Received: 17 October 2022 | Revised: 23 November 2022 | Accepted: 5 December 2022

DOI: 10.1111/apa.16617

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

ORIGINAL ARTICLE

Biochemical surveillance versus clinical observation of term infants born after prolonged rupture of membranes – A quality assurance initiative

Emma Rød[1] | Vilde Solberg[1] | Eydís Oddsdóttir Stenersen[1,2] | Håvard Tetlie Garberg[3] | Anders Batman Mjelle[4] | Per Arne Tølløfsrud[5] | Arild Erland Rønnestad[2,5] | Anne Lee Solevåg[5]

[1]Faculty of Medicine, University of Oslo, Oslo, Norway

[2]Institute of clinical medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

[3]Department of Paediatric and Adolescent Medicine, Drammen Hospital, Drammen, Norway

[4]Department of Paediatric and Adolescent Medicine, Haukeland University Hospital, Bergen, Norway

[5]Department of Neonatal Intensive Care, Division of Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway

Correspondence
Emma Rød, Faculty of Medicine, University of Oslo, P.O. Box 1078 Blindern, Oslo 0316, Norway.
Email: emma.rod@studmed.uio.no

Funding information
Eydis Oddsdóttir Stenersen was supported by the Research Council of Norway through the Medical Student Research Program at University of Oslo, Norway

Abstract

Aim: To examine whether biochemical surveillance vs clinical observation of term infants with prolonged rupture of membranes as a risk factor for early-onset sepsis is associated with differences in patient trajectories in maternity and neonatal intensive care units.

Methods: A retrospective study of live-born infants with gestational age ≥ 37 + 0 weeks born after prolonged rupture of membranes (≥24 h) in four Norwegian hospitals 2017–2019. Two hospitals used biochemical surveillance, and two used predominantly clinical observation to identify early-onset sepsis cases.

Results: The biochemical surveillance hospitals had more C-reactive protein measurements ($p < 0.001$), neonatal intensive care unit admissions ($p < 0.001$) and antibiotic treatment ($p < 0.001$). Hospitals using predominantly clinical observation initiated antibiotic treatment earlier in infants with suspected early-onset sepsis ($p = 0.04$) but not in infants fulfilling early-onset sepsis diagnostic criteria ($p = 0.09$). There was no difference in antibiotic treatment duration ($p = 0.59$), fraction of infants fulfilling early-onset sepsis diagnostic criteria ($p = 0.49$) or length of hospitalisation ($p = 0.30$), and no early-onset sepsis-related adverse outcomes.

Conclusion: The biochemical surveillance hospitals had more C-reactive protein measurements, but there was no difference in antibiotic treatment duration, early-onset sepsis cases, length of hospitalisation or adverse outcomes. Personnel resources needed for clinical surveillance should be weighed against the limitation of potentially painful procedures.

KEYWORDS
antibiotics, C-reactive protein, early-onset sepsis, prolonged rupture of membranes, term infant

Abbreviations: CRP, C-reactive protein; EOS, Early-onset sepsis; GA, Gestational age; GBS, Group B streptococcus; NICU, Neonatal intensive care unit; PROM, Prolonged rupture of membranes; SOP, Standard operating procedure.

1 | INTRODUCTION

Early-onset sepsis (EOS) is an important cause of neonatal morbidity and mortality.[1] Early suspicion and treatment are vital for a favourable outcome. However, clinical signs of EOS are often subtle and nonspecific, and a positive blood culture, the gold standard diagnostic criterion, may not be present before 36–48 h.[2] For these reasons, treatment of EOS may be delayed, and maternity units need reliable procedures for follow-up of infants with risk factors for EOS.

Prolonged rupture of membranes (PROM) is a risk factor for EOS and occurs in approximately 6% of term pregnancies.[3] Following rupture of the amniotic membrane, the foetus is more easily exposed to ascending bacteria from the maternal lower urinary tract and birth canal.[4] Other risk factors for EOS in term infants include maternal group B streptococcal (GBS) colonisation, −bacteriuria or -infection in the current pregnancy, invasive GBS infection in a previous infant, maternal fever during labour, and chorioamnionitis.[5] Some countries perform universal screening for GBS in pregnant women; however, there is no such practice in Norway.

Biochemical tests are frequently performed in EOS workup and surveillance and often include the inflammation marker C-reactive protein (CRP).[6] However, the utility of serum CRP in diagnosing EOS is disputed because of its low sensitivity in the early stages of the disease due to delayed synthesis.[6] Furthermore, elevated CRP values shortly after birth may have other causes than EOS, e.g., prolonged labour or meconium aspiration.[6] Several studies have found that the sensitivity of CRP in suspected EOS improved by performing serial measurements.[7–9] However, these studies did not evaluate serial CRP measurements for screening infants based on risk factors alone.

Thus, we aimed to examine term infants with PROM as a risk factor for EOS, assessing whether biochemical surveillance compared to predominantly clinical observation was associated with differences in patient trajectories in maternity and neonatal intensive care units (NICU).

Key notes

- We aimed to examine term infants with prolonged rupture of membranes as a risk factor for early-onset sepsis, assessing whether biochemical surveillance vs clinical observation was associated with differences in patient trajectories.
- We found that more C-reactive protein measurements in biochemical surveillance hospitals were not associated with clinically significant differences in patient trajectories.
- Future studies should examine the personnel costs associated with clinical surveillance against the disadvantage of painful procedures.

2 | PATIENTS AND METHODS

2.1 | Setting and study design

This was a quality assurance initiative of current practises regarding EOS surveillance in four hospitals in two Norwegian health care trusts. Included hospitals were Rikshospitalet and Ullevål Hospital from Oslo University Hospital, and Bærum and Drammen Hospital from Vestre Viken Hospital Trust. Rikshospitalet, Ullevål and Drammen Hospital are referral hospitals and treat both low- and high-risk patients. Bærum Hospital has a lower-risk birth population and does not have a department of paediatrics or NICU. Bærum Hospital transfers their sick infants primarily to Drammen Hospital. Infants with a strong suspicion of EOS have their blood culture drawn and antibiotic treatment initiated prior to transfer. The four hospitals cover a substantial fraction of the population in the South-Eastern Norway Regional Health Authority, with 23.2% of the deliveries in Norway during the study period.[10] There were, on average, 6952 annual deliveries at Ullevål Hospital, 2494 at Rikshospitalet, 1844 at Drammen Hospital and 1529 at Bærum Hospital during the study period.[10]

All four hospitals had standard operating procedures (SOP) for the follow-up of term infants (gestational age, GA ≥37 + 0 weeks) born after PROM (≥24 h) during the study period. Common for all the SOPs was that the attending paediatrician was to be consulted regarding any sign of EOS.

Based on their SOP, the four hospitals were divided into two groups: (1) with a biochemical surveillance protocol or (2) using predominantly clinical observation.

Rikshospitalet and Bærum Hospital used a biochemical surveillance protocol, introduced to reduce the workload of the paediatricians and improve patient safety. The SOPs included measurement of CRP, leukocyte- and platelet count at 1–2, 12 and 36 h of life, in addition to clinical observation. The SOPs did not specify specific biochemical threshold values for suspecting EOS but left it at the attending paediatrician's discretion.

The SOPs at Ullevål and Drammen Hospital included temperature measurement three times during the first day of life and observation for other signs of EOS, including increased respiratory- and heart rate, hypotonia and reduced feeding tolerance. Biochemical tests were only performed if there was a clinical suspicion of EOS.

2.2 | Study period, participants and data extraction

The study was initiated in late 2019 as a retrospective study of patient records. We included all live-born infants with GA ≥37 + 0 weeks born after PROM ≥24 h in the four hospitals from January 1, 2017, until December 31 2019.

Data were extracted from the patient electronic records DIPS (DIPS AS) and Partus (CSAM), and MetaVision electronic patient chart (iMDsoft). Electronically stored blood culture results were

TABLE 1 Background data on all live-born term infants born after prolonged rupture of membranes (PROM)

	Predominantly clinical observation (N = 2241)	Biochemical surveillance (N = 921)	p Value	OUS-Ullevål Hospital[c] (N = 1823)	VV-Drammen Hospital[c] (N = 418)	OUS-Rikshospitalet[d] (N = 573)	VV-Bærum Hospital[d] (N = 348)	p Value
Gestational age (weeks)[a]	40 (39–40)	39 (39–40)	0.31	40 (39–40)	40 (39–40)	39 (39–40)	40 (39–40)	0.41
Birth weight (grams)[a]	3475 (3170–3780)	3410 (3140–3730)	**0.01**	3470 (3170–3780)	3477 (3177–3771)	3395 (3140–3720)	3460 (3153–3748)	**.01**[e]
Female[b]	1125/2241 (50)	433/921 (47)	0.10	915/1823 (50)	210/418 (50)	267/573 (47)	166/348 (48)	0.43
PROM duration (hours)[a]	38 (29–49)	36 (28–46)	**0.01**	38 (29–49)	37 (29–47)	38 (29–48)	34 (27–43)	**<.001**[f]
Vaginal delivery[b]	1871/2241 (84)	775/921 (84)	0.65	1519/1823 (83)	352/418 (84)	485/573 (85)	290/348 (83)	0.88
Use of vacuum and/or forceps[b]	445/2241 (20)	226/921 (25)	**0.003**	368/1823 (20)	77/418 (18)	143/573 (25)	83/348 (24)	**.03**[g]

Abbreviations: OUS, Oslo University Hospita; PROM, Prolonged rupture of membranes; VV, Vestre Viken Hospital Trust.

[a]Median (IQR).

[b]*n*/*N* (%).

[c]Predominantly clinical observation.

[d]Biochemical surveillance.

[e]Significant difference between Rikshospitalet and Ullevål Hospital, Rikshospitalet and Drammen.

[f]Significant difference between Bærum and the other hospitals.

[g]Significant difference between Rikshospitalet and Ullevål Hospital.

retrieved from the Division of Microbiology at the respective hospitals. The extracted data included birth weight, GA, gender, mode of delivery, PROM duration, number of CRP measurements during the entire hospital stay, NICU admission, blood culture results, initiation and duration of antibiotic treatment, length of hospitalisation, and discharge status as dead or alive. We assessed all positive blood cultures from term infants during the study period, not only in infants born after PROM. Data were entered into IBM SPSS 28 (IBM Corporation) and Microsoft Office Excel (Microsoft). The data extractions were performed by three authors (ER, VS, EOS).

The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[11]

2.3 | Ethical considerations

The study was approved by the Data Protection Officer at Oslo University Hospital and Vestre Viken Hospital Trust, and the Regional Committee for Medical and Health Research Ethics (reference number 148990). As the study was considered a quality assurance initiative, we were not required to collect individual consent from the parents of the included infants.

2.4 | Definitions

In agreement with the National Institute for Health and Care Excellence (NICE), a 24 h PROM threshold was chosen for term infants in our hospitals' policies and guidelines for neonatal sepsis surveillance.[5] Thus, PROM was defined as confirmed rupture of membranes ≥24 h before the onset of labor.

We defined EOS as the onset of infection within the first 72 h of life.[12] We disregarded diagnostic codes specified in the infants' medical records and retrospectively applied Norwegian consensus criteria for an EOS diagnosis.[13] EOS was confirmed by the growth of a pathogenic microbe in blood culture. In the absence of a positive blood culture, the following four EOS diagnostic criteria should be met: (1) clinical signs of infection, (2) CRP >30 mg/L during the course of the disease, (3) ≥5 d of antibiotic treatment or death by clinical sepsis before 5 d, and (4) exclusion of other explanations for the clinical picture or increase in CRP levels.[13]

For study purposes, we constructed a group of "suspected EOS cases". Suspected EOS was defined as one of the following: (1) suspected EOS as the reason for NICU admission, (2) NICU admission due to elevated CRP levels or signs of infection during the first 72 h of life, or (3) initiation of antibiotics (excl. prophylaxis) during the first 72 h of life.

We defined "patient trajectories" in accordance with a systematic review by Pinaire et al as a care process established for a specific disease to improve patient care, facilitate health planning within institutions, ensure prevention, predict the course of the disease and prevent the onset of symptoms.[14]

2.5 | Statistical analyses

Continuous variables are presented as median with interquartile range (IQR). We compared the hospitals with biochemical surveillance of term infants born after PROM (Rikshospitalet and Bærum Hospital) with those using predominantly clinical observation (Ullevål and Drammen Hospital). Secondarily, we compared the four hospitals individually. Categorical variables were examined using the chi-square test (with *z*-test) and relative risk with 95% confidence interval. For continuous variables, we used non-parametric tests (Mann-Whitney *U* and Kruskal-Wallis) for non-normally distributed variables and parametric tests (*t*-test and ANOVA with Bonferroni post hoc test) for normally distributed variables. p Values <0.05 were considered statistically significant. The statistical analyses were performed using IBM SPSS 28 (IBM Corporation) for Mac.

3 | RESULTS

In total, 36 575 term infants were delivered in the four hospitals during the study period. Of these, 3162 (8.6%) were live-born PROM infants: 921 (29.1%) were born in the hospitals with biochemical surveillance and 2241 (70.9%) in the hospitals with predominantly clinical observation.

Baseline characteristics of the included infants are presented in Table 1. In the hospitals with biochemical surveillance, infants had lower birth weight, shorter PROM duration, and a higher rate of instrumental vaginal deliveries than in those using predominantly clinical observation. There was no difference in GA, gender distribution, or proportion of vaginal deliveries between hospitals with and without a biochemical surveillance protocol.

Outcome variables are presented in Table 2 and Figure 1. Hospitals with biochemical surveillance had more CRP measurements per infant, a higher number of CRP measurements in total, a higher proportion of infants who had CRP measured, more NICU admissions and more infants receiving antibiotics for suspected EOS compared to the hospitals with predominantly clinical observation. Other frequent causes of NICU admission in the cohort included respiratory problems, heart murmurs, hyperbilirubinemia and hypoglycaemia. In the hospitals using predominantly clinical observation, 19% of the infants had at least one CRP measurement, with a median of two measurements per infant that had CRP measured. In hospitals using predominantly clinical observation, antibiotic treatment was initiated earlier in infants with suspected EOS but not in infants fulfilling EOS diagnostic criteria. There was no difference in antibiotic treatment duration, the proportion of infants fulfilling EOS diagnostic criteria or NICU length of stay. For both groups, the median length of stay at the maternity unit was 3 d ($p = 0.57$). There were no EOS-related deaths or other adverse outcomes in either group during the study period.

There were 14 cases of culture-positive EOS among all term infants in the four hospitals during the study period; 12 cases among 33 413 term infants without PROM (0.36 per 1000), and two among the 3162 with PROM (0.63 per 1000). The relative risk associated with PROM was 1.76 (95% CI 0.39–7.87). Both infants with PROM and culture-positive EOS were born in Rikshospitalet, and both had GBS in their blood culture. The mothers of the infants had no known GBS history and did not receive prophylactic antibiotics prior to delivery. The infants were delivered vaginally and appeared healthy at birth. In both infants, the CRP level was slightly increased (6 mg/L and 18 mg/L, respectively) at 12 h of life, and clinical signs of EOS prompted an extra blood sample between 12 and 36 h of life with CRP of 112 mg/L and 58 mg/L, respectively. The first infant was admitted to the NICU at 34 h of life. This infant was also diagnosed with meningitis and treated with antibiotics for 21 d. The other infant was admitted to the NICU at 22 h of life and treated with antibiotics for 7 d.

4 | DISCUSSION

This study aimed to examine whether biochemical surveillance compared to predominantly clinical observation of term infants with PROM as a risk factor for EOS was associated with differences in patient trajectories in maternity units and NICUs. We found that the hospitals with a biochemical surveillance protocol had more CRP measurements, NICU admissions and infants treated with antibiotics for suspected EOS. Hospitals with predominantly clinical observation initiated antibiotic treatment earlier in infants with suspected EOS but not in infants eventually fulfilling EOS diagnostic criteria. There was no difference in antibiotic treatment duration, the proportion of infants fulfilling EOS diagnostic criteria or length of hospitalisation. We identified two cases of culture-positive EOS in the PROM cohort, both in one of the biochemical surveillance hospitals. Importantly, in these two infants, clinical signs of EOS rather than the surveillance protocol prompted NICU admission and initiation of antibiotics. No EOS-related deaths or adverse outcomes were observed in either group.

The number of CRP measurements indicates the amount of blood samples drawn in the EOS workup and follow-up in the respective hospitals. Not surprisingly, the hospitals with biochemical surveillance had significantly more CRP measurements per infant and a higher proportion of infants who had CRP measured, than those with predominantly clinical observation. The latter hospitals performed CRP measurements when clinically indicated, corresponding to approximately one in five PROM infants. Less CRP measurements in the hospitals with predominantly clinical observation potentially reflect fewer painful procedures, as well as lower expenditures associated with ordering, collecting, analysing and interpreting the results of blood samples.

We speculate that the higher number of NICU admissions in the hospitals that performed biochemical surveillance partially comprises well-appearing infants with abnormal biochemical findings, including elevated CRP. Several studies address the low specificity of CRP in the first days of life.[6,7] Elevated CRP after birth may be caused by prolonged vaginal delivery, which is associated

TABLE 2 Outcome variables

	Predominantly clinical observation (*N* = 2241)	Biochemical surveillance (*N* = 921)	*p* Value	OUS-Ullevål Hospital[c] (*N* = 1823)	VV-Drammen Hospital[c] (*N* = 418)	OUS-Rikshospitalet[d] (*N* = 573)	VV-Bærum Hospital[d] (*N* = 348)	*p* Value
Number of CRP measurements per infant[a,f]	0 (0–0)	3 (3–4)	**<0.001**	0 (0–0)	0 (0–0)	3 (3–5)	3 (3–4)	**<.001**[h]
Number of CRP measurements in total[f]	1092	3642	–	916	176	2349	1293	–
Proportion of infants who had CRP measured[b,f]	427/2239 (19.1)	909/919 (98.9)	**<0.001**	360/1822 (19.8)	67/417 (16.1)	567/573 (99,0)	342/346 (99.0)	**<.001**[h]
Admissions to NICU[b]	161/2241 (7.2)	102/921 (11.1)	**<0.001**	125/1823 (6.9)	36/418 (8.6)	71/573 (12.4)	31/348 (8.9)	**<.001**[i]
Admissions to NICU with suspected EOS at the time of admission[b]	82/2241 (3.7)	73/921 (7.9)	**<0.001**	66/1823 (3.6)	16/418 (3.8)	50/573 (8.7)	23/348 (6.6)	**<.001**[j]
Age at initiation of antibiotics in infants with suspected EOS (hours)[a,g]	11 (2–24)	19 (5–29)	**0.04**	11 (3–25)	3 (1–23)	19 (5–30)	22 (5–29)	0.13
Age at initiation of antibiotics in infants fulfilling EOS diagnostic criteria (hours)[a,g]	12 (2–24)	25 (9–30)	0.09	14 (3–24)	0 (–)[e]	24 (9–34)	26 (3–30)	0.33
Antibiotic treatment[b,g]	79/2239 (3.5)	68/920 (7.4)	**<0.001**	64/1822 (3.5)	15/417 (3.6)	53/573 (9.2)	15/347 (4.3)	**<.001**[k]
Antibiotic treatment duration (days)[a,g]	4.0 (2.0–5.0)	3.8 (2.5–5.0)	0.59	4.0 (2.0–5.0)	4.0 (3.0–5.0)	3.0 (2.5–4.0)	5.0 (3.0–5.0)	**.03**[l]
Infants fulfilling EOS diagnostic criteria[b,g]	25/2239 (1.1)	13/920 (1.4)	0.49	22/1822 (1.2)	3/417 (0.7)	7/573 (1.2)	6/347 (1.7)	0.65
Blood cultures for suspected EOS[b,g]	91/2239 (4.1)	71/920 (7.7)	**<0.001**	67/1822 (3.7)	24/417 (5.8)	53/573 (9.2)	18/347 (5.2)	**<.001**[k]
Culture-positive EOS[b,g]	0/2239 (0.0)	2/920 (0.2)	**0.03**	0/1822 (0.0)	0/417 (0.0)	2/573 (0.3)	0/347 (0)	**.03**[i]
NICU length of stay among infants with suspected EOS (days)[a,g]	4 (2.0–5.0)	3.0 (2.0–5.0)	0.30	4.0 (2.0–5.0)	4.0 (2.0–5.0)	3.0 (2.0–4.5)	4.5 (1.0–5.0)	0.69

Abbreviations: CRP, C-reactive protein; EOS, Early-onset sepsis; OUS, Oslo University Hospital; NICU, Neonatal intensive care unit; VV, Vestre Viken Hospital Trust.

[a]Median (IQR).

[b]*n/N* (%).

[c]Predominantly clinical observation.

[d]Biochemical surveillance.

[e]Age at initiation of antibiotics in infants fulfilling EOS diagnostic criteria at Drammen hospital: 0, 0 and 36 hours.

[f]Information missing for 4 infants.

[g]Information missing for 3 infants.

[h]Significant difference between Drammen and Bærum Hospital, Drammen Hospital and Rikshospitalet, Ullevål and Bærum Hospital, Ullevål Hospital and Rikshospitalet.

[i]Significant difference between Rikshospitalet and Ullevål Hospital.

[j]Significant difference between Rikshospitalet and Ullevål Hospital, Rikshospitalet and Drammen Hospital, Ullevål Hospital and Bærum Hospital.

[k]Significant difference between Rikshospitalet and the other hospitals.

[l]Significant difference between Rikshospitalet and Bærum Hospital.

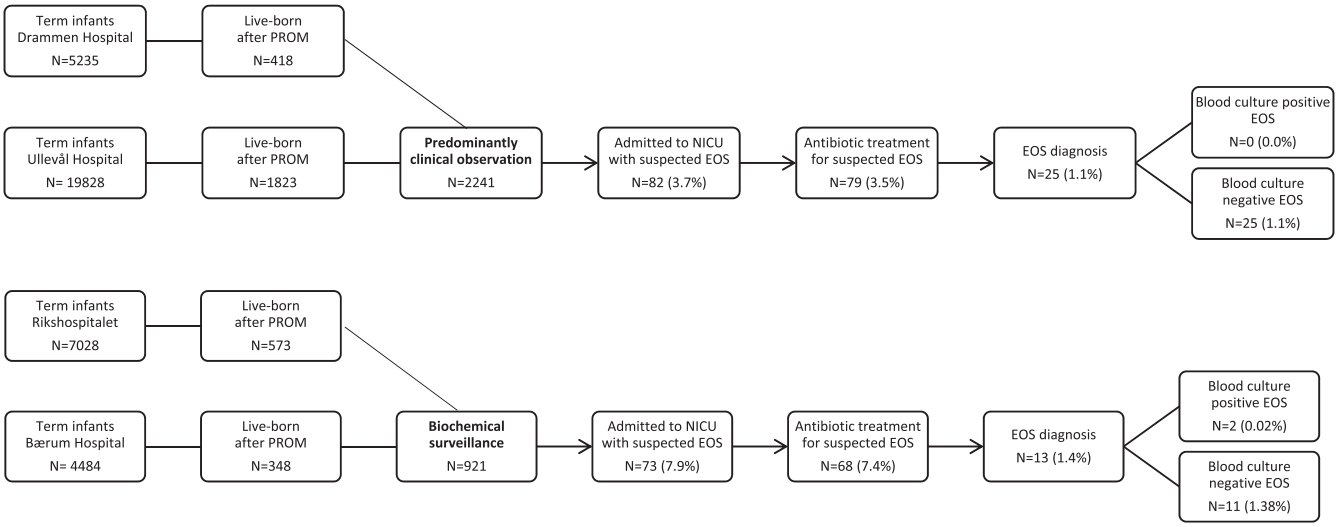

FIGURE 1 Term infants born 2017–2019 at the four hospitals. Abbreviations: EOS, Early-onset sepsis; NICU, Neonatal intensive care unit; PROM, Prolonged rupture of membranes.

with the use of instruments (vacuum and forceps).[15,16] In our study, the hospitals with biochemical surveillance had a higher proportion of instrumental vaginal deliveries, potentially reflecting more prolonged deliveries, causing elevated CRP and thus more NICU admissions. On the other hand, CRP has low sensitivity in the early stages of EOS because the rise in serum levels is delayed by six to 10 h.[6,17] Based on this, one may argue that biochemical surveillance for EOS is inexpedient, as it potentially has high false positives rates and, at the same time, may miss EOS in the first hours of life.

More infants born in the hospitals with a biochemical surveillance protocol received antibiotic treatment than in the hospitals with predominantly clinical observation. This is in accordance with a Swiss study showing a reduction in antibiotic use when less biochemical tests were performed in infants with risk factors for EOS.[18] The study also showed that the reduction in biochemical tests was associated with earlier antibiotic treatment in infants with suspected EOS,[18] also in agreement with our results. However, in our study, the hospitals without biochemical surveillance did not initiate antibiotics earlier in infants *fulfilling* EOS diagnostic criteria, which one may argue is the more important group of patients in this setting. Like our results, the Swiss study did not find a difference in the length of hospitalisation.[18]

Our study showed no difference in the proportion of infants fulfilling EOS diagnostic criteria in the hospitals with and without a biochemical surveillance protocol. Most EOS cases were "culture-negative", which is a disputed diagnosis.[2] There were 14 cases of culture-positive EOS among all term infants in the study period, but only two in the PROM cohort, both GBS and in the same hospital with a biochemical surveillance protocol. The other three hospitals had no cases of culture-positive EOS in the PROM cohort, which may suggest that PROM in term infants is not a powerful indicator of increased EOS risk. This potentially novel observation might indicate that additional measures for identification of EOS in these infants are not necessary, but this question is beyond the scope of our study.

The biochemical surveillance protocol for PROM infants was initially introduced at Rikshospitalet to reduce paediatrician workload and thus reduce hospital expenditures. As we have no information on total hospital costs associated with biochemical surveillance vs clinical observation, the question of cost effectiveness remains unanswered. However, more NICU admissions in the biochemical surveillance hospitals may raise questions regarding the cost effectiveness of such a SOP. Furthermore, some may argue that inflicting painful procedures on infants to reduce paediatrician workload is not justifiable.

In 2021, Vestre Viken Hospital Trust, including Bærum and Drammen Hospital, replaced their PROM SOPs with a newborn early warning score performed at 2, 12 and 24 h after birth and at clinical indication. The infants should be observed at the maternity unit for at least 48 h. The newborn early warning score is based on clinical evaluation only and does not include biochemical tests. Rikshospitalet and Ullevål Hospital use the same SOPs as they did during the study period.

Our study has limitations. Data were extracted by three authors individually, and different interpretations and assessments may have influenced data collection. We tried to limit this by applying detailed definitions of the different variables and reaching consensus about interpretations during and after the extractions. Another limitation is that we registered PROM as the only factor associated with EOS risk, and did not collect data on, e.g., maternal chorioamnionitis, fever or peripartum antibiotic treatment. Presumably, peripartum antibiotic treatment was more common in women with PROM, which may have accounted for the low rate of EOS in their infants. However, this does not detract from the observation that CRP measurements add little to assessment of this group of infants, which is still relevant in the setting of current practice. Furthermore, there are some differences in the birth populations and some baseline

characteristics, e.g., birth weight and rate of instrumental vaginal deliveries, among the included hospitals. This might cause a problem with case-mix and impose challenges to the interpretation of our results. Strengths of this study include its clinical relevance since CRP is frequently used in neonatal EOS workup. Our sample size was large, and we included a birth population representative of the Nordic context. Thus, the results of this study may be generalizable to other perinatal centres.

5 | CONCLUSION

The biochemical surveillance hospitals had more CRP measurements, but there were no significant differences in patient trajectory indicators such as antibiotic treatment duration, infants fulfilling EOS diagnostic criteria, length of hospitalisation, age at initiation of antibiotic treatment in infants fulfilling EOS diagnostic criteria or adverse outcomes. We found statistically significant differences in the proportions of NICU admissions, age at initiation of antibiotic treatment in infants with suspected EOS and proportions of infants who recieved antibiotic treatment. However, we speculate that these differences may reflect differences in hospital populations rather than the EOS surveillance procedure.

Considerations should be made to limit painful procedures that do not contribute to improved patient safety and to weigh the cost-effectiveness of personnel demanding clinical surveillance procedures. Future studies should address this as well as how routine biochemical tests affect clinical decision-making in maternity units and NICUs. Studies of alternative assessment procedures in the follow-up of infants with risk factors for EOS are also warranted.

FUNDING INFORMATION

Eydis Oddsdóttir Stenersen was supported by the Research Council of Norway through the Medical Student Research Program at the University of Oslo, Norway.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ORCID

Emma Rød https://orcid.org/0000-0001-8809-706X
Anders Batman Mjelle https://orcid.org/0000-0002-4927-7452
Anne Lee Solevåg https://orcid.org/0000-0002-8009-7169

REFERENCES

1. Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. Clin Microbiol RevClin Microbiol Rev. 2014;27(1):21-47.
2. Klingenberg C, Kornelisse RF, Buonocore G, Maier RF, Stocker M. Culture-negative early-onset neonatal sepsis – At the crossroad between efficient sepsis care and antimicrobial stewardship. Front PediatrFront Pediatr. 2018;6:285.
3. Endale T, Fentahun N, Gemada D, Hussen MA. Maternal and fetal outcomes in term premature rupture of membrane. World J Emerg Med. 2016;7(2):147-152.
4. Jefferies AL. Management of term infants at increased risk for early-onset bacterial sepsis. Paediatr Child HealthPaediatr Child Health. 2017;22(4):223-228.
5. NICE. Neonatal infection: antibiotics for prevention and treatment. Published April 20, 2021. Accessed February 26, 2022. https://www.nice.org.uk/guidance/ng195/chapter/Recommendations#risk-factors-for-and-clinical-indicators-of-possible-early-onset-neonatal-infection%20Publisert:%2020.02.21
6. Hofer N, Zacharias E, Müller W, Resch B. An update on the use of C-reactive protein in early-onset neonatal sepsis: current insights and new tasks. NeonatologyNeonatology. 2012;102(1):25-36.
7. Benitz WE, Han MY, Madan A, Ramachandra P. Serial serum C-reactive protein levels in the diagnosis of neonatal infection. PediatricsPediatrics. 1998;102(4):E41.
8. Hengst JM. The role of C-reactive protein in the evaluation and management of infants with suspected sepsis. Adv Neonatal CareAdv Neonatal Care. 2003;3(1):3-13.
9. Jaye DL, Waites KB. Clinical applications of C-reactive protein in pediatrics. Pediatr Infect Dis JPediatr Infect Dis J. 1997;16(8):735-746.
10. Folkehelseinstituttet. Medisinsk fødselsregister - statistikkbank. Published November 09, 2021. Accessed Janruary 07, 2022. http://statistikkbank.fhi.no/mfr/
11. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin EpidemiolJ Clin Epidemiol. 2008;61(4):344-349.
12. Fjalstad JW, Stensvold HJ, Bergseng H, et al. Early-onset sepsis and antibiotic exposure in term infants: a Nationwide population-based study in Norway. Pediatr Infect Dis JPediatr Infect Dis J. 2016;35(1):1-6.
13. Nakstad B, Lang A, Solevåg AL, Klingenberg C. Forslag til enhetlige nasjonale kriterier for diagnosekoder i nyfødtmedisin. Norsk Barnelegeforening. Published 2015. Updated October 2019. Accessed Janurary 04, 2022. https://www.helsebiblioteket.no/pediatriveiledere?menuitemkeylev1=11574&key=265569
14. Pinaire J, Azé J, Bringay S, Landais P. Patient healthcare trajectory. An essential monitoring tool: a systematic review. Health Inf Sci Syst. 2017;5(1):1.
15. Logan CA, Thiel L, Bornemann R, et al. Delivery mode, duration of labor, and cord blood adiponectin, leptin, and C-reactive protein: results of the population-based Ulm birth cohort studies. PLoS One. 2016;11(2):e0149918.
16. Mjelle AB, Guthe HJT, Reigstad H, Bjørke-Monsen AL, Markestad T. Serum concentrations of C-reactive protein in healthy term-born Norwegian infants 48-72 hours after birth. Acta PaediatrActa Paediatr. 2019;108(5):849-854.
17. Iroh Tam PY, Bendel CM. Diagnostics for neonatal sepsis: current approaches and future directions. Pediatr ResPediatr Res. 2017;82(4):574-583.
18. Duvoisin G, Fischer C, Maucort-Boulch D, Giannoni E. Reduction in the use of diagnostic tests in infants with risk factors for early-onset neonatal sepsis does not delay antibiotic treatment. Swiss Med WklySwiss Med Wkly. 2014;144:w13981.

How to cite this article: Rød E, Solberg V, Stenersen EO, Garberg HT, Mjelle AB, Tølløfsrud PA, et al. Biochemical surveillance versus clinical observation of term infants born after prolonged rupture of membranes – A quality assurance initiative. Acta Paediatr. 2023;112:391–397. https://doi.org/10.1111/apa.16617