guided by a sepsis calculator in suspected early-onset neonatal sepsis; preliminary results of a prospective observational study.

List of publications

Included in this thesis

Achten NB, Klingenberg C, Benitz WE, Stocker M, Schlapbach LJ, Giannoni E, Bokelaar R, Driessen GJA, Brodin P, Uthaya S, van Rossum AMC, Plötz FB
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Achten NB, Dorigo-Zetsma JW, van Rossum AMC, Oostenbrink R, Plötz FB
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Achten NB, Dorigo-Zetsma JW, van Rossum AMC, Oostenbrink R, Plötz FB
Sepsis calculator implementation reduces empiric antibiotics for suspected early-onset sepsis
In revision

van der Weijden BM, Achten NB, Bekhof J, Evers EE, Berk M, Kamps AWA, Rijpert M, ten Tusscher GW, van Houten MA, Plötz FB
Dutch multicenter study found that adherence to antibiotic recommendations for neonatal early-onset sepsis is low
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van der Weijden BM, Achten NB, Bekhof J, Evers EE, Dongen O, Kamps AWA, Rijpert M, ten Tusscher GW, van Houten MA, Plötz FB
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Achten NB, van Meurs M, Jongman RM, Juliana A, Molema G, Plötz FB, Zonneveld R
Markers of endothelial cell activation in suspected late onset neonatal sepsis in Surinamese newborns: a pilot study
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Benitz WE, Achten NB. Finding a role for the neonatal early-onset sepsis risk calculator. *EClinicalMedicine* 2020; 19: 100255. [partly included in introduction of this thesis]

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Supplemental Materials – Chapter 1

Supplemental Appendix 1. Data Sources for Figure

1. Freedman RM, Ingram DL, Gross I, Ehrenkranz RA, Warshaw JB, Baltimore RS. A half century of neonatal sepsis at Yale: 1928 to 1978. Am J Dis Child 1981; 135: 140–4.
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Supplemental Materials – Chapter 3

Supplemental Table 1. Risk of Bias

Study	Source of data	Partici-pants	Out-comes	Predic-tors	Sample size	Missing data	Model eval-uation	Results	Overall
Kuzniewicz 2017	Low	Low	Low	Low	Low	Unclear	Low	Low	Low
Achten 2018	High	High	Low	High	High	Low	Low	Unclear	High
Dhudasia 2018	High	Low	Low	Low	High	Low	Low	Unclear	Low
Strunk 2018	Low	High	High	Low	High	Unclear	Low	Unclear	High
Gievers 2018	High	Low	High	Low	High	Unclear	Low	High	High
Beavers 2018	High	Low	Unclear	Unclear	High	Low	Low	Unclear	Unclear
Shakib 2015	High	High	High	Low	High	Low	Low	Unclear	High
Kerste 2016	High	High	High	Low	High	High	Low	High	High
Warren 2017	High	High	High	Low	High	High	Low	High	High
Money 2017	High	High	High	Low	High	Unclear	Low	High	High
Carola 2017	High	Low	High	High	High	High	Low	High	High
Joshi 2019	High	High	Low	Low	High	Unclear	Low	Unclear	High
Klingaman 2018	Low	Unclear	Unclear	Unclear	High	Unclear	Low	Unclear	Unclear

Supplemental Table 2. Safety Concerns Related to Management Guided by the EOS Calculator, Other Than Missed EOS Cases

	Safety concern				
Study	Incidence	Delay in AB	Readmissions	Mortality/ morbidity	Other adverse events
Kuzniewicz 2017	No change	No increase in AB 48-72hrs postpartum	No change	No change	None reported
Achten 2018	No change	No delay in AB	n/a	NR	None reported
Dhudasia 2018	No change	NR	NR	No change	'No safety concerns'
Strunk 2018	No change	No increase in AB 48-72hrs postpartum	No change	No change	'No adverse events'
Gievers 2018	No change	NR	No change	NR	None reported
Beavers 2018	No change	NR	NR	No change	'No negative outcomes'
Klingaman 2018	NR	NR	NR	NR	None reported

Supplemental Table 3. Management of Symptomatic and Asymptomatic EOS Cases in as Guided by the EOS Calculator or Conventional Strategy

		Management guided by EOS calculator			Conventional management strategy		
Study design	EOS cases (n)	N	Symptomatic	Asymptomatic	N	Symptomatic	Asymptomatic
Before-after studies	AB <24 hrs, n (%)	13	11	2	20	15	5
	AB >24 hrs ('missed'), n (%)	5	4	1	8	5	3
Hypothetical database analysis studies	AB <24 hrs, n (%)	7	7	0	n/a	n/a	n/a
	AB >24 hrs ('missed'), n (%)	5	2	3	n/a	n/a	n/a
Totals	AB <24 hrs, n (%)	20	18 (90)	2 (10)	20	15 (75)	5 (25)
	AB >24 hrs ('missed'), n (%)	10	6 (60)	4 (40)	8	5 (63)	3 (38)

PRISMA-P Review Protocol

Systematic Review Sepsis Calculator – Review Protocol –Version 1.4

Administrative information

Title

1a. Title Evaluation of the neonatal sepsis calculator; a systematic review.

1b. Update This review is not an update of a previous investigation

Registration

2. Registration This review was registered in PROSPERO as of Nov 12, 2018. Significant amendments to the protocol will be reflected in updated of the registration where possible.

Authors

3a. Contact Protocol corresponding authors:
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3b. Contribution NA: authored protocol
FP: reviewed protocol, guarantor.
RB: reviewed protocol

Amendments

4.

22-11-2018; version 1.1

Finalizing additions and refinements in Appendix 2, made to enhance and precise data extraction and collections. If necessary, data-extraction was repeated according to protocol, for any changed definitions.

14-12-2018; version 1.2

Adding refinements to outcomes related to missed EOS cases and delay in antibiotics, as discussed and used in data extractions. If necessary, data-extraction was repeated according to protocol, for any changed definitions.

29-1-2019; version 1.3

Enhancement of definitions regarding missed EOS cases. Adding methodology and decision-making for meta-analysis as a result of insights and expertise of additional co-authors. Addition of MOOSE guideline/checklist adherence.

24-4-2019; version 1.4

Refining exclusion criteria in order to ensure independence of results by preventing datasets involved in EOS calculator development entering the analysis.

Support

5a. No sources of financial or other support for the review to be reported.

5b. No external sponsors to be reported.

5c. No role of external funders, sponsors or institutions to be reported.

Introduction

Rationale

6. There is worldwide a growing interest in using the newborn sepsis calculator because of its promising results to reduce empiric antibiotic use in early onset sepsis (EOS). Studies evaluating the effects of the sepsis calculator in different neonatal populations are critical for responsible and successful adoption. A comprehensive overview of such studies hitherto performed will allow informed decision-making when practitioners consider the sepsis calculator, and can help identify current lacunas and shortcomings that need to be addressed.

Objectives

7. PICO statement

Patients: Newborns born at 34 weeks of gestational age or later

Intervention: Use of sepsis calculator as provided by Kaiser Permanente

Comparison: Current, previous, or alternative management of suspected EOS

Outcomes: Primary: reduction in empiric antibiotics Secondary: number of adverse events

Methods

Eligibility criteria

8. Eligibility criteria:

Studies will be selected according to the criteria below.

Study characteristics

» Any study design validating the sepsis calculator or comparing sepsis calculator results with alternative management strategies according to PICO characteristics previously stated under Objectives.

» Original data; we will exclude studies without original data, but we will include any studies generating new information by pooled analysis of previously included studies such as meta-analysis.

» We will include studies that report results related to either the primary outcome (use of antibiotics in the first 72hrs of life) and/or on the secondary (safety) outcomes; including to EOS incidence/cases, blood and or cerebrospinal fluid cultures, readmissions, EOS mortality, severe EOS disease, prolonged hospital stay, and adversities mentioned by authors.

» To ensure independence of outcome estimates, we excluded datasets that were used to develop the EOS calculator. (Post-hoc decision; amendment 24-4-2019)

» No other restrictions on study characteristics.

Report characteristics

» Peer-reviewed; we will only include publications that are peer-reviewed, meaning the exclusion of dissertations, thesis, abstracts and other non-peer-reviewed publications.

» Publishing date in or after the 2011 calendar year; we will only include publications from 2011 or later, since the model of subject was not published until 2011.

» Language: we aim to include published reports in all languages. If required title and/or abstract, or required full-text publications are not available in languages spoken by one of the main reviewers, other authors will be consulted for translations. If the publication was in a language that could not be translated, we will attempt to contact main authors for a translation or to confirm non-eligibility of the publication. If unsuccessful, we will review if translation of title/abstract through Google Translate is sufficiently adequate to confirm non-eligibility. If this is unsuccessful, publications will be excluded from the review.

9. Information sources

Literature searches will be developed using the resources below. We will use a search strategy developed by NA and reviewed by FP to find eligible publications in Cochrane, PubMed/Medline and EMBASE libraries. To ensure literature saturation, we will additionally search Google Scholar and Web of Science for publications that cite one or both of the publications detailing the sepsis calculator itself (section 10A).

Source	Coverage date	URL
Cochrane library	Nov 9, 2018	cochranelibrary.com
MEDLINE/PubMed	Nov 9, 2018	ncbi.nlm.nih.gov/pubmed
EMBASE	Nov 9, 2018	elsevier.com/solutions/embase-biomedical-research
Google Scholar	Nov 9, 2018	scholar.google.com
Web of Science	Nov 9, 2018	apps.webofknowledge.com

Search strategy

10. General search strategy for primary electronic databases

General search terminology and strategy for electronic databases is detailed in the table below. Exact search syntax for each electronic database can be found in Appendix 1.

Search terms				
All fields				
'sepsis calculator'				
'eos calculator'				
'sepsis risk calculator'				
'eos risk calculator'				
OR				
Title/abstract				
'predictive'	AND		AND	'early onset sepsis'
'risk'		'model'		'early onset neonatal sepsis'
'quantitative'		'algorithm'		'EOS'
'stratification'				

Like 'OR' Dotted lines mark interchangeable search terms.

Search strategy for reviewing citations

A. Reviewing papers citing original sepsis calculator publications:

» Puopolo, Karen M., et al. "Estimating the probability of neonatal early-onset infection on the basis of maternal risk factors." *Pediatrics* (2011): peds-2010. https://scholar.google.com/scholar?cites=17123481009097227542&as_sdt=2005&sciodt=0,5&hl=en

http://apps.webofknowledge.com/CitingArticles.do?product=WOS&SID=E3Fh1qobGFDBM1NVJf6&search_mode=CitingArticles&parentProduct=WOS&parentQid=1&parentDoc=1&REFID=424305078

» Escobar, Gabriel J., et al. "Stratification of risk of early-onset sepsis in newborns≥ 34 weeks' gestation." *Pediatrics* 133.1 (2014): 30-36.
https://scholar.google.com/scholar?cites=2777091998604103995&as_sdt=2005&sciodt=0,5&hl=en
http://apps.webofknowledge.com/CitingArticles.do?product=WOS&SID=D4qMrvKsaI7c6VxcdlW&search_mode=CitingArticles&parentProduct=WOS&parentQid=2&parentDoc=2&REFID=464004160

B. Reviewing Citations of Included articles
For all publications included after full-text review, all publications cited by these articles will be evaluated. Title and abstract and if necessary full-text of any publications not present among results of initial search will be evaluated according to eligibility criteria. If any eligible publications, we will evaluate the reason for exclusion from the initial search. If deemed necessary, this will prompt a more broaden search, and possibly amendments to protocol.

C. Repetition of search
To avoid missing recent publications, the search of this review will be repeated towards the end of this review. Any publications not included in the original search results will be evaluated as detailed before.

Study records

11a. Data management

Search results will be imported in reference software (Mendeley). Duplicates will be merged manually. Where possible, citations will be completed with full (English) title an abstract if not already available through search results, will be obtained.

After the selection process, reviewers will examine studies for overlap in study process and/or study population. If the data from the same study is published multiple times, these publications will be combined to avoid overrepresentation of study data in review results.

11b. Selection process

Independent review of title and abstract of each unique search result using the eligibility criteria will be performed by two reviewers (NA, RB). Discrepancies were resolved by discussion. If necessary, the full-text publication will be obtained to help with discussion.

Next, for all search results that required obtaining of full-text publication, said full-text publication will be independently reviewed by two reviewers (NA, RB), for eligibility.

Discrepancies will be resolved through discussion, if necessary using the expertise of a third reviewer (FP).

We will record the reasons for exclusion at both stages (title/abstract and full-text screening) using predefined categories based on eligibility criteria: 'non relevant' (i.e. not concerning the sepsis calculator), 'no original data', ' no data on outcomes', 'not peer-reviewed', and 'ineligible due to language'.

11c. Data collection process

Using pre-specified data extraction sheets (appendix 2), two reviewers will (NA, RB) will independently extract relevant data on study design, setting, population, methods, and results for each included study. Discrepancies be resolved by discussion, and a third reviewer (FP) will help unresolved disagreements. We will contact study authors to resolve any uncertainties.

Data items

12. Data items

For each study, we will extract data on the authors, year of publication, location, setting, design, sepsis calculator implementation method, study population (size of birth cohort, size of sepsis calculator population, size of comparison population, gestational age, presence of EOS risk factors), population EOS incidences, used EOS incidence for sepsis calculator.

Outcome and prioritization

13. Outcome and prioritization

For the primary outcome, we will look at (changes or differences in) rate/number of newborns treated with or selected for empiric antibiotics for (suspected) EOS, which may translate to all (start of) empiric antibiotic therapy within 24 and/or 72 hours. Preference will be given to the 72 hours timeframe, and for studies to be included in meta-analysis, original authors of the study will be contacted to resolve any uncertainty and ensure data is valid for the 72 hours timeframe.

Wherever possible, primary outcome data (reduction in empiric antibiotics), we will calculate the relative reduction (RR) that occurs by using the sepsis calculator compared to the compared approach in the respective study, to ensure a consistent outcome measure across studies. Calculations will be reviewed by a second (NA or RB) and third reviewer (FP), to check and correct for mistakes.

For secondary (safety) outcomes, we will extract data on 'missed' or delayed EOS cases, readmissions, changes in EOS incidence, changes in use of antibiotics, changes in mortality, changes in morbidity, changes in need for intensive care. To allow for nuanced interpretation of safety results, we will extract description of these safety outcomes where reported by the authors. To ensure no safety data is missed, reviewers will extract all adverse events or safety concerns given by the authors of the studies. We will also distinct

between 'not reported' and 'absence' for each safety outcome. An EOS case was defined as missed if the management strategy did not allocate antibiotics within 24 hours after birth. In case of before-after implementation studies, we will look at actual management of the case in the cohort/epoch in which the respected management strategy was used. In case of the calculator, a case assigned observation with check of vitals, which showed clinical symptoms within 24 hours is seen as a missed EOS case. 'Well-appearing' was considered asymptomatic, unless otherwise specified by the study. However reported EOS cases that were assigned vitals will be included in the safety outcome table, for completeness.

For delay in antibiotics as outcome, we will include any delay in antibiotics reported by authors, or any increase in antibiotics between 24 and 72 hours after birth as possible EOS delays.

Risk of bias in individual studies

14. Risk of bias in individual studies

Given the nature of the intervention covered by this systematic review – a prediction modeling tool designed for use in daily clinical practice – we will deviate from standard risk of bias assessment as described in the Cochrane Handbook for Systematic Review of Interventions, and use instead the dedicated CHARMS-checklist (CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies) to assess individual studies for risk of bias. In accordance with this checklist, we will evaluate risk of bias for each study on the following domains: data source, outcomes, candidate predictors, sample size, missing data, model performance, model evaluation and results. As the review intends to review studies evaluating results sepsis calculator, items that refer to model development will not be assessed, as they not applicable (appendix 3).

Using these items, two reviewers (NA, RB) will discuss each study and categorize the risk of bias as 'high', 'low' or 'unclear'. Disagreements will be resolved through expertise of a third reviewer (FP). We will not attempt blinding for this process, as by this stage the reviewers will have sufficient knowledge of the studies to render true blinding impossible. We plan to include studies regardless of risk-of-bias, but we will discuss the general risk of bias of included studies in our discussion to allow for a balanced interpretation of results.

Data synthesis

15a. Describe criteria under which study data will be quantitatively synthesized.

At the time of commencement of this review, we do not plan to quantitatively synthesize study data, mainly for two reasons:

First, the goal of this review is to provide a comprehensive overview of available sepsis calculator evidence rather than calculating a precise, universal estimate of the effect size(s) of sepsis calculator implementation. Because actual implementation and use of the sepsis

calculator is likely to be different for each institution according to the particular setting and dynamics of early onset sepsis, a universal estimate would be of little relevance.

Second, based on the wide variation in strategies for management of newborns at risk for early onset sepsis, significant heterogeneity in study population, comparators and sepsis calculator implementation strategies is expected, limiting the possibilities for reliable and useful meta-analysis.

However, we cannot rule out the development of different insights through either the nature of initial review results, the input of a large group of co-authors/collaborators, and/or the input and viewpoints of peer-reviewers. In that case, providing sufficient homogeneity among studies, we plan to conduct meta-analysis using a random-effects model, because of expected differences in study population sizes. Exact methods of handling and combining of data, assessing of consistency and additional analysis however, will depend on aforementioned insights and viewpoints. Before commencing any meta-analysis, this protocol will be amended with precise protocols for data synthesis and analysis.

Amendment
Following review of our data and initial results by added co-authors with specific expertise in meta-analyze, we will explore possibilities to meta-analyze primary outcomes for those studies that provide reasonably comparable, separate populations for the management guided by the EOS calculator and existing management strategies, such as before-after implementation studies. Pooling of results missed EOS cases will be performed if deemed appropriate by consulted epidemiologists.

15b. Planned methods for data synthesis
Not applicable, see 15a.

Amendment
Data will be tested for statistic heterogeneity before pooling using I^2 and comparison of confidence intervals. 0-40 % might not be important, whereas higher I^2 values may represent moderate (30-60 %), substantial (50-90 %) or considerable heterogeneity (75-100 %). Subgroups analysis may be performed if deemed logical and useful given heterogeneity in results and study designs or populations. Analysis will be performed using using RevMan version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). Reporting of all outcomes and

15c. Proposed additional analyses
Not applicable, see 15a.

15d. Type of summary

Data on number and characteristics of included studies will presented in results. Systematic tables will be provided for both main and secondary outcomes, including detailed study characteristics for each included study. Narrative synthesis for both main and secondary outcomes will be provided, highlighting congruencies as well as discrepancies within study results. We plan on including results regardless of risk of bias in synthesis of results. For safety outcomes, results will be accompanied with descriptions of events or cases as provided by authors of included studies when relevant for interpretation.

Amendment

For pooling or meta-analysis of data of multiple studies, results will be presented as a forest-plot with effect size estimates and confidence intervals for each study as well as the overall effect, or by pooled data results in table format and appropriate statistical test results where necessary.

Meta-bias(es)

16. Planned assessment of meta-bias(es)

Currently, there is no register widely used for validation and impact studies, limiting the potential to assess and control for publication bias. Selective outcome reporting bias will be limited for the main outcome, since this is represented by a single outcome measure that is defined as a criterion for study eligibility. As for secondary outcomes, we will report on any selective outcome reporting by comparing methods with results within studies.

17. Assessment of strength of evidence

Using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework as a guideline, we evaluate evidence on both the main outcome as well as secondary outcomes for strengths. Where applicable and possible, authors will assess the available evidence on the GRADE domains; risk of bias, imprecision, inconsistency, indirectness, and/or publication bias. Rather than reporting the strength of evidence as a main study result, this review will use these assessments as a ground for recommendations for future research or implementation efforts.

Protocol appendix 1 – Search syntax

Cochrane

("sepsis calculator" OR "eos calculator" OR "sepsis risk calculator" OR "eos risk calculator") OR (("predictive":ti,ab OR "risk":ti,ab OR "quantitative":ti,ab OR "stratification":ti,ab) AND ("model":ti,ab OR "algorithm":ti,ab) AND ("early onset sepsis":ti,ab OR "early onset neonatal sepsis":ti,ab OR "EOS":ti,ab))

MEDLINE/PubMed

((((((("EOS"[Title/Abstract]) OR "early onset sepsis"[Title/Abstract]) OR "early onset neonatal sepsis"[Title/Abstract])) AND ((((("predictive"[Title/Abstract]) OR "risk"[Title/Abstract]) OR

"quantitative"[Title/Abstract]) OR "stratification"[Title/Abstract]) AND (("model"[Title/Abstract]) OR "algorithm"[Title/Abstract]))) OR ("sepsis calculator" OR "eos calculator" OR "eos risk calculator" OR "sepsis risk calculator") AND (("2011/01/01"[PDat] : "3000/12/31"[PDat]))

EMBASE

('eos calculator' OR 'sepsis calculator' OR 'sepsis risk calculator' OR 'eos risk calculator' OR (('predictive':ti,ab OR 'risk':ti,ab OR 'quantitative':ti,ab OR 'stratification':ti,ab) AND ('model':ti,ab OR 'algorithm':ti,ab) AND ('early onset sepsis':ti,ab AND 'early onset neonatal sepsis':ti,ab OR 'early onset neonatal sepsis'/exp OR 'early onset neonatal sepsis' OR 'eos':ti,ab))) AND [2011-2018]/py

Protocol appendix 2 – Search syntax

Data extraction sheet

The following data will be recorded for each study. If no data was available on a particular item/variable 'NR' will be reported. Data will be noted as reported by the authors, but also recalculated by reviewers using listed formulas. In case of discrepancies, both numbers were extracted.

Study characteristics and primary outcome

Author	Last name of 1st author of study, et al if applicable
Year of publication	Last name of 1st author of study, et al if applicable
Location	Country where study was conducted. 'Multiple' if conducted in multiple countries.
Setting	'Tertiary' for academic, referral, or university-affiliated institutions, 'Regional' for other intitutions, 'Mixed' for a combination of tertiary and regional.
Study design	Retrospective/Prospective/Cross-sectional and Cohort/(nested) Case-Control/Clinical (randomized) trial
Implementation	'Yes' if sepsis calculator was actually (partly) or completely implemented in daily clinical workflow.
Gestational age	(range) of gestational age of newborns in whom the sepsis calculator was tested.
N (births)	Number of live births during the study period, in the range of gestational age used in the particular study.
Included subset	If applicable, criteria/selection for the subset in which the sepsis calculator was tested. 'N/A' newborns in the study if the sepsis calculator was tested in all.
N (subset)	If applicable, N=number of newborns in subset among which the sepsis calculator was tested.
Comparison	Description of alternative approach used as comparison management strategy as opposed to the sepsis calculator. I.e. CDC guidelines, National guideline, local protocol, 'AB in all cases of chorioamniotitis', etc.
N (comparison)	If applicable, N=number of newborns in comparison strategy. Only if sepsis calculator and comparison estimates results were derived from different data (actual implementation studies.
AB (calculator)	Rate (%) of newborns included treated with empiric antibiotics for (suspected) EOS when the sepsis calculator was used. Preferably ≤72 hrs for EOS indication, but any antibiotics ≤72 hrs, ≤48hrs or 24 hrs postpartum or antibiotics described as EOS-related allowed as proxy. (Refer to section 13 for more detail.)

AB (comparator)	Rate (%) of newborns included treated with empiric antibiotics for (suspected) EOS when the comparative management strategy was used. Refer to 'AB (calculator)' and section 13 for more detail.
AB (change, absolute)	Absolute reduction (or increase) in empiric antibiotics, if the sepsis calculator was used, compared to the comparator strategy. Both as reported by the authors (if reported and as calculated using; [AB (comparator)] - [AB (calculator)]
AB (change, relative)	Relative reduction (or increase) in empiric antibiotics, if the sepsis calculator was used, compared to the comparator strategy. Both as reported by the authors (if reported and as calculated using; 100- [AB (calculator)]/ [AB (comparator)]
EOS incidence	Population EOS incidence among newborns in study, or for newborns in the study institution. As reported by the authors, and as calculated using [proven EOS cases]/[newborns in study period]
Subset incidence	EOS incidence among newborns included for sepsis calculator testing, as reported by the authors, and as calculated using [proven EOS cases]/ [newborns eligible for inclusion].
Calculator incidence	EOS incidence as used for sepsis calculator appliance in the study; the particular setting used in the calculator when the calculator was applied.

Secondary outcomes - safety

To ensure no safety data is missed, reviewers will extract all adverse events or safety concerns given by the authors of the studies. We will also distinct between 'not reported' and 'absence' for each safety outcome.

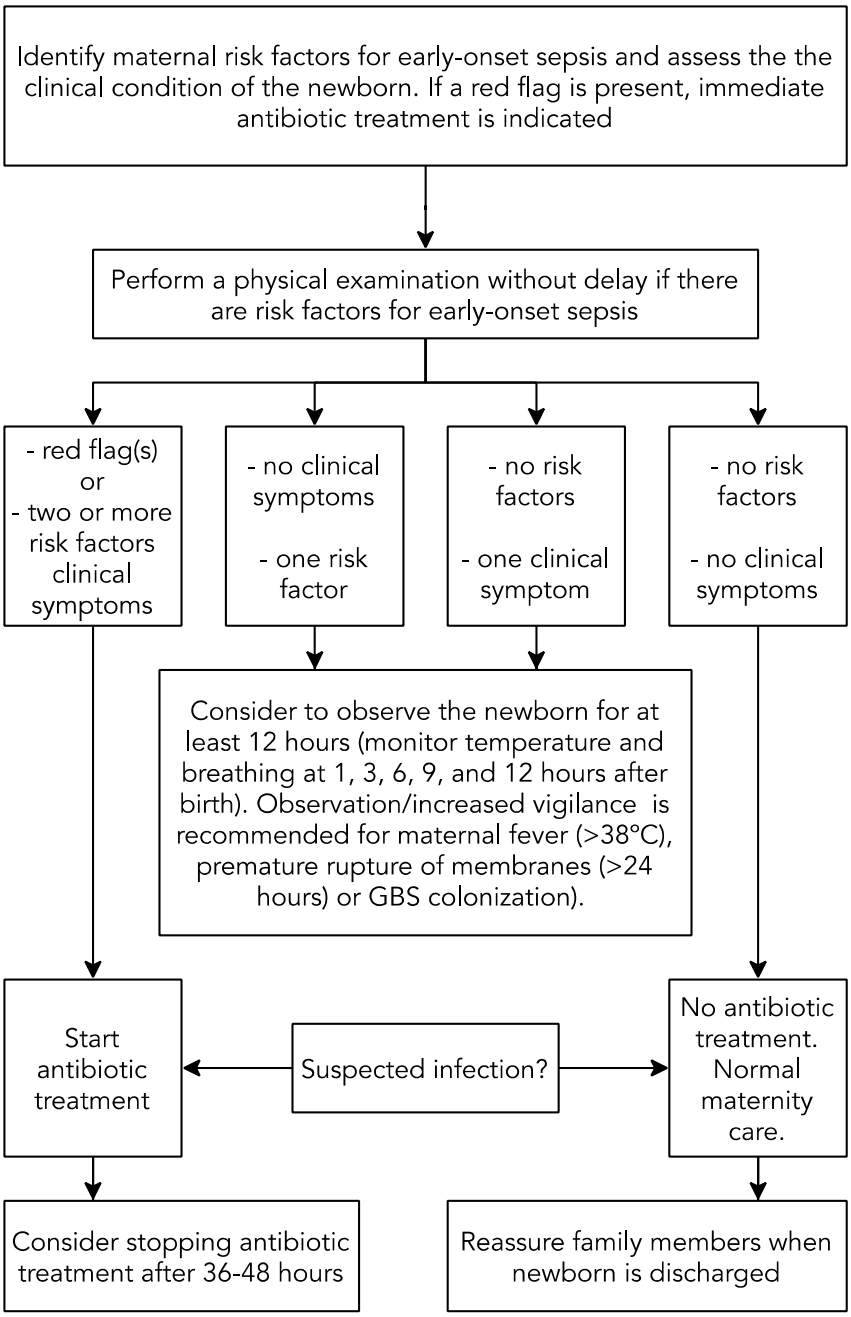
Missed EOS cases	Description of EOS proven cases that were not selected for antibiotics by the sepsis calculator and/or the comparative strategy. Description preferably include: » if the case was or would have been selected for antibiotics using the different strategy in the study » if the case was or would have been selected for antibiotics using national guidelines » if antibiotics were started within 24hrs, within 72hrs, after 72hrs, or not at all » if the newborn deteriorated, and if this happened within 24hrs » if cultures were taken at start of antibiotics and what the results were » a brief description of the clinical course » other remarks deemed relevant by the authors of the study.
Incidence change	If a change in sepsis calculator was seen after implementation of the sepsis calculator.
Antibiotics change	If the rate (%) of empiric antibiotics started ≥24 hrs after birth changed after implementing the sepsis calculator.
Mortality/morbidity	If a change in mortality and or morbidity (such as need for intensive care) was seen after implementation of the sepsis calculator.
Adverse events	Any adverse events or safety concerns listed by the authors of the studies. We will also distinct between 'not reported' and 'absence' for each safety outcome

Protocol appendix 3 – Evaluation of Risk of Bias

Using items below, based on the CHARMS checklist, reviewers will discuss each study and categorize the risk of bias as 'high', 'low' or 'unclear'.

Source of data	Source of data (e.g., cohort, case-control, randomised trial participants, or registry data)
Participants	Participant eligibility and recruitment method (e.g., consecutive participants, location, number of centres, setting, inclusion and exclusion criteria). Participant description; details of treatments received, if relevant; study dates.
Outcomes	Definition, consistency, blinding.
Predictors	Definition, method of measuring. Specifically; whether a priori sepsis risk was adequately adjusted for study population.
Sample size	Number of participants, number of EOS cases, number of events per predictor.
Missing data	Number of participants with any missing data (on predictors or outcomes); number of participants with missing data for each predictor; handling of missing data.
Model performance	Calibration (calibration plot, calibration slope, Hosmer-Lemeshow test) and Discrimination (C-statistic, D-statistic, log-rank) measures with confidence intervals; Classification measures (e.g., sensitivity, specificity, predictive values, net reclassification improvement) and whether a priori cut points were used
Model evaluation	Method used for testing model performance: development dataset only (random split of data, resampling methods, e.g., bootstrap or cross-validation, none) or separate external validation (e.g., temporal, geographical, different setting, different investigators); In case of poor validation, whether model was adjusted or updated (e.g., intercept recalibrated, predictor effects adjusted, or new predictors added)
Results	Comparison of the distribution of predictors (including missing data) for development and validation datasets

Supplemental Materials – Chapter 8



Supplemental Figure 1. Flowchart adapted from Dutch guidelines Shown is the adaptation of the algorithm used in the guidelines to provide guidance for antibiotic treatment prescription according to the number of present maternal risk factors and/or clinical symptoms ((non-)red flags)

Supplemental Table 1. Maternal and Neonatal Risk Factors for EOS in the Dutch guidelines. The Dutch adaptation (9) of the NICE guidelines (8) omits 6 neonatal risk factors included in the original NICE guidelines, all categorized as non-red flags: jaundice within 24 hours of birth; unexplained bleeding, thrombocytopenia, or abnormal coagulation; persisting oliguria; hypo- or hyperglycaemia; metabolic acidosis; tachycardia. Both maternal and neonatal risk factors are accompanied with specific detailed nuances in both guidelines.

Maternal risk factors	Neonatal risk factors
Red flags	
Parenteral antibiotic treatment given to the woman for confirmed or suspected invasive bacterial infection (such as septicaemia) at any time during labour, or in the 24-hour periods before and after the birth	Respiratory distress starting more than 4 hours after birth
Suspected or confirmed infection in another neonate in case of a multiple pregnancy	Neonatal epileptic seizures
	Need for mechanical ventilation in a term neonate
	Signs of shock
Non-red flags	
Invasive group B streptococcal infection in a previous neonate	Altered behaviour, -responsiveness or -muscle tone
Maternal group B streptococcal colonisation, bacteriuria or infection in the current pregnancy	Feeding difficulties (feed refusal, gastric retention, vomiting, distended abdomen)
Suspected or confirmed rupture of membranes without contractions for more than 24 hours in a term birth	Apnoea and bradycardia
Preterm birth following spontaneous labour (before 37 weeks' gestation)	Signs of respiratory distress (tachypnoea, moaning, retractions, nasal flaring)
Suspected or confirmed rupture of membranes for more than 18 hours in a preterm birth	Hypoxia (for example, central cyanosis or reduced oxygen saturation level)
Intrapartum fever higher than 38°C or suspected or confirmed chorioamnionitis	Neonatal encephalopathy
	Need for cardio-pulmonary resuscitation
	Need for mechanical ventilation in a preterm neonate
	Persistent pulmonary hypertension
	Temperature abnormality (lower than 36°C or higher than 38°C) unexplained by environmental factors
	Local signs of infection (for example, affecting the skin or eyes)