

BRIEF REPORT

Neonatal early-onset sepsis calculator recommended significantly less empiric antibiotic treatment than national guidelines

1 | INTRODUCTION

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 and widespread antibiotic use cause widespread overtreatment. Strategies for identifying high-risk neonates include categorical risk factor assessments, multivariate risk assessments and risk assessments primarily based on the infants' clinical condition. The Netherlands issued revised guidelines in 2017, adapted from the UK National Institute for Health and Care Excellence (NICE) 2012 guidelines. The Dutch risk assessment includes eight maternal and 15 neonatal factors and uses red flags to indicate whether to start antibiotic treatment. Prospective evaluation of these guidelines showed that strict adherence led to empiric antibiotic recommendations in 42.8% of neonates at risk for EOS.¹

The EOS clinical decision calculator is an alternative to categorical methods.² 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 that combines individual risk assessments with clinical recommendations for managing neonates.² A meta-analysis and systematic review contained good evidence in favour of the EOS calculator for reducing antibiotic therapy, but limited evidence for non-inferiority of the EOS calculator when it comes to safety.³ The EOS calculator also has been introduced to various countries and continents, including the USA, Europe and Australia.

This study compared the Dutch guidelines and the EOS calculator to see whether they recommended antibiotics for 1024 neonates born at 34 weeks or more at risk for EOS. The calculator was developed for this age group. This was a planned sub-study of a prospective multi-centre observational study.¹ Data were collected in seven hospitals in The Netherlands between September 1, 2018, and November 1, 2019. The study was approved by the Zwolle Medical Ethics Review Committee (number 180220), and informed consent was obtained from the patients' caregivers. The risk of EOS was

defined as one or more of the following: maternal intrapartum fever higher than 38.0°C, ruptured membranes for 18 hours or longer, premature birth at less than 37 weeks, mother positive for Group B Streptococcus, intrapartum antibiotic prophylaxis, and, or, clinical symptoms suggesting EOS within the first 72 hours of life. The clinical maternal and neonatal data were prospectively collected by clinicians, including data needed to evaluate the Dutch guidelines and EOS calculator. Clinical appearance was categorised into well-appearing, equivocal or clinical illness, in line with the EOS calculator instructions.¹ The calculator's baseline EOS incidence was 0.6 per 1000 live births. The recommendations to start antibiotic treatment were retrospectively compared for both methods and did not affect the clinical decisions. The antibiotic recommendation rates were compared using chi-square and reported as relative frequencies. The statistics were analysed with SPSS 26 (IBM Corp.), and statistical significance was an alpha level of .05.

We had sufficient data on 890/976 (91.2%) of the eligible neonates born at 34 weeks to compare the recommendations from the calculator and guidelines. Table 1 presents the demographic data, maternal and neonatal risk factors, red flag data and antibiotic recommendations. The Dutch guidelines recommended antibiotic treatment for 363/890 (40.8%) neonates versus 101/890 (11.3%) for the EOS calculator ($P < .01$). Of these 90/890 (10.1%) children, antibiotic treatment was recommended by both methods, including the two neonates with positive blood cultures.

Our findings echo the results of a systematic review and meta-analysis of retrospective and prospective studies on the EOS calculator.³ All of them reported that the use of empiric antibiotics decreased, but most compared the calculator to American guidelines. Only one UK study compared the NICE guideline to the EOS calculator, and this indicated that it had the potential to reduce antibiotic treatment by 74% among all late preterm and term-born infants.⁴ This was the first study to compare the EOS calculator with the Dutch adaptations of the NICE guidelines. The nearly fourfold difference in antibiotic treatment highlights the need to use more precise methods than categorical risk factors. Further research should determine the best way to use the EOS calculator for multivariate risk assessments, but it appears to be a valid alternative to the Dutch

Abbreviations: EOS, early-onset sepsis; NICE, National Institute for Health and Care Excellence.

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TABLE 1 Patient characteristics, risk factors and antibiotic treatment recommendations for the Dutch guidelines and EOS calculator

	Total cohort	Dutch guidelines antibiotic recommendations		EOS calculator antibiotic recommendations	
		Yes	No	Yes	No
Number of recommendations	890	363 (40.8%)	527 (59.2%)	101 (11.3%)	789 (88.7%)
Male	57.5%	62.3%	54.3%	66.3%	56.4%
Gestational age, weeks 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%)
Premature rupture of membranes	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 (54.4%)	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%)
Total red flags ^a	55 (100%)	55 (100%)	0 (0%)	20 (36.4%)	35 (63.6%)
Total non-red flags ^a	1353 (100%)	863 (63.8%)	490 (36.2%)	272 (20.1%)	1081 (79.9%)

Abbreviation: EOS, early-onset sepsis.

^aThe Dutch guidelines use eight maternal and fifteen neonatal risk factors, each categorised as either red flag or non-red flag. Antibiotic treatment is recommended in the presence of at least one red flag and/or two or more non-red flags.

guidelines. The NICE guidelines have severe and potentially dangerous limitations. They were predominantly randomised controlled trials, with few high-quality studies, and they largely ignored other types of evidence, such as observational or registry studies. They also lack data on adherence in clinical practice and the impact on patient outcomes. In contrast, the EOS calculator has been associated with good adherence and significant reductions in empiric antibiotic treatment and EOS-related healthcare use and costs.^{3,5}

New guidelines need to adopt better strategies for allocating empiric antibiotics for suspected EOS, together with periodical monitoring, validation and evaluation of the effects of the guidelines.

KEYWORDS

antibiotic therapy, newborn, sepsis calculator

CONFLICTS OF INTEREST

None.

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REFERENCES

1. van der Weijden BM, Achten NB, Bekhof J, et al. Dutch multicentre study found that adherence to antibiotic recommendations for neonatal early-onset sepsis is low. *Acta Paediatr*. Submitted.
2. Escobar GJ, Puopolo KM, Wi S, et al. Stratification of risk of early-onset sepsis in newborns \geq 34 weeks' gestation. *Pediatrics*. 2014;133:30-36.
3. Achten NB, Klingenberg C, Benitz WE, et al. Association of use of the neonatal early-onset sepsis calculator with reduction in antibiotic therapy and safety. *JAMA Pediatr*. 2019;173:1032-1040.
4. Goel N, Shrestha S, Smith R, et al. Screening for early onset neonatal sepsis: NICE guidance-based practice versus projected application of the Kaiser Permanente sepsis risk calculator in the UK population. *Arch Dis Child - Fetal Neonatal Ed*. 2020;105(2):118-122.
5. Achten NB, Visser DH, Tromp E, Groot W, van Goudoever JB, Plötz FB. Early onset sepsis calculator implementation is associated with reduced healthcare utilization and financial costs in late preterm and term newborns. *Eur J Pediatr*. 2020;179:727-734.