Variation in Current Management of Term and Late-preterm Neonates at Risk for Early-onset Sepsis

An International Survey and Review of Guidelines

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Background: Uncertainty about the presence of infection results in unnecessary and prolonged empiric antibiotic treatment of newborns at risk for early-onset sepsis (EOS). This study evaluates the impact of this uncertainty on the diversity in management.

Methods: A web-based survey with questions addressing management of infection risk-adjusted scenarios was performed in Europe, North America, and Australia. Published national guidelines (n = 5) were reviewed and compared with the results of the survey.

Results: 439 Clinicians (68% were neonatologists) from 16 countries completed the survey. In the low-risk scenario, 29% would start antibiotic therapy and 26% would not, both groups without laboratory investigations; 45% would start if laboratory markers were abnormal. In the high-risk scenario, 99% would start antibiotic therapy. In the low-risk scenario, 89% would discontinue antibiotic therapy before 72 hours. In the high-risk scenario, 35% would discontinue therapy before 72 hours, 56% would continue therapy for 5–7 days, and 9% for more than 7 days. Laboratory investigations were used in 31% of scenarios for the decision to start, and in 72% for the decision to discontinue antibiotic treatment. National guidelines differ considerably regarding the decision to start in low-risk and regarding the decision to continue therapy in higher risk situations.

Conclusions: There is a broad diversity of clinical practice in management of EOS and a lack of agreement between current guidelines. The results of the survey reflect the diversity of national guidelines. Prospective studies regarding management of neonates at risk of EOS with safety endpoints are needed.

Key Words: early-onset sepsis, newborn disease, sepsis, biological markers, sepsis diagnosis

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Infections are globally the single largest cause of neonatal deaths.[1] Up to 15% of all term and late-preterm neonates are evaluated for suspected early-onset neonatal sepsis (EOS), and up to 10% are treated with intravenous antibiotics for suspected bacterial sepsis within the first 3 days of life, consuming a significant amount of resources in neonatal units worldwide.[2–4] However, the incidence of culture-proven EOS in term and late preterm neonates is less than 0.1%.[2–6] Early diagnosis and treatment of EOS are essential to prevent severe and life threatening complications. Nevertheless, diagnosis is difficult because of the often subtle, nonspecific clinical presentation and low predictive values of any biomarkers.[3,7–9] Uncertainty about the presence of infection may result in unnecessary and prolonged empiric antibiotic treatment.[10]

Guidelines play a crucial role in supporting decision-making for this vulnerable group of patients. Recently published reports of effects after implementation of new guidelines demonstrate the challenges those entail.[11,12] Best practice and future guidelines should aim at reducing the number of neonates unnecessarily treated with antibiotics and the duration of treatment although capturing 100% of neonates with proven EOS. In view of the significant impact of treatment of EOS on the health care system, it is important to know the current standard of practice. Knowledge regarding the current standard is critical for the development of future studies and strategies to improve management of newborns at risk for EOS. The aim of this study was to describe the current management of suspected EOS in term and late preterm infants among clinicians in different countries and on different continents by conducting a survey and comparing the results to a review of the recent national guidelines for EOS.

MATERIALS AND METHODS

International Survey

Between March 2011 and March 2012, a web-based survey (SurveryMonkey, SurveyMonkey, Paolo Alto, CA), developed by the NEonatal Sepsis Trial NETwork (NEST-NET, www.nest-net.org), was sent by e-mail to pediatricians and neonatologists in Europe, North America and Australia. The questionnaire was drafted by 2 authors (S.P., M.S.) and revised after review by the group of authors. The selection of countries and regions for email distribution of the survey was based on the national (United Kingdom, Canada, the Netherlands) or regional (all other countries) network of the NEST-NET group members. All potential participants were e-mailed background information on the study with an invitation to anonymously

participate. Consent was implied upon completion of the study questionnaire. Those who did not respond received a reminder within 2 months. Response rates were calculated by comparing the number of sent e-mails with the number of participants who answered the questionnaires. Ethical approval for the study was obtained from the Hamilton Integrated Research Ethics Board, McMaster University, Hamilton Health Sciences, Canada.

There were 3 sections of the questionnaire: 6 questions regarding clinical management, 2 questions regarding use of laboratory investigations (biomarkers, cultures) and 4 demographic items. Questions regarding the decision to start and discontinue antibiotic therapy were introduced by scenarios rated as low, medium and high risk for neonatal EOS, based on risk factors and clinical signs of infection (Table 1). The possible answers for the decision to start/discontinue antibiotic therapy were investigating the dependency on laboratory investigations. Additionally, we determined the proportion of physicians using newer infection markers such as procalcitonin (PCT) and interleukins, compared with conventional markers such as complete blood count (CBC) and C-reactive protein (CRP). Questions about demographic factors with a potential influence on management of suspected EOS were asked (country, level of training, number of patients with EOS treated by this physician per month and recent experiences of fatal cases).

Review of Guidelines

Published national guidelines in English language were selected for review. Guidelines were searched in PubMed using the terms "neonatal early-onset sepsis" and "guideline or recommendation" on December 1, 2014. The most recent available version was selected, and the review was focused on (i) the decision to start antibiotic treatment for suspected EOS, (ii) duration of antibiotic therapy and (iii) use of laboratory markers for management of suspected EOS. Comparison of the guidelines was done by 2 authors (W.v.H., M.S.), to describe the variation in current guidelines on the management of suspected EOS.

Comparison

The survey results were compared with the published national guidelines using the infection risk-adjusted scenarios. For each country, the national recommendations for each specific scenario

TABLE 1. Scenarios Regarding the Start/Discontinuation of Antibiotic Therapy, Rated as Low/Medium/High Risk of Infection

Severity of Risk	Case Description	Possible Interventions
Start of antibiotic therapy		
Low risk (solely risk factors)	• Spontaneous vaginal delivery • Two maternal risk factors for infection: maternal fever 38.5°C, rupture of membranes for 28 h, GBS negative • Term newborn without clinical signs of infection 2 h after delivery	A. Start antibiotic therapy, laboratory investigations not necessary for decision B. No antibiotic therapy, laboratory investigations not necessary for decision C. Start antibiotic therapy if laboratory investigations are abnormal
Medium risk (clinical signs without risk factors)	• Spontaneous vaginal delivery • No maternal risk factors for infection • Term newborn with respiratory distress (respiratory rate 70/min, retractions, intermittent grunting, SpO_2 95% in room air), pale, capillary refill time 3 seconds. All signs detected 2 h after delivery	
High risk (risk factors and clinical signs)	• Spontaneous vaginal delivery • Two maternal risk factors for infection: maternal fever 38.5°C, rupture of membranes for 28 h, GBS negative • Term newborn with respiratory distress (respiratory rate 70/min, retractions, intermittent grunting, SpO_2 95% in room air), pale, capillary refill time 3 seconds. All signs detected 2 h after delivery.	
Discontinuation of antibiotic therapy (duration)		
Low risk (risk factors, clinical signs resolved early on the first day)	• Spontaneous vaginal delivery • Two maternal risk factors for infection: maternal fever 38.5°C, rupture of membranes for 28 h, GBS negative • Term newborn with respiratory distress (respiratory rate 70/min, retractions, intermittent grunting, SpO_2 95% in room air), pale, capillary refill time 3 s. • All clinical signs detected 2 h after delivery and resolved 6 h later • Cultures remained negative (blood, cerebrospinal fluid)	A. Antibiotic therapy **≤ 72 h**, **independent** of laboratory investigations (except cultures) B. Antibiotic therapy **≤ 72 h**, but **dependent** on laboratory investigations (except cultures) C. Antibiotic therapy **5 to a maximum of 7 d**, **independent** of laboratory investigations (except cultures) D. Antibiotic therapy **5 to a maximum of 7 d**, but **dependent** on laboratory investigations (except cultures) E. Antibiotic treatment **≥ 7 d**, **independent** of laboratory investigations (except cultures) F. Antibiotic treatment **≥ 7 d**, but **dependent** on laboratory investigations (except cultures)
Medium risk (no risk factors, clinical signs resolved on the second day)	• Spontaneous vaginal delivery • No maternal risk factors for infection • Term newborn with respiratory distress (respiratory rate 70/min, retractions, intermittent grunting, SpO_2 95% in room air), pale, capillary refill time 3 s. • All signs detected 2 h after delivery and resolved after 24–36 h • Cultures remained negative (blood, cerebrospinal fluid)	
High risk (risk factors, clinical signs resolved late after the third day)	• Spontaneous vaginal delivery • Two maternal risk factors for infection: maternal fever 38.5°C, rupture of membranes for 28 h, but GBS negative • Term newborn with respiratory distress (respiratory rate 70/min, retractions, intermittent grunting, SpO_2 95% in room air), pale, capillary refill time 3 s. • All signs detected 2 h after delivery and resolved after 72 h • Cultures remained negative (blood, cerebrospinal fluid)	

GBS indicates group B streptococcus.

regarding decision to start/stop antibiotic therapy and the dependency on laboratory results were compared with the results of the survey.

Statistics

Completed surveys were entered and tabulated by Survey monkey. Descriptive analyses were used for comparison of answers. Answers were compared using χ^2 tests with 2 degrees of freedom. A P value <0.05 was considered statistically significant with a confidence interval at 95%.

RESULTS

Survey

The demographics of the participants are shown in Table 2. A total of 439 pediatricians and neonatologists responded; 367 (83.6%) respondents answered all 11 questions. The response rate was calculated in 6 countries: Australia, 30%; Czech Republic, 61%; Netherlands, 20%; Norway, 40%; Slovakia, 80% and Switzerland, 40%. In all other countries, the response rate was not calculated because of the unknown number of physicians approached.

When asking about initiating antibiotic treatment in the low-risk scenario, 29% would start and 26% would not start treatment irrespective of laboratory investigations; 45% would start treatment if laboratory markers were abnormal. In the high-risk scenario, 99% of the respondents would start antibiotic therapy (Table 3). Regarding the discontinuation of antibiotic therapy, 89% of respondents would discontinue therapy before 72 hours in the low-risk scenario. In the high-risk scenario, 35% of respondents would discontinue therapy before 72 hours, 56% of respondents would continue therapy for 5–7 days, and 9% of respondents for more than 7 days (Table 3). Overall, participants based their decision to start antibiotic treatment significantly less often on laboratory investigations than their decision to discontinue antibiotic treatment (31% vs. 72%, $P < 0.0001$). The majority of respondents relied on conventional infection parameters such as CBC (92%) and/or CRP (92%). Only a minority used newer markers of inflammation such as PCT (17%) and/or interleukins (9%; CRP vs. PCT: $P < 0.0001$). Almost all respondents (98%) indicated drawing blood cultures before starting antibiotic therapy. Most respondents performed a lumbar puncture depending on the clinical presentation (81%), whereas only 3% always obtained a cerebrospinal fluid culture. Regular use of body surface cultures (including umbilical stump or skin) was reported by 31% and regular use of urine cultures by 26%. The results were not influenced by demographic factors. We observed a marked variability in the decision whether to start/discontinue antibiotic therapy in low- and high-risk scenario depending on countries of origin (Table 4).

Review of National Guidelines

Table 5 summarizes the most important aspects focusing on initiation and duration of antibiotic therapy in 5 national guidelines (Canada, United States, United Kingdom, Switzerland, Belgium).[13–17] In low-risk scenarios such as chorioamnionitis without clinical signs, 2 guidelines (US and Belgium) recommend immediate treatment; one guideline (Canada) recommends treatment if the laboratory results are abnormal, and 2 guidelines (United Kingdom and Switzerland) advice to observe the neonate. In low-risk scenarios with other risk factors without clinical signs, one guideline (US) recommends treatment if the laboratory results are abnormal, 1 guideline (United Kingdom) recommends treatment if there are ≥ 2 risk factors, and 3 guidelines (Canada, Switzerland and Belgium) advice to observe the neonate. All 5 clinical guidelines agree to treat newborns with clinical signs possibly related to infection. The guidelines uniformly recommend re-evaluating the need for further antibiotic therapy after 36–48 hours and discontinuing antibiotic therapy if infection is unlikely. On the other hand, advice on duration of treatments in newborns with prolonged clinical signs possibly related to infection or increased levels of infection markers is either unspecific or not provided. All guidelines advocate using conventional infection markers (CBC and CRP) and 1 out of 5 includes PCT.[17]

Comparison of Survey with Review of Guidelines

In 4 countries (Switzerland, Canada, US and United Kingdom), survey results can be compared with their national guidelines (Table 3). The majority of the respondents in the survey followed their national guidelines regarding the decision to start/discontinue antibiotic therapy.

DISCUSSION

This study surveyed management practices of EOS in high-income countries across Europe, North America and Australia and compared the results with published guidelines. As expected, we found a broad agreement within the survey as well as in the review of the guidelines to start empiric antibiotic treatment in high-risk

TABLE 2. Demographics of Participants in Percentage of All Respondents (n = 439)

Country		Level of Training		Number of Treated Patients with Suspected EOS; Per Physician Per Month in %		Number of Recent Fatal Cases of EOS in Last 12 Mo in %	
13.9%	United Kingdom	68.3%	Board-certified neonatologists	11.0%	Low caseload (0–2 cases)	44.4%	None
12.3%	The Netherlands					36.7%	1–2 Fatal cases
10.5%	Czech Republic	6.2%	Trainees in neonatology	40.1%	Medium caseload (2–10 cases)	5.0%	≥ 3 Fatal cases
9.6%	US						
6.2%	Switzerland	11.8%	Pediatricians	35.5%	High caseload (>10 cases)	13.9%	Not known
5.7%	Canada	13.7%	Not known	13.4%	Not known		
5.5%	France						
5.5%	Slovakia						
4.6%	Australia						
4.3%	Norway						
3.0%	Sweden						
2.5%	Other countries (Germany, Spain, Belgium, Finland, Poland)						
16.4%	Not known						

TABLE 3. Comparison of National Survey Results with Their National Guidelines Regarding the Decision to Start/Discontinuation of Antibiotic Therapy

Start of antibiotic therapy

Severity of risk	Country	Advice national guideline	Survey results in % of respondents: Observe	Start therapy independent on laboratory results	Start therapy dependent on laboratory results
Low risk (solely risk factors)	Overall	Not applicable	26%	29%	45%
	Canada	Observe	**40%**	28%	32%
	US	Treat, if laboratory results are abnormal	10%	26%	**64%**
	United Kingdom	Treat	5%	**79%**	16%
	Switzerland	Observe	**56%**	7%	37%
Medium risk (no risk factors, clinical signs possible related to infection)	Overall	Not applicable	**10%**	**57%**	**33%**
High risk (risk factors and clinical signs)	Overall	Not applicable	1%	86%	13%
	Canada	Treat	0%	**96%**	4%
	US	Treat	0%	**98%**	2%
	United Kingdom	Treat	0%	**100%**	0%
	Switzerland	Treat	4%	**85%**	1%

Discontinuation of antibiotic therapy (duration)

Severity of risk	Country	Advice national guideline: Re-evaluation at 48 h and	Survey results in % of respondents (% that is dependent on laboratory results): Discontinues ≤72 h	Continues for 5–7 d	Continues for >7 d
Low risk (risk factors, clinical signs resolved early on the first day)	Overall	Not applicable	**89% (68%)**	10% (7%)	1% (0.3%)
	Canada	Discontinue if infection unlikely, laboratory not mentioned	**88%** (48%)	8% (8%)	4% (0%)
	US	Discontinue if infection unlikely, laboratory results helpful	**98% (50%)**	2% (2%)	0%
	United Kingdom	Discontinue if infection unlikely and CRP reassuring	**87% (77%)**	13% (10%)	0%
	Switzerland	Discontinue if infection unlikely, laboratory results helpful	**93% (52%)**	7% (7%)	0%
Medium risk (clinical signs possible related to infection resolved after 24–36 h)	Overall	Not applicable	74% (56%)	**26% (18%)**	1% (0.3%)
High risk (risk factors, clinical signs resolved late after the third day)	Overall	Not applicable	35% (28%)	**56% (34%)**	8% (5%)
	Canada	Discontinue if infection unlikely, continue for at least 5 d if progress consistent with sepsis	28% (24%)	**60%** (44%)	12% (4%)
	US	Discontinue if infection unlikely, laboratory results helpful	**45% (24%)**	**45% (12%)**	10% (5%)
	United Kingdom	Discontinue if infection unlikely + CRP reassuring, continue 7 d if progress is consistent with sepsis	33% (26%)	**66% (31%)**	2% (2%)
	Switzerland	Discontinue if infection unlikely, laboratory results helpful	30% (15%)	**63% (41%)**	7% (4%)

situations such as newborns with clinical signs suggestive of infection.[13–17] On the other hand, we found a high diversity in the approach to when to start antibiotic therapy in low-risk situations such as asymptomatic infants born to mothers with risk factors for EOS. The differences in the decision to start antibiotic therapy in low-risk situations raise the question of justifiable risk threshold for laboratory investigations and/or treatment. A retrospective analysis estimated that in order to ensure treatment of all proven cases of EOS within a given risk stratum in term and late-preterm newborns, the number needed to treat (NNT) in the high-risk group (empirical antibiotic therapy) is 118, the NNT in the medium-risk group (entering a pathway of observation and clinical investigations) is 823, and the NNT in the low-risk group (observation only) is 9370.[18] These numbers juxtapose the reported mortality of proven EOS for term and late preterm infants between 1.3% and 1.7%.[2,19] Accepting the reported threshold means treating more than 6900 or performing laboratory investigations in more than 48000 newborns at risk for EOS to save 1 child who would die because of sepsis. The societal and economic justification for any numbers remains within the respective national health system acknowledging national differences as percentage of group B streptococcus screening, home births and follow-up strategies. But beside the financial burden and use of resources, antibiotic treatment of asymptomatic newborns raises the question of the safety of this strategy. The increased risk on the development of necrotizing enterocolitis, late-onset sepsis and death from prolonged antibiotic treatment of premature infants is well documented.[20–23] Additionally, recent cohort studies report an increased risk of recurrent wheezing demanding corticosteroid therapy within the first few years of age for infants treated with antibiotics in the first week of life.[24,25]

TABLE 4. Geographical Distribution of Starting and Discontinuation of Antibiotic Therapy (in %, Dependent and Independent on Lab Combined)

		Start of Antibiotic Therapy			Discontinuation of Antibiotic Therapy >72 h (duration)		
Country	Number of Respondents	Low Risk (Solely Risk Factors), %	Medium Risk (No Risk Factors, Clinical Signs Possible Related to Infection), %	High Risk (Risk Factors and Clinical Signs), %	Low Risk (Risk Factors, Clinical Signs Resolved Early on the First Day), %	Medium Risk (Clinical Signs Possible Related to Infection Resolved After 24–36 h), %	High Risk (Risk Factors, Clinical Signs Resolved Late After the Third Day), %
United Kingdom	61	95.1	96.7	100	14.1	29.5	77.2
The Netherlands	54	55.6	94.4	100	3.8	26.0	64.8
Czech Republic	46	50.0	89.1	100	8.7	37.0	76.1
US	42	90.5	92.9	97.6	2.4	23.8	55.8
Switzerland	27	44.4	77.8	96.3	7.4	18.5	71.4
Canada	25	60.0	84.0	96.0	12.0	16.0	72.0
France	24	91.7	100	100	20.9	25.1	76.6
Slovakia	24	95.8	91.7	100	16.9	37.5	66.7
Australia	20	70.0	90.0	100	20.0	15.0	45.0
Norway	19	73.7	84.2	100	5.3	31.6	78.4

We found a high agreement to discontinue antibiotic therapy before 72 hours in the low-risk scenario in the survey and in all guidelines.[13–17] On the other hand, our results demonstrate a high diversity regarding duration of antibiotic therapy in the high-risk setting. Blood cultures, which are the gold standard to diagnose sepsis, are often falsely negative because of a limited volume of blood drawn for culture and/or intrapartum antibiotics administered to the mother.[26] Serial negative laboratory parameters such as neutrophil values and indices, CRP or PCT have shown a high–negative-predictive value and may serve to decide when to discontinue empirical antibiotic treatment.[27–29] However, clinical situations with elevated laboratory markers of inflammation or prolonged clinical signs suggestive of infection are far more common than culture-proven infection and may have unintended consequences as the illustrative example of the 2012 guidelines of the American Academy for Pediatrics (AAP) revealed.[16] The AAP recommends that all asymptomatic neonates born to mothers with signs of chorioamnionitis should receive antibiotic therapy if the CBC and/or the CRP are abnormal. A retrospective population based data analysis showed that through implementation of the guideline, 96% of empirically treated neonates born to mothers with signs of chorioamnionitis were clinically well, but 20% were treated with prolonged antibiotic therapy for at least seven days based solely on abnormal laboratory tests.[11] Recently, authors of the AAP guidelines 2012 made a statement in response to this publication: "Commonly used laboratory tests have a limited positive predictive accuracy and should never be used as a rational to continue antibiotic treatment in an otherwise healthy term infant at 48 to 72 hours of life."[30] The diversity with regards to duration of antibiotic therapy in higher risk situations raises the question, what are safe strategies to minimize duration of antibiotic therapy without under-treatment of truly septic neonates? Currently, the duration of antibiotic therapy is controversial even for proven infections.[31–33] Prospective, international, multicenter trials studying newer infection markers with a safety endpoint may be helpful in answering this question.[34] As shown in our survey, clinicians are ready to discontinue antibiotic therapy depending on infection markers. This is in agreement with previous reviews.[7–9,35]

Interpretation of national-based data from our survey alone is not possible because of the low number of participants in each country. Nevertheless, the data reflect the trends of the recommendations of the national guidelines. The guidelines of the United Kingdom and US recommend treating newborns in our low-risk scenario and more than 90% of respondents in the United Kingdom and US agree based on their responses.[15,16] The Swiss guideline only recommends observing newborns in our low-risk scenario and only 44% of clinicians in Switzerland would start antibiotic treatment, most of them if laboratory markers were abnormal.[17] Interestingly, there is no obvious geographically common pattern for North America or Europe. The agreement between respondents and the national guidelines suggests that guidelines are relevant in the decision-making process of clinicians at the bedside. However, consequences of published guidelines may be different than expected. After implementation of the National Institute for Health and Care Excellence (NICE) guideline in the United Kingdom recommending measurement of CRP concentration 18–24 hours after the start of antibiotic therapy, a report showed a greater consistency in management, but more investigations including lumbar punctures, and a greater length of stay for newborns with suspected EOS.[12] Guidelines have to be as clear and concise as possible, and implementation of new guidelines has to be followed by population-based studies asking for impact and unintended adverse effects.

This study has limitations. The low and only partially known response rate may introduce selection bias. Whereas response rates are usually judged as measurement of response bias, a recently published review of pediatric surveys shows evidence that this may not be necessarily be the case.[36] The impact of a possible selection bias is small if the approached group of participants is closely targeted as in our survey.[36–38] Another limitation is the low number of participants per country. Therefore, interpretation of national-based data from the survey alone is not possible.

CONCLUSIONS

There are large differences between clinicians in the management of term and late preterm neonates at risk for EOS. In particular, this was observed regarding the decision to start antibiotic therapy in low-risk situations and the decision on duration of antibiotic therapy in high-risk situations. Dependence on laboratory investigations is low for decisions to start and high for decisions to discontinue antibiotic therapy. Only a minority of respondents

TABLE 5. Recommendation for the Management of EOS in Current Guidelines

Guideline	Canadian Paediatric Society[13] 2007 (Reaffirmed 2011)	American Academy for Pediatrics[16] 2012	National Institute for Health & Care Excellence[15] 2012	Swiss Society of Neonatology[17] 2013	Belgian Pediatric Management Guidelines[14] 2014
Country	Canada	US	United Kingdom	Switzerland	Belgium
Target	EOS in general	EOS in general	EOS in general	EOS in general	GBS-EOS
Start of antibiotic therapy	CS: treat RF: observe CAM: treat if abnormal Lab	CS: treat RF: treat if abnormal Lab CAM: treat	CS: treat RF: treat if ≥ 2 RF CAM: observe	CS: treat RF: observe CAM: observe	CS: treat RF: observe CAM: treat
Duration of antibiotic therapy	Re-evaluation within 48 h, discontinue if infection unlikely Findings/progress consistent with sepsis, treat at least 5 d	Re-evaluation within 48 h, discontinue if infection unlikely Recommendations for positive cultures Bacteremia without an identifiable focus of infection is generally treated for 10 d	Re-evaluation within 48 h, discontinue if infection unlikely and CRP is reassuring Recommendations for positive cultures Findings/progress consistent with sepsis, treat at least 7 d	Re-evaluation within 48 h, discontinue if infection unlikely No further recommendations	Re-evaluation within 48 h, discontinue if infection unlikely Recommendations for positive cultures and elevated CRP
Cultures	Blood culture: always Lumbar puncture: yes, always when clinical signs of sepsis, except respiratory distress alone Urine culture: no Body surface cultures: not mentioned	Blood culture: always Lumbar puncture: yes, if there is a positive blood culture, a strong suspicion of bacterial sepsis or worsening during therapy Urine culture: no Body surface culture: no	Blood culture: always Lumbar puncture: yes, if there is a positive blood culture, a strong suspicion of bacterial sepsis or meningitis or if CRP >10 mg/L after starting antibiotic therapy Urine culture: no Body surface culture: no	Blood culture: always Lumbar puncture: yes, if there is a positive blood culture and/or in critically ill newborns Urine culture: no Body surface culture: no	Blood culture: always Lumbar puncture: yes, always if high suspicion of infection Urine culture: not mentioned Body surface culture: no
Laboratory investigations before start of therapy	CBC on indication PPV and NPV of single tests are low except for WBC $<5.0 \times 10^9$/L	CBC ± CRP if there are CS, RF or CAM PPV and NPV of single tests are low	CRP indicated if you start treatment	At the discretion of the responsible physician PPV and NPV of single tests are low	CBC, CRP if there are CS, RF or CAM PPV and NPV of single tests are low
Laboratory investigations for decision to discontinue therapy	Not mentioned	Serial negative CRP measurements are helpful to discontinue antibiotic therapy	CRP indicated during antibiotic therapy at 18–24 h after starting	Serial negative CRP or PCT measurements are helpful to discontinue antibiotic therapy	Serial negative CRP measurements are helpful to discontinue antibiotic therapy Continue therapy if CRP is rising

GBS indicates group B streptococcus; CS, clinical symptoms, corresponds to the medium-risk and high-risk scenario of the survey; RF, solely risk factors without clinical signs, corresponds to the low risk scenario of the survey; CAM, solely chorioamnionitis without clinical signs, corresponds to the low risk scenario of the survey; Lab, laboratory investigations; WBC, white blood count; CBC, complete complete blood count including differentiation of cells; PPV, positive predictive value; and NPV, negative predictive value.

uses newer infection markers such as PCT and interleukins. A discussion leading to terms of a threshold to treat neonates with a low infection risk, prospective studies of strategies regarding early discontinuation of unnecessary antibiotic therapy with safety endpoints acknowledging different backgrounds of health care systems and clear and concise guidelines followed by research to study the impact are mandatory to improve management of term and late preterm newborns at risk for EOS.

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