Reduction in antibiotic therapy and safety associated with use of the early-onset neonatal sepsis calculator - A systematic review and meta-analysis

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Date of revision: May, 16, 2019
Word count: 3499

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Key points

Question: What is the effectiveness and safety of management guided by the EOS calculator in reducing empirical antibiotic therapy for suspected EOS?

Findings: Management guided by an EOS calculator was associated with a significant reduction in empirical antibiotic therapy compared to conventional management, with a relative risk of 56% in before-after implementation studies. Safety data were limited, but we found no evidence of inferiority compared to conventional management strategies.

Meaning: Management guided by the EOS calculator is associated with a substantial reduction in empirical antibiotic therapy, but more studies are needed to inform on safety.

Abstract

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

Objective: To assess effectiveness in reduction of antibiotic therapy and safety of management guided by the EOS calculator compared to conventional management strategies.

Data Sources: Electronic searches in MEDLINE, EMBASE, Web of Science and Google Scholar were conducted from 2011 (EOS calculator model introduction), through January, 2019.

Study Selection: We included all studies with original data, comparing management guided by the EOS calculator to conventional management strategies for allocating antibiotic therapy to newborns suspected for EOS.

Data Extraction and Synthesis: Following PRISMA(-P) guidelines, 2 authors independently extracted relevant data from full text papers and supplements. CHARMS and GRADE tools were used to assess 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 Outcome(s) and Measure(s): The difference in percentage of newborns treated with empirical antibiotics for suspected or proven EOS between management guided by the EOS calculator and conventional management strategies. Safety-related outcomes involved missed EOS cases, 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, 2.5 to 60.2%) for empirical antibiotic therapy, favoring the EOS calculator. Meta-analysis revealed a relative risk 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 EOS cases 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 EOS calculator is associated with a substantial reduction in empirical antibiotics for suspected EOS. Available evidence regarding safety of use of the EOS calculator is limited, but shows no indication of inferiority compared to 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 (eAppendix 1 in Supplement**)**. 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.[27,28,33,34,38–40] Studies used a retrospective (n=7),[27,28,33,34,36,39,40] prospective (n=3),[15,26,38] or combined approach (n=3).[30,35,37] Ten of 13 studies were performed in the US.[15,27–30,33,36–38,40]

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 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 Netherlands.[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.

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.[41] 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.[41–44] 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.[45,46] 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.

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.[3,15,29,47] 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.[15,26,37,48]

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.[49] 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.[50,51] 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.[52] This allows for customization of this aspect according to setting and populations, although this feature is controversial and has thus far not been validated.[52,53]

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.[1,54,55] On average, around ~5% of term newborns in the US are treated with empirical antibiotics,[56] while percentages vary between 2.3 and 7.9% across Europe.[57,58] 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,[33,53,59] epidemiological data supports the safety of limited use of empirical antibiotics.[57,60] 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,[46] whereas some other countries use strategies based on risk factors.[61] 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.[62,63] 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.[62,64]

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.[33,37,65] Ideally, implementation of a prediction model in a different setting is preceded by validation in that setting.[66] 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.[14,15,67,68] 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,[39,42] and laboratory marker candidates.[63,69]

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.

Acknowledgements

We are grateful to all authors (G. Escobar, T. Strunk, L. Gievers, C. Klingaman, J.

Beavers, and J. Blau) who provided data and/or clarification on their studies. Dr. Achten had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. E. Giannoni is supported by the Leenaards Foundation. A.M.C. van Rossum reports grants from Sophia Foundation and grants from Coolsingel Foundation outside the submitted work.

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Tables and Figures

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

	Study and location	Setting	Design	Births	Included	EOS calculator		Conventional strategy			Reduction in empirical AB	
						n	Empiric AB, n (%)	Strategy	n	Empiric AB, n (%)	Absolute %	Relative risk, % (95% CI)
Before-after analysis	Kuzniewicz 2017, US	Mixed	Prospective	204 485	GA ≥ 35 w	56 261	1698 (3.0)	CDC informed	95 543	5226 (5.5)	2.5	55.2 (52-58)
	Achten 2018, Netherlands	Regional	Retro- and prospective	3953	GA ≥ 35 w	1877	51 (2.7)	National guideline informed	2076	100 (4.8)	2.1	56.4 (40-79)
	Dhudasia 2018, US	Tertiary	Retro- and prospective	11 782	GA ≥ 36 w	6090	222 (3.6)	CDC/AAP informed	5692	356 (6.3)	2.6	58.3 (49-69)
	Strunk 2018, Australia	Tertiary	Prospective	4233	GA ≥ 35 w	2502	206 (8.2)	Adaptation AAP guideline	1732	237 (13.7)	5.5	60.2 (50-72)
	Gievers 2018, US	Tertiary	Retro- and prospective	9039	Chorioamnionitis, GA ≥ 35 w	143	13 (9.1)	CDC informed	213	203 (95.3)	86.2	9.5 (6-16)
	Beavers 2018, US	Tertiary	Retrospective	NR	Chorioamnionitis GA ≥ 35 w	76	28 (36.8)	Pre-implementation	180	168 (93.3)	57.0	39.3 (29-53)
	Shakib 2015, US	Tertiary	Retrospective	20 262	Chorioamnionitis, well-appearing, GA ≥ 34 w	698	39-86 (5.6-12.3) [a]	Actual practice (CDC/CFN informed)	n/a	430 (61.6)	49.3–56.0 [a]	9.1–20.0 [a]
	Kerste 2016, Netherlands	Regional	Retrospective	2094	AB for suspected EOS, GA ≥ 34 w	108	51 (47.2)	Actual practice (national guideline informed)	n/a	108 (100)	52.8 [b]	47.2 (39-58) [b]
	Warren 2017, US	Tertiary	Retrospective	NR	AB for suspected EOS, GA ≥ 34 w	202	47 (23.3)	CDC guideline	n/a	188 (93.1)	69.8 [c]	25.0 (19-32) [c]
	Money 2017, US	Tertiary	Retrospective	19 525	Chorioamnionitis well-appearing for 24 hours [c], GA ≥ 35 w	362	9 (2.5)	Current protocol (CDC/AAP informed)	n/a	361 (99.7)[c]	97.2 [c]	2.5 (1-5) [c]

	Carola 2017, US	Tertiary	Retrospective	17 908	Chorioamnionitis, GA ≥ 35 w	896	209 (23.3)	Actual practice (AB if chorioamnionitis)	n/a	896 (100)	76.7	23.3 (21-27)
	Joshi 2019, US	Tertiary	Retrospective	10 002	Chorioamnionitis, well-appearing at birth, GA ≥ 34 w	596	53 (8.9)	Institutional practice (AB if chorioamnionitis)	n/a	596 (100)	91.1	8.9 (3-11)
	Klingaman 2018, US	Tertiary	Prospective	505	GA ≥35 w	505	2 (0.4)	CDC informed	n/a	9 (17.8)	1.4	22.2 (5-102)

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.

[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%).

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

Study	Management guided by EOS calculator				Conventional management strategy				*P* value
	Births	**EOS cases**	**AB <24 h**	**AB >24 h ('missed')**	**Births**	**EOS cases**	**AB <24 h**	**AB >24 h ('missed')**	
Kuzniewicz 2017	56 261	12	8	4	95 543	24	18	6	
Achten 2018	1877	2	2	0	2076	2	0	2	
Dhudasia 2018	6090	3	2	1	5692	1	1	0	
Strunk 2018	2502	1	1	0	1731	1	1	0	
Totals, n (%)	67 019	18	13 (72%)	5 (28%)	105 365	28	20 (71%)	8 (29%)	0.95

Abbreviations: AB: antibiotics; EOS; early-onset sepsis; h; hours; w: weeks; n/a: not applicable

[a] Only studies with EOS cases included in table.

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

Study[a]	Included population	EOS cases (n)	AB <24 h	AB >24 h ('missed')
Shakib 2015	GA ≥ 34 w, chorioamnionitis	1	1	0
Money 2017	GA ≥ 37 w, chorioamnionitis	1	0	1
Carola 2017	GA ≥ 35 w, chorioamnionitis	5	3	2
Joshi 2019[b]	GA ≥ 34 w	5	3	2
	Totals, n (%)	12	7 (58%)	5 (42%)

Abbreviations: AB: antibiotics; EOS; early-onset sepsis; h; hours; w: weeks GA: gestational age

[a] Only studies with EOS cases included in table. Kerste 2016 omitted due to overlap in cases with the Achten 2018 study included in Table 2.

[b] Data from update provided by original authors; 5 cases among n=12 901 total births ≥34 weeks' gestation.

Figure 1. Study selection process

Flowchart of search results and study selection. [a]Studies excluded because dataset was used in EOS calculator development.

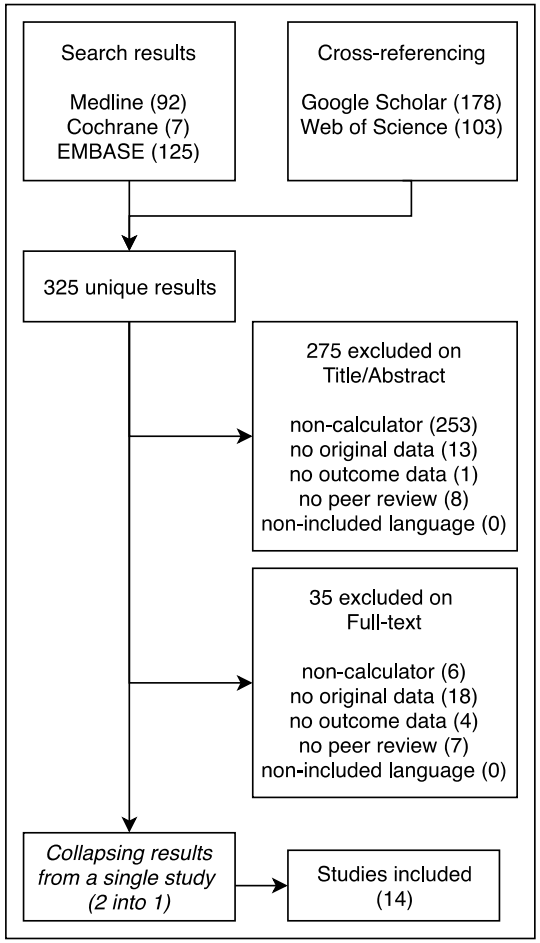

Figure 2. Forest plot presenting relative risk for use of empirical antibiotics

Data presented for before-after studies included in the meta-analysis. Data were pooled under the assumption of a random effects model.