

# Early-Onset Sepsis Risk Calculator: A Review Of Its Effectiveness And Comparative Study With Our Evidence-Based Local Guidelines

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## Research

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# Abstract

## Background

According to most early-onset sepsis management guidelines, approximately 10% of the total neonatal population are exposed to antibiotics in the first postnatal days with subsequent increase of neonatal and pediatric comorbidities. Early-onset sepsis risk calculator has been developed with the purpose of avoiding antibiotic overtreatment among neonates  $\geq 34$  weeks' gestational age: a review of literature demonstrates its effectiveness in reducing antibiotic overtreatment, laboratory testing, painful procedures and NICU admission; however, some missed cases of culture-positive early-onset sepsis have also been described.

## Methods

All neonates with birth weight  $\leq 1500$  g, 34–36 weeks' gestational age neonates with suspected intraamniotic infection and neonates with three clinical signs of early-onset sepsis or two signs and one risk factor for early-onset sepsis receive empirical antibiotics. Neonates  $\geq 34$  weeks' gestational age with risk factors for early-onset sepsis or with one clinical indicator of early-onset sepsis undergo serial measurements of C-reactive protein and procalcitonin in the first 48–72 hours of life; they receive empirical antibiotics in case of abnormalities at blood exams with one or more clinical signs of early-onset sepsis. We therefore compared the number of patients for which antibiotics were needed, based on early-onset sepsis calculator, and the number of patients we treated with antibiotics during the study period. Comparisons between the groups were performed using McNemar's test and statistical significance was set at  $p < 0.05$ .

## Results

During the study period (1st January 2018-31st December 2018) 32/265 (12.1%) neonates  $\geq 34$  weeks' gestational age at risk for early-onset sepsis received antibiotics within the first 12 hours of life. According to early-onset sepsis calculator: 55/265 (20.7%) patients would have received antibiotics with early-onset sepsis incidence 2/1000 live births ( $p < 0.0001$ ); 44/265 (16.6%) patients would have received antibiotics with early-onset sepsis incidence 0.1/1000 live births ( $p < 0.025$ ). One patient with culture-negative early-onset sepsis would not have received antibiotics with an early-onset sepsis incidence of 0.1/1000 live births.

## Conclusion

Our evidence-based protocol for treatment decision-making of neonatal early-onset sepsis entails a further decrease of antibiotic overtreatment compared to early-onset sepsis risk calculator. No negative

consequences for patients were observed.

## Background

In most high-income countries, the incidence of culture-confirmed early-onset sepsis (EOS) has decreased to 0.4–0.8 cases per 1000 live-born term infants over the last years; the overall incidence has reached about 1–2 cases per 1000 live newborns<sup>1,2</sup>. This result has been achieved through a continuous update of current evidence (Table 1)<sup>3–9</sup>.

Table 1

Title: Milestones towards current management of EOS

Legends: CAM, chorioamnionitis; CBC, cell blood count; CRP, C-reactive protein; EOS, early-onset sepsis; GA, gestational age; GBS, Group B Streptococcus; IAP, intrapartum antibiotic prophylaxis; WBC, white blood cell.

CDC, 1996	Implementation of GBS IAP <sup>3-5</sup>
CDC, 2002	Introduction of universal antepartum GBS screening <sup>4,5</sup>
CDC, 2010	<p>Empirical antibiotic therapy for all newborns with signs of sepsis and for well-appearing newborns with suspected maternal CAM<sup>5</sup>.</p> <p>Observation <math>\geq</math> 48 hours for well-appearing infants <math>\geq</math> 37 weeks and 0 days' GA with duration of membrane rupture before delivery <math>&lt;</math> 18 hours and not received or inadequate indicated maternal IAP<sup>5</sup>.</p> <p>Limited evaluation (blood culture at birth and CBC with differential and platelets at birth and/or at 6–12 hours of life) and observation <math>\geq</math> 48 hours for well-appearing infants born to mothers who received no or inadequate indicated GBS IAP with either <math>&lt;</math> 37 weeks and 0 days' GA or duration of membrane rupture before delivery <math>\geq</math> 18 hours<sup>5</sup></p>
ACOG, 2011	CDC 2010 revised guidelines for EOS management have been approved by ACOG <sup>6</sup>
AAP, 2012	<p>Diagnostic tests (blood culture at birth, total/differential WBC count <math>\pm</math> CRP at age 6–12 hours) and empirical antibiotic therapy even for well-appearing preterm infants with duration of membrane rupture before delivery <math>\geq</math> 18 hours or inadequate indicated maternal IAP<sup>7</sup>.</p> <p>Diagnostic tests (total/differential WBC count <math>\pm</math> CRP at age 6–12 hours) for term asymptomatic infants with sepsis risk factors other than CAM (duration of membrane rupture before delivery <math>\geq</math> 18 hours or inadequate indicated GBS IAP)<sup>7</sup>.</p> <p>Longer antibiotic therapy is recommended in well-appearing preterm infants with negative blood culture and abnormal total/differential WBC count or CRP<sup>7</sup>.</p> <p>Longer antibiotic therapy is recommended in asymptomatic term newborns with maternal CAM, negative blood culture and abnormal total/differential WBC count or CRP<sup>7</sup></p>
NICE, 2012	Empirical antibiotic therapy in newborns with any red flags or with at least two “non-red flag” risk factors or clinical indicators <sup>8</sup>
AAP, 2013	Agreement with the CDC guidelines as regards the starting of empirical antibiotic therapy in case of well-appearing infants at 35 to 36 weeks' GA with sepsis risk factors other than maternal CAM (duration of membrane rupture before delivery $\geq$ 18 hours or inadequate indicated maternal IAP) <sup>9</sup>

As the incidence of EOS has decreased over the last two decades, clinicians raised concerns about antibiotic exposure among uninfected newborns: according to Group B Streptococcus (GBS) EOS prevention guidelines, approximately 10% of the total neonatal population are exposed to antibiotics in the first postnatal days, and almost 100% of the extremely preterm population are exposed to ampicillin and an aminoglycoside<sup>10</sup>. Early antibiotic exposure is associated with the emergence of antibiotic-resistant pathogenic microorganisms and with the decrease of intestinal microbial diversity, which can cause very difficult to treat infections<sup>10</sup>. Antibiotics administration in the neonatal period has also been

linked with late onset sepsis, necrotizing enterocolitis, increased mortality and long term health outcomes such as childhood asthma, obesity, inflammatory bowel disease, celiac disease and type 1 diabetes<sup>10</sup>. Furthermore, administration of antibiotics to neonates often results in admission to intensive care unit, decreased breastfeeding, invasive procedures and increased hospital costs<sup>11</sup>.

For all these reasons, it is important to avoid unnecessary antibiotics administration to patients during the early post-natal period<sup>11</sup>. However, the clinical diagnosis of sepsis is challenging for neonatologists because many signs of sepsis are nonspecific and are observed with other non-infectious conditions<sup>7</sup>. On the other side, low-level bacteremia (4 colony-forming units/mL or less), inadequate blood specimens (less than 1 mL) or maternal antibiotic treatment before or during delivery may result in negative blood cultures<sup>1,7</sup>. It has been estimated that the incidence of culture-negative EOS is 6 to 16 times higher than that of culture-confirmed EOS<sup>1</sup>. Total white blood cell (WBC) count with its subcomponents and platelet count have also shown a poor predictive accuracy<sup>7</sup>. Both protein and genetic biomarkers have been evaluated in patients with suspected or proven EOS<sup>12</sup>. However, the specificity and selectivity of genetic biomarkers are yet to be fully evaluated<sup>12</sup>. Protein biomarkers demonstrate high specificity and sensitivity and include C-reactive protein (CRP), Procalcitonin (PCT), Serum amyloid A, Lipopolysaccharide-binding protein,  $\alpha$ -1 antitrypsin, lactoferrin, haptoglobin, fibronectin and neopterin<sup>12</sup>. CRP and PCT are the most commonly used protein biomarkers for the diagnosis of sepsis and monitoring of antibiotic therapy<sup>13–15</sup>. CRP is secreted 4–6 hours after stimulation and peaks at about 36–48 hours; its half-life is about 19 hours<sup>16</sup>. PCT is secreted 2 hours after stimulation and reaches a peak at 12–24 hours; its half-life is about 24 hours<sup>16</sup>. Both CRP and PCT have a physiologic increase over the first 24–48 hours of life; baseline concentrations of both markers are mainly affected by birth weight and gestational age (GA)<sup>16</sup>. It has been estimated that for each 100 g increase in birth weight, the PCT concentration decreases by 2.2% and CRP concentration increases by 2.4%<sup>16</sup>. PCT concentration decreases by 11.4% with each week of increasing GA, while CRP concentration increases 6% per week<sup>16</sup>. Concentration of CRP is also increased by 0.4% per hour of ruptured membranes, 14.5% per hour of active labor, 40% for antenatal steroid administration and 28% for intrapartum antimicrobial prophylaxis (IAP)<sup>16</sup>. Concentration of PCT increases significantly after rupture of membranes  $\geq$  18 hours, respiratory distress syndrome, hemodynamic failure, perinatal asphyxia, intracranial hemorrhage, pneumothorax and resuscitation<sup>14,16</sup>. On these basis, different attempts have been done to establish the appropriate cut-off values of both PCT and CRP<sup>17–19</sup>. As regards EOS diagnosis, it has been estimated that the mean sensitivity of PCT and CRP is 73.6% and 65.6%, respectively<sup>16</sup>. The mean specificity of PCT is 82.8% versus 82.7% for CRP<sup>16</sup>. Umbilical blood PCT and CRP have also been tested for EOS diagnosis; cut-off values were different among studies (0.5-2 ng/ml for PCT and 1–10 mg/l for CRP)<sup>20</sup>. Sensitivity of cord blood PCT and CRP is 82% and 71%, respectively; specificity is 86% for cord blood PCT and 71% for cord blood CRP<sup>20</sup>.

After June 2005, several studies have assessed the safety of monitoring neonates at risk for EOS with serial physical examinations: this approach resulted in less laboratory exams and antibiotics exposure without missing any case of EOS<sup>21–23</sup>.

In December 2012 the Kaiser Permanente EOS calculator has been developed with the purpose of avoiding antibiotic overtreatment<sup>24</sup>. The EOS calculator is based on a multivariate predictive risk model which allows clinicians to estimate a newborn's individual risk for EOS given objective maternal risk factors and the infant's clinical presentation<sup>24</sup>. This model permits to overcome some disadvantages of the CDC algorithm, such as the dichotomization of the continuous variables and the inclusion of maternal chorioamnionitis (CAM) as an impactful risk factor for starting antibiotic therapy<sup>24</sup>. A vast majority of studies about the EOS calculator demonstrates its efficacy in reducing antibiotic overtreatment, laboratory testing, painful procedures and NICU admission with increased opportunities for mother-child bonding and breastfeeding (Table 2)<sup>11,25-50</sup>.

Table 2

Reference	Patient population	Results
Escobar et al, 2014 <sup>25</sup>	≥ 34 weeks' GA	According to 2010 CDC guidelines, 11% of infants were treated with empirical antibiotics, although only 0.04% had blood culture-confirmed sepsis. Using a risk stratification scheme based on maternal and neonatal data, 4% of infants would have been treated with empirical antibiotics
Shakib et al, 2015 <sup>26</sup>	≥ 34 weeks' GA well-appearing infants exposed to maternal CAM	Reduction of patients with testing/initial antibiotics by at least 80% if using the EOS calculator compared with 2010 CDC guidelines
Kuzniewicz et al, 2017 <sup>27</sup>	≥ 35 weeks' GA	Reduction of blood culture use from 14.5% (2010 CDC guidelines) to 4.9% (EOS calculator). Reduction of empiric antibiotic administration in the first 24 hours from 5.0% (2010 CDC guidelines) to 2.6% (EOS calculator) with subsequent decrease of antibiotic days per 100 births from 16.0 to 8.5 days
Money et al, 2017 <sup>28</sup>	≥ 37 weeks' GA well-appearing infants exposed to maternal CAM	Reduction of empiric antibiotic treatment from 99.7% (2010 CDC guidelines) to 2.5% (EOS calculator). One patient with culture-positive EOS would not have received antibiotics based on the EOS calculator
Warren et al, 2017 <sup>29</sup>	≥ 34 weeks' GA infants who received antibiotics at birth for suspected EOS	Reduction of empiric antibiotic treatment from 93% (2010 CDC guidelines) to 23% (EOS calculator). Both 2010 CDC guidelines and the EOS calculator recommended treatment for 7 patients with culture-negative EOS
Beavers et al, 2018 <sup>30</sup>	≥ 34 weeks' GA exposed to maternal CAM	NICU admissions rates decreased from 91–37%, the number of blood cultures decreased from 92–50% and antibiotic administration rates decreased from 94–37% when 2010 CDC guidelines were replaced with EOS calculator recommendations
Carola et al, 2018 <sup>31</sup>	≥ 35 weeks' GA infants exposed to maternal CAM	Only 0.43% of neonates born to mothers with CAM had culture-proven EOS. Empiric antibiotics would have been recommended in 23.5% of the patients according to EOS calculator (76.5% reduction in empirical antibiotic administration compared with 2010 CDC guidelines). Blood culture only was recommended for 8.9% of the neonates; treatment with antibiotics would have been recommended for 3 of the 5 neonates with positive blood culture. All 5 neonates with positive blood cultures had abnormal CBC and CRP values at 6–12 hours
Dhudasia et al, 2018 <sup>32</sup>	≥ 36 weeks' GA	Reduction in antibiotics administration from 6.3–3.7% when current CDC guidelines were compared to EOS calculator. There was also a reduction in use of laboratory tests for suspected EOS from 26.9–4.9%

Reference	Patient population	Results
Gievers et al, 2018 <sup>33</sup>	≥ 35 weeks' GA infants exposed to maternal CAM	Compared to the 2010 CDC guidelines, EOS calculator yields a reduction of antibiotic exposure from 95 to 9%, laboratory evaluation from 96 to 22% and NICU observation from 73 to 10%
Klingaman et al, 2018 <sup>34</sup>	≥ 35 weeks' GA	Compared to the 2010 CDC guidelines, EOS calculator yields a reduction in CBCs by 88%, blood cultures by 94%, and antibiotic administration by 78%
Strunk et al, 2018 <sup>35</sup>	≥ 35 weeks' GA infants requiring evaluation and/or treatment for suspected EOS	Reduction of patients admitted to NICU from 24.2–21.2%, decrease of blood culture sampling from 15.2–11.1% and reduction of empiric antibiotic administration from 12.0–7.6% when using EOS calculator and not local guidelines based on AAP recommendations
Akangire et al, 2019 <sup>36</sup>	≥ 34 weeks' GA	Compared to current CDC/AAP guidelines, the EOS calculator-based approach yields a reduction of empiric antibiotic administration from 11.0–5.0% and blood culture use from 14.8–7.6%
Arora et al, 2019 <sup>37</sup>	≥ 34 weeks' GA infants admitted to NICU	Significant reduction in the rate of both antibiotic prescriptions (70.3% vs. 49.6%) and sepsis evaluations (90.9% vs. 68.8%) after implementation of the EOS calculator. 92% overlap in blood culture recommendations and 95% overlap between antibiotic recommendations when current CDC guidelines were compared to EOS calculator
Benaim et al, 2019 <sup>11</sup>	≥ 34 weeks' GA	Over the period of study, antibiotic administration decreased by 38.0% with updated local EOS guidelines. Reduction of antibiotic administration would have been 31.0% (for an EOS incidence of 0.6/1000) and 1.0% (for an EOS incidence of 2/1000) with the EOS calculator
Bridges et al, 2019 <sup>38</sup>	≥ 37 weeks' GA infants exposed to maternal CAM	Compared with 2010 CDC guidelines, 93.0% of patients were not admitted to the NICU and only 11.0% required laboratory evaluation; rates of exclusive breastfeeding increased from less than 10.0% to greater than 50.0% after implementation of the EOS calculator. The length of the NICU stay decreased from an average of 138 to 12 days with no negative consequences
Eason et al, 2019 <sup>39</sup>	≥ 37 weeks' GA infants with risk factors for EOS or suspected EOS	The percentage of infants screened with a suspected infection receiving 5 days of antibiotics reduced from 31.0% with NICE guidelines to 5.0% with EOS calculator. Clinically well infants with risk factors alone receiving 36 hours of antibiotics, reduced from 63.0% with NICE guidelines to 3.0% with EOS calculator
Fowler et al, 2019 <sup>40</sup>	≥ 34 weeks' GA	6 patients with culture-positive EOS were identified in the study period and recommendations from the calculator were in alignment with current CDC/AAP guidelines

Reference	Patient population	Results
Goel et al, 2019 <sup>41</sup>	≥ 34 weeks' GA	16% of infants were started on antibiotics as per NICE recommendations compared with 4.3% with EOS calculator. There were seven positive blood cultures (three infants were recommended antibiotics by both, three were not identified in the asymptomatic stage by either; one was a contaminant)
Gong et al, 2019 <sup>42</sup>	≥ 34 weeks' GA infants exposed to maternal intrapartum fever	Compared to the CDC/AAP guidelines, the EOS calculator-based approach yields a net monetary benefit (3998 \$ per infant), largely by preventing unnecessary antibiotic treatment (67.4% decrease in antibiotic use in the calculator arm)
Hershkovich-Shporen et al, 2019 <sup>43</sup>	≥ 35 weeks' GA newborns with the following inclusion criteria: treated with antibiotic, born to mothers with risk factors for EOS, born to mothers with clinical CAM or that received IAP	15.0% of the patients received antibiotic treatment according to 2010 CDC recommendations; 8.0% of the patients would have received antibiotic treatment according to EOS calculator. Only 2/89 (2.25%) newborns treated for maternal clinical CAM according to 2010 CDC guidelines, had proven EOS. Three of the mothers whose newborn developed EOS, had no risk factors so there was no need for the EOS calculator
Joshi et al, 2019 <sup>44</sup>	≥ 34 weeks' GA well-appearing newborns exposed to maternal CAM	Compared to the CDC/AAP guidelines, the usage of the EOS calculator yields a reduction of empirical antibiotics administration from 100% of patients to 8.9%
Leonardi et al, 2019 <sup>45</sup>	≥ 35 weeks' GA newborns exposed to maternal CAM and/or intrapartum fever	228/312 (73.1%) infants did not require admission to the NICU based on their risk assessment using the EOS calculator; according to local guidelines, all infants would have been admitted to the NICU for evaluation and treatment of presumed sepsis, regardless of clinical appearance. Breastfeeding rates at discharge were 89.0% for infants remaining with their mothers in the newborn nursery, and 37.0% for infants admitted to the NICU
Stipelman et al, 2019 <sup>46</sup>	≥ 34 weeks' GA infants exposed to maternal CAM	Reduction in antibiotics administration from 7.0% (according to CDC/AAP guidelines) to 1.0% after implementation of the EOS calculator. 2 missed cases of culture-positive EOS with EOS calculator

Reference	Patient population	Results
Benincasa et al, 2020 <sup>47</sup>	≥ 34 weeks' GA neonates who received EOS antibiotics according to the hospital's current practice	219/384 (57.0%) patients received antibiotics by EOS calculator and 64/384 (16.7%) by evaluation of clinical signs. All patients with positive blood culture were detected by both EOS calculator and clinical signs surveillance. Estimated costs were US\$ 415.576 for EOS calculator and US\$ 314.353 for evaluation of clinical signs
Morris et al, 2020 <sup>48</sup>	≥ 34 weeks' GA infants with EOS confirmed on blood or cerebrospinal fluid culture	Within 4 hours of birth, antibiotics were recommended for 39/70 (55.7%) infants with NICE guidelines, compared with 27/70 (38.6%) with the EOS calculator. The 12 infants advised early treatment only by NICE guidelines remained well, only one showing mild symptoms after 4 hours. Another 4 babies received antibiotics by 4 hours outside NICE and EOS calculator guidance. The remaining 27 infants (38.6%) received antibiotics when symptomatic after 4 hours. Only one infant who was unwell from birth, died. Both NICE guidelines and EOS calculator were poor in identifying EOS within 4 hours; NICE guidelines were superior to the EOS calculator in identifying asymptomatic cases
Perez et al, 2020 <sup>49</sup>	≥ 35 weeks' GA	Compared to the current AAP guidelines, the usage of the EOS calculator yields 54.0% reduction in the number of infants undergoing sepsis workup evaluations and 51.0% decrease in the number of infants receiving antibiotics
van der Weijden et al, 2020 <sup>50</sup>	≥ 34 weeks' GA neonates at risk for EOS	Dutch guidelines recommended antibiotic treatment for 363/890 (40.8%) neonates versus 101/890 (11.3%) with EOS calculator (p < 0.01). Antibiotic treatment was recommended by both methods for 90/890 (10.1%) neonates, including 2 patients with positive blood culture

Table 2

Title: Summary of main articles about EOS calculator included for review.

Legends: CAM, chorioamnionitis; CBC, cell blood count; CRP, C-reactive protein; EOS, early-onset sepsis; GA, gestational age; IAP, intrapartum antibiotic prophylaxis.

The objective of our study was to compare the administration of antibiotics based on our local EOS guidelines derived from current evidence with the calculator's recommendations in neonates born at ≥ 34 weeks' GA.

## Methods

This was a single-center retrospective study from 1st January 2018 to 31st December 2018 conducted in the Division of Neonatology at Santa Chiara Hospital (Pisa, Italy). The parents of all subjects signed a written consent form and the study was approved by the ethics committee of the Meyer Children's

Hospital of Florence. Based on our local guidelines, neonates born at  $\geq 34$  weeks' GA are divided into three categories (high, medium and low EOS risk), as shown in Table 3.

Table 3

Title: EOS risk categories for neonates born at  $\geq 34$  weeks' GA.

Legends: EOS, early-onset sepsis; GA, gestational age; GBS, Group B Streptococcus; IAP, intrapartum antibiotic prophylaxis.

<b>EOS risk categories</b>	<b>Included patients</b>
High-risk patients	Neonates with birth weight $\leq 1500$ g
	34–36 weeks' GA neonates with suspected intraamniotic infection
	Neonates with three clinical signs of EOS
	Neonates with two clinical signs and one risk factor for EOS
Medium-risk patients	34 weeks' GA neonates without suspicion of intraamniotic infection
	$\geq 35$ weeks' GA neonates from mothers with previous infant affected by invasive GBS disease and inadequate IAP
	$\geq 35$ weeks' GA neonates from mothers with GBS bacteriuria during any trimester of the current pregnancy and inadequate IAP (not if a cesarean delivery is performed before onset of labor on a woman with intact amniotic membranes)
	$\geq 35$ weeks' GA neonates from mothers with positive GBS vaginal-rectal screening culture within 5 weeks before delivery and inadequate IAP (not if a cesarean delivery is performed before onset of labor on a woman with intact amniotic membranes)
	35–36 weeks' GA neonates with unknown GBS maternal status at the onset of labor and inadequate IAP (not if a cesarean delivery is performed before onset of labor on a woman with intact amniotic membranes)
	$\geq 35$ weeks' GA neonates from mothers with amniotic membrane rupture $\geq 18$ hours and inadequate IAP
	35–36 weeks' GA neonates from mothers with intrapartum temperature $\geq 38.0$ °C
	$\geq 37$ weeks' GA neonates with suspected intraamniotic infection and inadequate IAP
	$\geq 37$ weeks' GA neonates with maternal intrapartum temperature $\geq 38.0$ °C and inadequate IAP
	$\geq 34$ weeks' GA neonates with one or two clinical indicators of EOS
Low-risk patients	Well-appearing neonates with no risk factors for EOS

High-risk patients undergo a full diagnostic evaluation (cord blood CRP and PCT or measurement of both markers within the first hour of life or at the onset of symptoms, blood culture and complete blood count - CBC- before starting antibiotic therapy) and receive empirical antibiotics pending the results of the evaluation. In these patients CRP and PCT are repeated at  $24 \pm 4$ ,  $48 \pm 4$  and  $72 \pm 4$  hours of life. Patients at medium risk for EOS undergo a limited evaluation (cord blood CRP and PCT or measurement of both markers within the first hour of life or at the onset of symptoms, CRP and PCT at  $24 \pm 4$  and  $48 \pm 4$  hours of life; symptomatic patients and preterm newborns undergo a further measurement of both markers at  $72 \pm 4$  hours of life). Medium-risk patients undergo CBC and blood culture, and receive empirical antibiotics in presence of one or two clinical indicators of EOS and one of the following conditions: 1) Abnormal cord blood PCT; 2) Abnormal neonatal PCT before 28 hours of life; 3) Abnormal neonatal CRP and PCT after 28 hours of life. Low-risk patients are managed through routinely observation for  $\geq 48$  hours before discharge.

Screening for vaginal-rectal GBS colonization and use of IAP are based on CDC 2010 guidelines; however, at our institution, intrapartum intravenous ampicillin or cefazolin (1 g every 8 hours until delivery) is also administered in case of amniotic membrane rupture  $\geq 18$  hours and negative vaginal-rectal screening culture. IAP is considered adequate when intravenous penicillin, ampicillin or cefazolin is administered  $\geq 4$  hours before delivery, in accordance with CDC 2010 guidelines<sup>5</sup>.

The quantities of blood used for laboratory analyses were as follows: 200  $\mu$ L for CRP or PCT, 300  $\mu$ L for both CRP and PCT, 400  $\mu$ L for CBC and 1 mL for blood culture. Measurement of CRP and/or PCT was even possible on capillary blood samples. Cord blood CRP  $\geq 10$  mg/L and cord blood PCT  $\geq 0.6$  ng/mL were considered pathological; CRP  $\geq 10$  mg/L was considered abnormal even when performed on neonatal blood samples. PCT required adjustment of the cut-off point with time, when performed on neonatal blood samples; thus, we decided to consider the age-specific 95% reference intervals by Chiesa et al<sup>17</sup>.

Administered empirical antibiotics consist of intravenous ampicillin-sulbactam and gentamicin. Prophylaxis with empirical antibiotics is interrupted at  $72 \pm 4$  hours of life in asymptomatic patients with negative blood culture and normal neonatal CRP and PCT. Antibiotic treatment is continued for another 4–11 days, for a total of 7–14 days, in the following cases: 1) Patients with clinical indicators of EOS at  $72 \pm 4$  hours of life; 2) Abnormal CRP and/or PCT at  $72 \pm 4$  hours of life; 3) Positive blood culture.

The study population included all inborn infants  $\geq 34$  weeks' GA at medium or high risk for EOS. Exclusion criteria were the following ones: clinical indicators of EOS appearing for the first time after 12 hours of life, genetic or metabolic diseases at onset before 12 hours of life, major congenital anomalies, hypoxic ischemic encephalopathy, proven viral infection at onset before 12 hours of life, lack of necessary data; misclassified patients were also excluded (Fig. 1). All included patients have been managed in accordance with our local guidelines.

FIGURE 1

Title: Selection process of the study population.

Legends: EOS, early-onset sepsis; GA, gestational age.

Neonates born at  $\geq 34$  weeks' GA during the study period at our institution were identified using admission logs. Thus, we retrospectively reviewed maternal and neonatal charts and collected data for input into the EOS calculator. These data included GA, highest maternal antepartum temperature, duration of maternal membrane rupture, maternal status for GBS, type and timing of IAP. We also collected other risk factors for EOS (birth weight  $\leq 1500$  g, suspected intraamniotic infection, previous infant with invasive GBS disease, GBS bacteriuria during any trimester of the current pregnancy), mode of delivery, duration of labor, presence and type of clinical indicators of EOS with the time in which they appeared, relevant laboratory results (cord blood CRP and PCT or neonatal CRP and PCT within the first hour of life or at the onset of symptoms, neonatal CRP and PCT at  $24 \pm 4$ ,  $48 \pm 4$  and  $72 \pm 4$  hours of life, blood culture), type and duration of antibiotic therapy. These data were obtained in order to verify physicians' compliance with our local guidelines and the correct classification of medium- and high-risk patients into non-septic patients, patients with culture-positive EOS and patients with culture-negative EOS. Thus, we calculated both culture-positive EOS and culture-negative EOS plus culture-positive EOS incidence rates at our institution. Thereafter, misclassified patients have been excluded from the study (Fig. 1). We then classified each patient as well appearing, equivocal, or with clinical illness as specified on the Kaiser Permanente website (<https://neonatalepsiscalculator.kaiserpermanente.org>). Each patient's EOS risk and subsequent management recommendation were determined using the EOS calculator with culture-positive EOS incidence rate; we also re-calculated EOS risk and management recommendation for each patient based on culture-negative EOS plus culture-positive EOS incidence rate. Possible management recommendations were as follows: 1) No culture, no antibiotics, routine vitals; 2) No culture, no antibiotics, vitals every 4 hours for 24 hours; 3) Blood culture, vitals every 4 hours for 24 hours; 4) Strongly consider starting empiric antibiotics, vitals per NICU; 5) Empiric antibiotics, vitals per NICU. We recorded all management recommendations and classified them into 2 categories, as shown in Table 4: A) No antibiotics needed (recommendations No. 1, No. 2, No. 3); B) Antibiotics needed (recommendations No. 4, No. 5).

Table 4

Title: Classification of EOS calculator's management recommendations according to our study protocol.

Legends: EOS, early-onset sepsis; NICU, neonatal intensive care unit.

EOS calculator's management recommendations		Our study protocol
No. 1	No culture, no antibiotics, routine vitals	No antibiotics needed (A)
No. 2	No culture, no antibiotics, vitals every 4 hours for 24 hours	
No. 3	Blood culture, vitals every 4 hours for 24 hours	
No. 4	Strongly consider starting empiric antibiotics, vitals per NICU	Antibiotics needed (B)
No. 5	Empiric antibiotics, vitals per NICU	

We therefore compared the number of patients for which antibiotics were needed, based on EOS calculator, and the number of patients we treated with antibiotics during the study period. We used R Software version 3.6.2 for statistical evaluations; comparisons between the groups were performed using McNemar's test and statistical significance was set at  $p < 0.05$ .

## Results

A total of 1667 neonates born at  $\geq 34$  weeks' GA during the study period at our institution were identified using admission logs. Patients at low risk for EOS (1394/1667, 83.6%) and those who met exclusion criteria (8/1667, 0.5%) were excluded from the study. Thus, a total of 265 (15.9%) patients fulfilled inclusion criteria and were enrolled in the study.

According to our guidelines, 32/265 (12.1%) neonates were initiated on antibiotics in the first 12 hours of life; none was initiated on antibiotics at 13–72 hours of life.

A retrospective analysis of blood culture, CRP and PCT results was performed to calculate the incidence rate of EOS during the study period. No cases of culture-positive EOS were observed among the study population; 4 cases of culture-negative EOS were reported among inborn infants  $\geq 34$  weeks' GA. All 4 patients with culture-negative EOS had no risk factors for EOS and were medium-risk patients with one or two clinical signs of EOS within the first 12 hours of life. They all presented simultaneous increase of both CRP and PCT at the onset of symptoms or increase of PCT at the onset of symptoms followed by an increase of CRP. Thus, the incidence of EOS among inborn infants  $\geq 34$  weeks' GA during the study period was 2.4/1000 live births.

After entering the data into the EOS calculator with local EOS incidence of 2/1000 live births, the recommendations were as follows: 1) No culture, no antibiotics, routine vitals (168 patients); 2) No culture, no antibiotics, vitals every 4 hours for 24 hours (7 patients); 3) Blood culture, vitals every 4 hours for 24 hours (35 patients); 4) Strongly consider starting empiric antibiotics, vitals per NICU (1 patient); 5) Empiric antibiotics, vitals per NICU (54 patients). Thus, according to EOS calculator, antibiotics were needed in 55/265 (20.7%) patients in the first 12 hours of life. The difference with our local guidelines resulted statistically significant ( $p < 0.0001$ ). Data are shown in Fig. 2.

FIGURE 2

Title: Comparison between our local guidelines and EOS calculator. Neonates  $\geq$  34 weeks' GA.

Legends: EOS, early-onset sepsis; GA, gestational age; GBS, Group B Streptococcus; IAP, intrapartum antibiotic prophylaxis; R1, recommendation No. 1 (No culture, no antibiotics, routine vitals); R2, recommendation No. 2 (No culture, no antibiotics, vitals every 4 hours for 24 hours); R3, recommendation No. 3 (Blood culture, vitals every 4 hours for 24 hours); R4, recommendation No. 4 (Strongly consider starting empiric antibiotics, vitals per NICU); R5, recommendation No. 5 (Empiric antibiotics, vitals per NICU).

As no cases of culture-positive EOS were observed during the study period, we also entered the same data into the EOS calculator with the lowest possible local EOS incidence (0.1/1000 live births). The recommendations were as follows: 1) No culture, no antibiotics, routine vitals (218 patients); 2) No culture, no antibiotics, vitals every 4 hours for 24 hours (1 patient); 3) Blood culture, vitals every 4 hours for 24 hours (2 patients); 4) Strongly consider starting empiric antibiotics, vitals per NICU (40 patients); 5) Empiric antibiotics, vitals per NICU (4 patients). Thus, according to EOS calculator, antibiotics were needed in 44/265 (16.6%) patients in the first 12 hours of life; the difference with our local guidelines resulted statistically significant even in this case ( $p < 0.025$ ).

A full-term newborn with culture-negative EOS starting with respiratory distress 6 hours after birth received antibiotics according to our local guidelines; when using EOS calculator, this patient was classified as "equivocal" and would not have received antibiotics with EOS incidence 0.1/1000 live births.

As regards treatment, overlap between EOS calculator recommendations and our local guidelines was 88.3% (234/265 patients) when using EOS calculator with EOS incidence 2/1000 live births, and 90.9% (241/265 patients) when using EOS calculator with EOS incidence 0.1/1000 live births. Data are shown in Fig. 2.

The patients enrolled in the study were hence assessed by dividing them into 2 groups: 1) 34–36 weeks' GA neonates; 2)  $\geq$  37 weeks' GA neonates.

Inborn infants 34–36 weeks' GA were 95/265 (35.8%). According to our local guidelines, 26/95 (27.4%) of these neonates were initiated on antibiotics in the first 12 hours of life. Neither culture-positive nor culture-negative EOS were observed among infants 34–36 weeks' GA during the study period. After entering data into the EOS calculator with the lowest possible local EOS incidence (0.1/1000 live births), the recommendations for patients 34–36 weeks' GA were as follows: 1) No culture, no antibiotics, routine vitals (62 patients); 2) No culture, no antibiotics, vitals every 4 hours for 24 hours (0 patients); 3) Blood culture, vitals every 4 hours for 24 hours (0 patients); 4) Strongly consider starting empiric antibiotics, vitals per NICU (29 patients); 5) Empiric antibiotics, vitals per NICU (4 patients). Thus, according to EOS calculator, antibiotics were needed in 33/95 (34.7%) patients 34–36 weeks' GA in the first 12 hours of life; the difference with our local guidelines was not statistically significant ( $p = 0.146$ ), although 7 more patients would have been treated using EOS calculator compared to our approach. Data are shown in Fig. 3.

### FIGURE 3

Title: Comparison between our local guidelines and EOS calculator. Neonates 34–36 weeks' GA.

Legends: EOS, early-onset sepsis; GA, gestational age; GBS, Group B Streptococcus; IAP, intrapartum antibiotic prophylaxis; R1, recommendation No. 1 (No culture, no antibiotics, routine vitals); R2, recommendation No. 2 (No culture, no antibiotics, vitals every 4 hours for 24 hours); R3, recommendation No. 3 (Blood culture, vitals every 4 hours for 24 hours); R4, recommendation No. 4 (Strongly consider starting empiric antibiotics, vitals per NICU); R5, recommendation No. 5 (Empiric antibiotics, vitals per NICU).

Inborn infants  $\geq 37$  weeks' GA were 170/265 (64.2%). According to our local guidelines, 6/170 (3.5%) of these neonates were initiated on antibiotics in the first 12 hours of life. A retrospective analysis of blood culture, CRP and PCT results showed no cases of culture-positive EOS and 4 cases of culture-negative EOS among the 1532 inborn infants  $\geq 37$  weeks' GA during the study period. Thus, the calculated incidence rate of EOS was 2.6/1000 live births. After entering data into the EOS calculator with local EOS incidence of 2/1000 live births, the recommendations were as follows: 1) No culture, no antibiotics, routine vitals (131 patients); 2) No culture, no antibiotics, vitals every 4 hours for 24 hours (4 patients); 3) Blood culture, vitals every 4 hours for 24 hours (17 patients); 4) Strongly consider starting empiric antibiotics, vitals per NICU (0 patients); 5) Empiric antibiotics, vitals per NICU (18 patients). Thus, according to EOS calculator, antibiotics were needed in 18/170 (10.6%) patients in the first 12 hours of life; the difference with our local guidelines resulted statistically significant ( $p = 0.001$ ). Data are shown in Fig. 4.

### FIGURE 4

Title: Comparison between our local guidelines and EOS calculator. Neonates  $\geq 37$  weeks' GA.

Legends: EOS, early-onset sepsis; GA, gestational age; GBS, Group B Streptococcus; IAP, intrapartum antibiotic prophylaxis; R1, recommendation No. 1 (No culture, no antibiotics, routine vitals); R2, recommendation No. 2 (No culture, no antibiotics, vitals every 4 hours for 24 hours); R3, recommendation No. 3 (Blood culture, vitals every 4 hours for 24 hours); R4, recommendation No. 4 (Strongly consider starting empiric antibiotics, vitals per NICU); R5, recommendation No. 5 (Empiric antibiotics, vitals per NICU).

As no cases of culture-positive EOS were observed among inborn infants  $\geq 37$  weeks' GA, we also entered the same data into the EOS calculator with the lowest possible local EOS incidence (0.1/1000 live births). The recommendations were as follows: 1) No culture, no antibiotics, routine vitals (156 patients); 2) No culture, no antibiotics, vitals every 4 hours for 24 hours (1 patient); 3) Blood culture, vitals every 4 hours for 24 hours (2 patients); 4) Strongly consider starting empiric antibiotics, vitals per NICU (11 patients); 5) Empiric antibiotics, vitals per NICU (0 patients). Thus, according to EOS calculator, antibiotics were needed in 11/170 (6.5%) patients in the first 12 hours of life; the difference with our local guidelines was

not statistically significant ( $p = 0.131$ ), although 5 more patients would have been treated using EOS calculator compared to our approach. Data are shown in Fig. 4.

## Discussion

Early diagnosis and treatment decision-making of neonatal EOS are challenging for clinicians; at the same time antibiotic resistance is an increasing problem, thus antibiotic overexposure among neonates should be avoided. For this purpose, we revisited the antibiotic stewardship program at our institution and drew up a protocol for management of neonates at risk for EOS.

The neonatal EOS calculator has been introduced to support the clinician's treatment decision-making of neonatal EOS. Most of Authors agree on the efficacy of the EOS calculator in reducing antibiotic overtreatment; however, some Authors have also reported patients with culture-positive EOS who would not have received antibiotics based on the EOS calculator. In our study, according to our local guidelines, antibiotics were needed in 32/265 enrolled patients  $\geq 34$  weeks' GA in the first 12 hours of life; based on the EOS calculator, antibiotics would have been needed in 44/265 patients when using an EOS incidence of 0.1/1000 live births, and in 55/265 patients when using an EOS incidence of 2/1000 live births. As both differences resulted statistically significant, the use of our protocol is advantageous in clinical practice.

When using the EOS calculator with an EOS incidence of 0.1/1000 live births, 44/44 patients previously classified as "clinical illness" would have received antibiotics (including 3 patients with culture-negative EOS); however, one full-term newborn with culture-negative EOS and equivocal presentation would not have received antibiotics but only routine care. When using the EOS calculator with an EOS incidence of 2/1000 live births, 44/44 patients previously classified as "clinical illness" (including 3 patients with culture-negative EOS), 10/72 patients with equivocal presentation (including one patient with culture-negative EOS) and 1 in 149 well-appearing patients would have received antibiotics. Thus, a missed case of culture-negative EOS was observed when using the EOS calculator with EOS incidence 0.1/1000 live births; however, this EOS incidence includes only culture-positive EOS cases and, probably, underrates the true incidence of EOS at our institution.

The use of our protocol was numerically advantageous even when considering  $\geq 37$  weeks' GA and 34–36 weeks' GA neonates separately; however, the only statistically significant difference was that between the number of full-term patients which received antibiotics according to our protocol (6 patients) and the number of full-term patients which would have received antibiotics according to EOS calculator with EOS incidence 2/1000 live births (18 patients). The EOS calculator with EOS incidence of 2/1000 live births was not tested for 34–36 weeks' GA neonates because neither culture-positive nor culture-negative EOS have been diagnosed among these patients, thus we only used the lowest possible EOS incidence. When using the EOS calculator all patients classified as "clinical illness" would have received antibiotics regardless of EOS incidence; according to our local guidelines 26/44 of these neonates received antibiotics with no negative consequences.

We think that the effectiveness of our protocol results from the inclusion of anamnestic data, clinical evaluation and laboratory exams. Anamnestic data permitted us to identify neonates with risk factors for EOS or elements which could explain clinical presentation (for example gestational diabetes, meconium aspiration or short labor in patients with respiratory distress). Thus, not all neonates classified as “clinical illness” received antibiotics according to our protocol. Clinical evaluation is very important since none of the patients with culture-negative EOS had risk factors for EOS, thus they were identified for the presence of clinical signs. Clinical evaluation is even crucial to decide whether to start antibiotic therapy because of the possibility of false-negatives with blood culture and false-positives with measurement of CRP and PCT. However, serial CRP and PCT measurements allowed us to identify patients with EOS, to control the efficacy of antibiotic therapy, and to decide when to stop antibiotic treatment. We think EOS calculator is an effective tool to reduce unnecessary antibiotics administration to neonates but it also has several limitations. First, the highest possible EOS incidence is 4/1000 live births, thus EOS calculator cannot be utilized in contexts with EOS incidence higher than 4/1000 live births. Second, its use is limited in the first 12 hours of life but EOS can manifest itself between 12 and 72 hours of life, although rarely, and serial measurements of CRP and PCT in the first 72 hours of life allow us to identify all cases of EOS. Third, antibiotics are indicated to all neonates classified as “clinical illness” (persistent need for nCPAP/HFNC/mechanical ventilation outside of the delivery room, hemodynamic instability requiring vasoactive drugs, neonatal encephalopathy/perinatal depression, need for supplemental  $O_2 \geq 2$  hours to maintain oxygen saturations  $> 90\%$  outside of the delivery room); we think that careful consideration of risk factors for EOS, anamnestic data and alternative diagnoses should further reduce unnecessary antibiotics administration. Fourth, equivocal patients can present with tachycardia, tachypnea, temperature instability or respiratory distress; however other clinical indicators of possible EOS (altered behaviour or responsiveness, feeding difficulties etc.) should be considered. Fifth, laboratory exams should be considered to reduce the number of patients receiving unnecessary antibiotics, above all among patients classified as “clinical illness”, and to identify patients with EOS appearing after 12 hours of life. Furthermore, our protocol incorporates the new definition for CAM: this disease is now defined as intraamniotic infection or “Triple I” and requires more clinical features for diagnosis. Thus, we make difference between neonates from mothers with “Triple I” and those with isolated maternal fever: this contributes in reducing the number of neonates receiving antibiotics.

However, even our protocol has many limitations. First, the number of 34–36 weeks’ GA neonates receiving antibiotics is too high (26/95, none with EOS). Thus, we should re-evaluate clinical criteria for starting antibiotics and the optimal cut-off point for both CRP and PCT in late-preterm infants. Birth weight  $\leq 1500$  g should also be re-evaluated as a criteria to start antibiotics. Second, reducing antibiotics administration is money-saving. However, laboratory exams, above all PCT, are quite expensive. Third, we need serial clinical evaluations to identify neonates with clinical signs of EOS, especially those without maternal risk factors. However, even applying the EOS calculator requires serial clinical evaluations in the first 12 hours of life. Fourth, serial blood samplings are needed for measurement of CRP and PCT; however, the first measurement is usually performed on cord blood, and blood sampling at  $48 \pm 4$  hours of life is the same for the newborn screening test. The remaining measurements sometimes coincide with

blood samplings for gas analysis or glycemia evaluation. Fifth, our study is retrospective. Even if the course of each patient is well documented, the classification of neonates into well-appearing, equivocal or clinically ill is partly dependent on whomever is analyzing the medical records. Sixth, we should consider an earlier interruption of antibiotics at 48 hours of life in well-appearing neonates with negative laboratory exams in order to reduce both antibiotics exposure and laboratory exams.

## Conclusion

EOS calculator has been proven to be an effective tool for treatment decision-making of neonatal EOS, however we have shown a further decrease in antibiotics administration through a continuous evidence-based update of local guidelines. Thus, continuous review of recommendations and updated guidelines are necessary to reduce both antibiotics administration and microbial resistance, with consequent reduction of related comorbidities, and to pursue the best possible antibiotic stewardship.

## Abbreviations

CAM  
maternal chorioamnionitis  
CBC  
complete blood count  
CRP  
C-reactive protein  
EOS  
early-onset sepsis  
GA  
gestational age  
GBS  
group B Streptococcus  
IAP  
intrapartum antimicrobial prophylaxis  
NICU  
neonatal intensive care unit  
PCT  
Procalcitonin  
WBC  
white blood cell

## Declarations

ACKNOWLEDGEMENTS

Not applicable

## AUTHORS' CONTRIBUTIONS

LG reviewed literature data and wrote the manuscript. CM developed our protocol for treatment decision-making of neonatal early-onset sepsis. LG collected the patient data. CM, TC, SE, MM and CA analyzed and interpreted the patient data and critically revised the manuscript. All authors read and approved the final manuscript.

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## AVAILABILITY OF DATA AND MATERIALS

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the ethics committee of the Meyer Children's Hospital of Florence and was performed in compliance with the Declaration of Helsinki and its later amendments. Parents gave written informed consent to the processing of personal data at the time of enrolment.

## CONSENT FOR PUBLICATION

Not applicable

## COMPETING INTERESTS

The authors declare that they have no competing interests.

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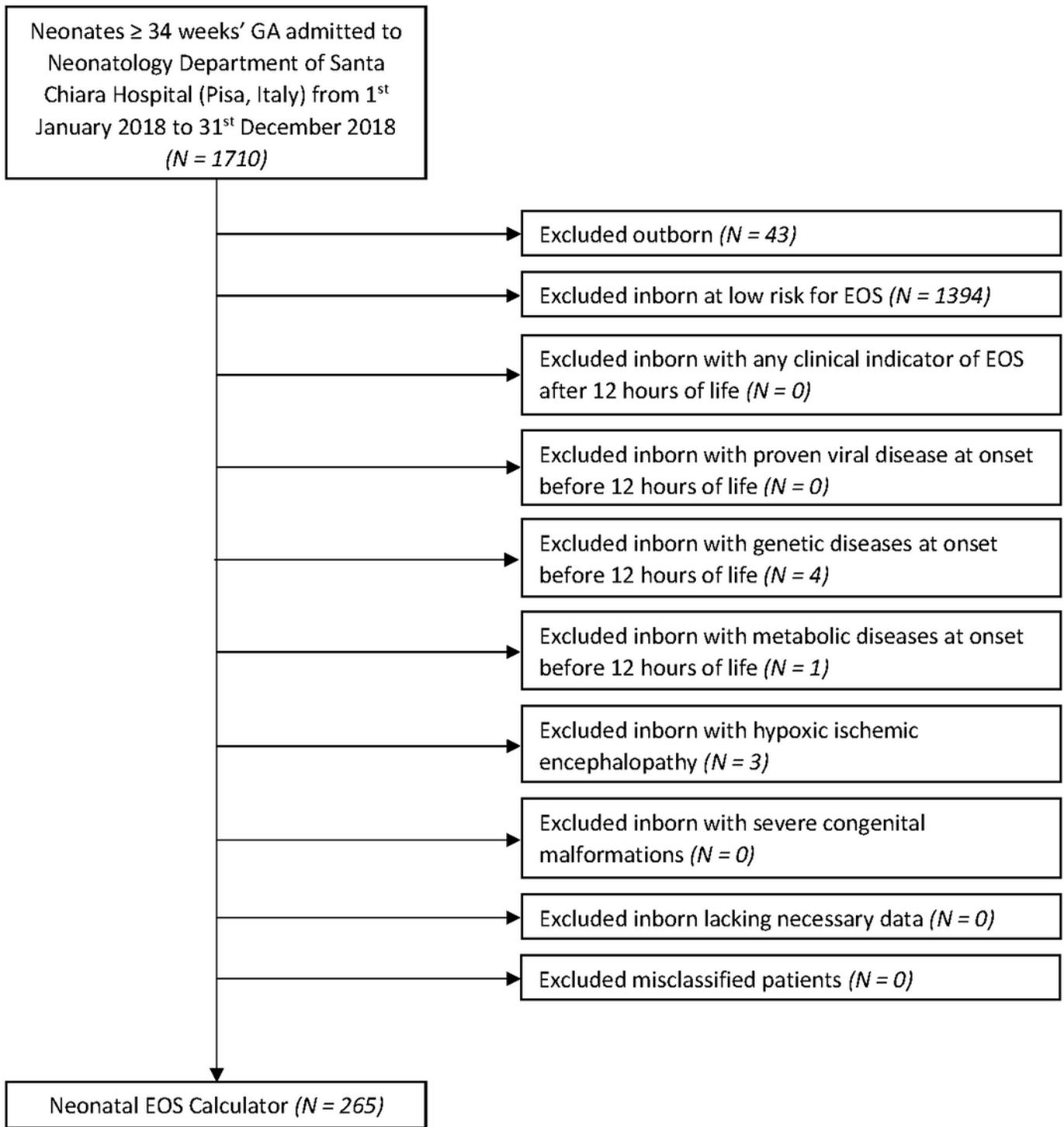
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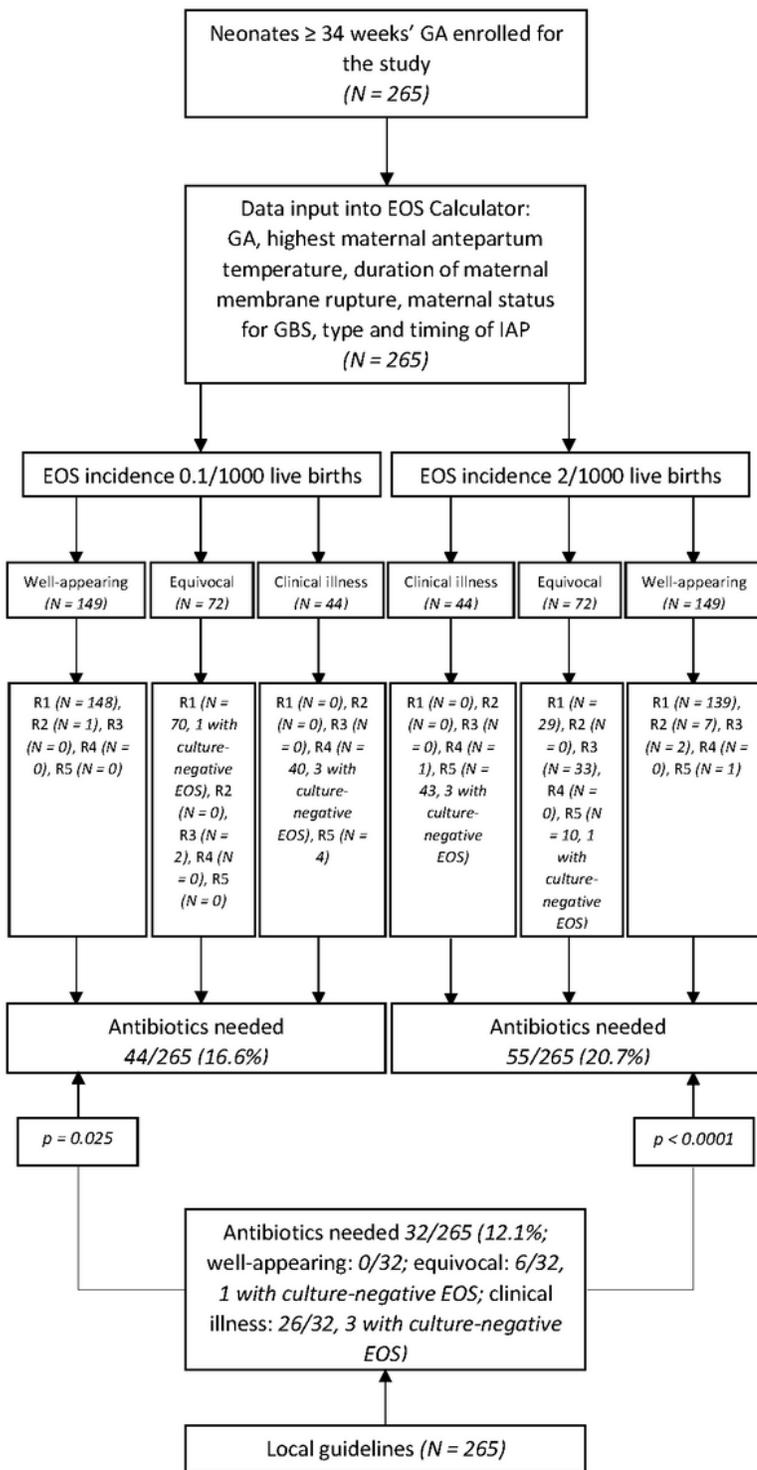
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## Figures



**Figure 1**

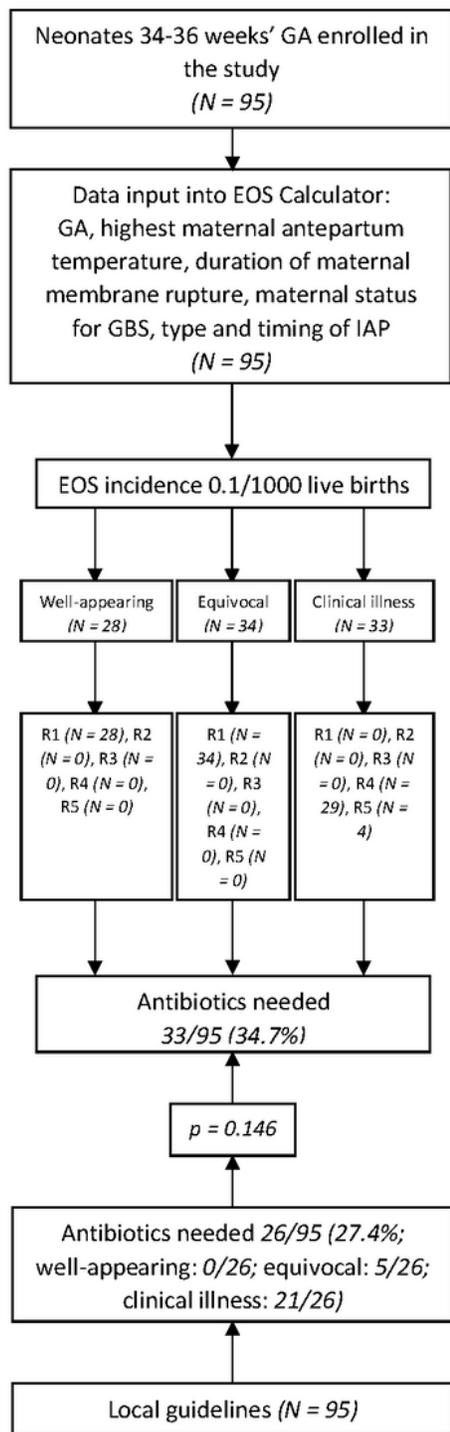
Selection process of the study population. Legends: EOS, early-onset sepsis; GA, gestational age.



**Figure 2**

Comparison between our local guidelines and EOS calculator. Neonates  $\geq 34$  weeks' GA. Legends: EOS, early-onset sepsis; GA, gestational age; GBS, Group B Streptococcus; IAP, intrapartum antibiotic prophylaxis; R1, recommendation No. 1 (No culture, no antibiotics, routine vitals); R2, recommendation No. 2 (No culture, no antibiotics, vitals every 4 hours for 24 hours); R3, recommendation No. 3 (Blood

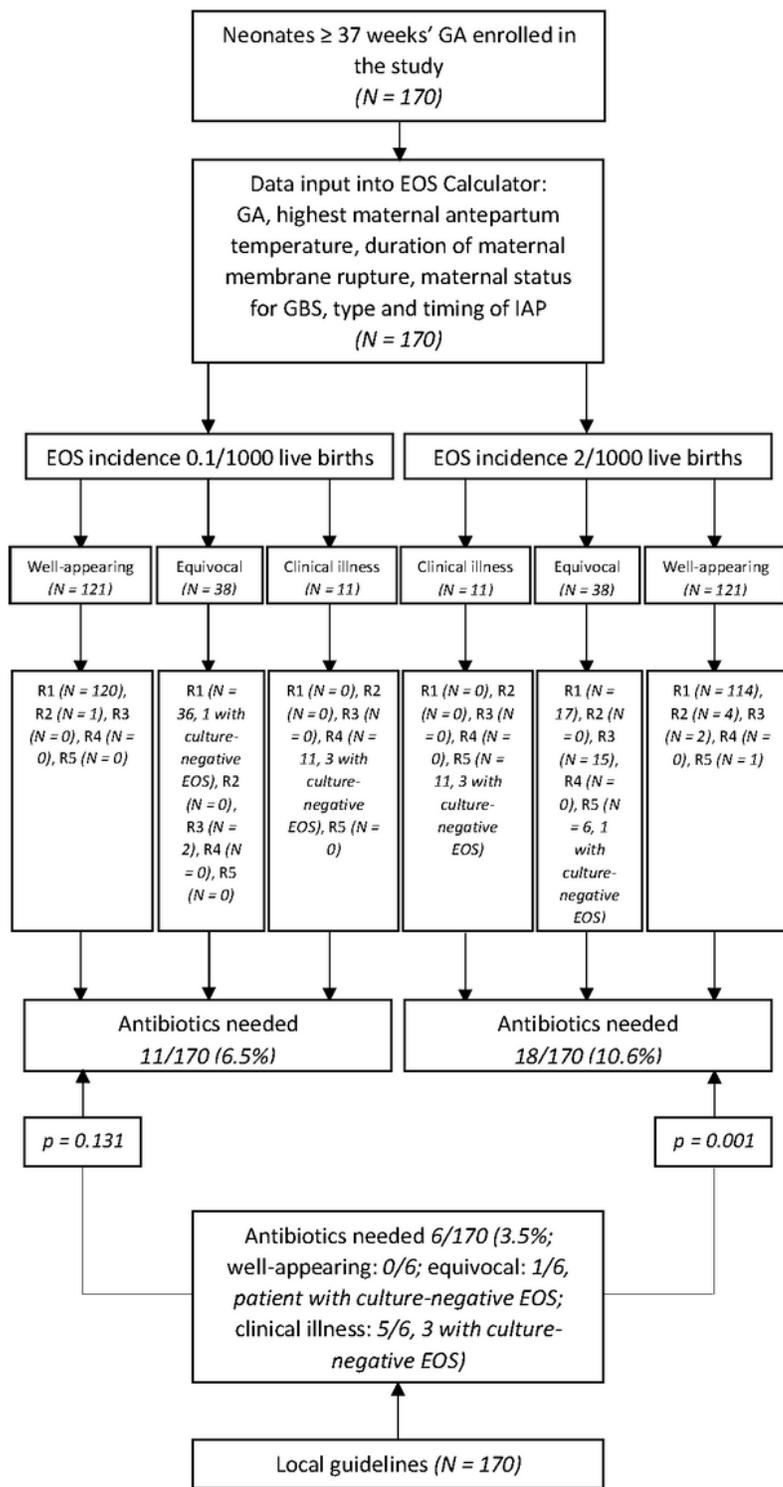
culture, vitals every 4 hours for 24 hours); R4, recommendation No. 4 (Strongly consider starting empiric antibiotics, vitals per NICU); R5, recommendation No. 5 (Empiric antibiotics, vitals per NICU).



**Figure 3**

Comparison between our local guidelines and EOS calculator. Neonates 34-36 weeks' GA. Legends: EOS, early-onset sepsis; GA, gestational age; GBS, Group B Streptococcus; IAP, intrapartum antibiotic prophylaxis; R1, recommendation No. 1 (No culture, no antibiotics, routine vitals); R2, recommendation

No. 2 (No culture, no antibiotics, vitals every 4 hours for 24 hours); R3, recommendation No. 3 (Blood culture, vitals every 4 hours for 24 hours); R4, recommendation No. 4 (Strongly consider starting empiric antibiotics, vitals per NICU); R5, recommendation No. 5 (Empiric antibiotics, vitals per NICU).



**Figure 4**

Comparison between our local guidelines and EOS calculator. Neonates  $\geq 37$  weeks' GA. Legends: EOS, early-onset sepsis; GA, gestational age; GBS, Group B Streptococcus; IAP, intrapartum antibiotic

prophylaxis; R1, recommendation No. 1 (No culture, no antibiotics, routine vitals); R2, recommendation No. 2 (No culture, no antibiotics, vitals every 4 hours for 24 hours); R3, recommendation No. 3 (Blood culture, vitals every 4 hours for 24 hours); R4, recommendation No. 4 (Strongly consider starting empiric antibiotics, vitals per NICU); R5, recommendation No. 5 (Empiric antibiotics, vitals per NICU).