REGULAR ARTICLE

Active antibiotic discontinuation in suspected but not confirmed early-onset neonatal sepsis—A quality improvement initiative

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Abstract

Aim: To study whether a simple targeted intervention could reduce unwarranted antibiotic treatment in near-term and term neonates with suspected, but not confirmed early-onset sepsis.

Methods: A quality improvement initiative in three Norwegian neonatal intensive care units. The intervention included an inter-hospital clinical practice guideline for discontinuing antibiotics after 36-48 hours if sepsis was no longer suspected and blood cultures were negative in neonates ≥ 34+0 weeks of gestation. Two units used procalcitonin in decision-making. We compared data 12-14 months before and after guideline implementation. The results are presented as median with interquartile ranges.

Results: A total of 284 infants (2.5% of all births ≥ 34+0 weeks of gestation) received antibiotics before and 195 (1.8%) after guideline implementation (P = .0018). The two units that used procalcitonin discontinued antibiotics earlier after guideline implementation than the unit without procalcitonin. Neonates not diagnosed with sepsis were treated 49 (31-84) hours before and 48 (36-72) hours after guideline implementation (P = .68). In all infants, including those diagnosed with sepsis, antibiotic treatment duration was reduced from 108 (60-144) to 96 (48-120) hours (P = .013).

Conclusion: Antibiotic treatment duration for suspected, but not confirmed early-onset sepsis did not change. However, treatment duration for all infants and the proportion of infants commenced on antibiotics were reduced.

KEYWORDS
newborn infant, antibiotics, early-onset sepsis, duration, quality improvement

1 | INTRODUCTION

Due to the challenges of early diagnosis and a potential fatal outcome if treatment is delayed, clinicians often empirically administer intravenous (IV) antibiotics to newborns at risk or with subtle signs of early-onset sepsis (EOS).[1,2] However, prolonged antibiotic treatment is associated with adverse effects on the individual and societal level, including frequent exposure to painful procedures, parent-infant separation and antibiotic resistance.[3,4] Recent clinical initiatives [5] and current international guidelines [6,7] strongly recommend discontinuation of antibiotics within 36-48 hours (h) if blood cultures remain negative and the clinical suspicion of EOS has substantially decreased.

A population-based study in Norway 2009-11 showed that 2.3% of all term neonates received IV antibiotics in the first week of life, but only 0.05% had a positive blood culture.[8] The number needed to treat for one culture-proven infection was 44, which is relatively low compared with many other countries.[9] However, the median treatment duration in infants commenced on antibiotics but not diagnosed with sepsis was four days (96h), substantially longer than recommended.

A large multicentre study showed that procalcitonin (PCT)-guided decision-making was superior to standard care in reducing unwarranted antibiotic treatment of neonates with suspected, but not confirmed EOS.[9] Implementing an 'automatic stop order (ASO)' after 48-h antibiotic treatment is another approach to reduce antibiotic overuse. Treatment beyond 48 h then requires clinical assessment and justification. ASO reduced prolonged and unnecessary antibiotic therapy in some studies.[10,11]

We performed a quality improvement (QI) project in three Norwegian neonatal intensive care units (NICUs) after developing a joint inter-hospital clinical practice guideline (CPG). The primary goal of this study was to investigate whether a simple targeted intervention using this CPG could reduce unwarranted antibiotic therapy in near-term and term infants with suspected, but not confirmed EOS.

2 | PATIENTS AND METHODS

2.1 | Setting and study design

The QI project was designed as a collaborative effort between the NICUs at Akershus University Hospital (AHUS), Ostfold Hospital Trust (OHT) and University Hospital of North Norway (UNN). All three hospitals have a well-defined catchment area and are suited for population-based studies. A common CPG entitled 'Active antibiotic discontinuation in near-term and term neonates' was developed in 2016. The CPG was intended to support clinicians' decision to discontinue antibiotics in infants ≥ 34+0 weeks of gestation when symptoms and laboratory findings after 36-48 hours made EOS a less likely diagnosis. The CPG consisted of a simple bundle with the following two main elements. First, we introduced an ASO for antibiotics after 48 hours. Second, we recommended discontinuing antibiotics within 36-48 hours if the newborn's symptoms had improved,

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Key notes

- This study compared antibiotic treatment duration in suspected early-onset sepsis in three Norwegian neonatal intensive care units before and after implementation of an evidence-based guideline.
- We observed a reduction in treatment duration in all infants commenced on antibiotics; but not in infants not diagnosed with sepsis.
- Increased focus on reducing unwarranted antibiotic treatment resulted in a lower proportion of near-term and term infants receiving antibiotics after guideline implementation.

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there was an absence of persistent respiratory or cardiovascular symptoms and/or a more likely underlying cause of the symptoms had been identified. In addition, it was strongly recommended to trust a negative blood culture result after 36-48 hours.[11]

In Norway, there is no universal screening for rectovaginal colonisation with group B streptococcus in asymptomatic pregnant women, and prophylactic antibiotics are not routinely given to newborn infants of mothers with chorioamnionitis. Norwegian NICUs use a beta-lactam (ampicillin or benzylpenicillin) and gentamicin as empiric therapy for suspected EOS.[8] There is no national guideline on when to initiate antibiotic therapy in newborn infants with risk factors for and/or symptoms of EOS, but most units strongly emphasise clinical symptoms and seldom start antibiotics based on risk factors alone.

C-reactive protein (CRP) is extensively used as a biomarker for EOS in Norway, and it was left to the discretion of the attending physician to define 'reassuring' values. Two of the NICUs (OHT and UNN) included PCT as a new biomarker in the CPG. PCT was analysed at onset of antibiotic therapy and after 24-36 hours. We used previously published reference values for PCT the first week of life.[12] The CPG was based on international guidelines and initiatives [5,7,13] and recent research.[9] In all three NICUs, we provided education to the physicians and nursing staff about the CPG and its evidence base. Moreover, small pamphlets with information about the QI project were disseminated. Importantly, as the aim of the project was to reduce treatment duration in infants already commenced on antibiotics, and not to change criteria for initiating therapy, the local guidelines on which risk factors, clinical symptoms and findings that should prompt antibiotic treatment were not changed in the participating units.

2.2 | Study period, participants and data extraction

The QI project was launched in October-November 2016. We decided a priori to evaluate the project by comparing data from all three NICUs 12-14 months prior to and 12-14 months after guideline implementation. Background data were extracted from the Norwegian neonatal network's (NNN) web-based electronic database, that includes

clinical data and day-to-day treatment of all infants admitted to a Norwegian NICU.[8] We included all infants with a gestational age (GA) ≥34 + 0 weeks who received IV antibiotics in the first week of life. Duration of antibiotic therapy was counterchecked with drug prescription files, and we extracted hours of therapy from the first to the last dose of antibiotic. We summarised the total number of treatment days for each of the two periods by adding hours from the first to the last dose for all infants receiving antibiotics, divided by the number of infants born at the three hospitals. Other data extracted were birthweight, gestational age, delivery route, symptoms, respiratory support, CRP and PCT values at disease onset and during the following 24-48 hours, and blood culture result. Readmissions within 14 days, relevant sequelae and fatalities were also registered.

2.3 | Ethical considerations

The project was approved by the Regional Committee for Medical Research Ethics South East as a QI project with no need for individual consent from the parents of infants included in the project, as the project intervention was considered the new 'standard of care'.

2.4 | Definitions and statistical analysis

According to the International Statistical Classification of Diseases and Related Health Problems 10th revision, the diagnosis 'Unspecified bacterial sepsis' (P36.9) is used when there are clinical and biochemical signs of sepsis, but a negative or missing blood culture. The Norwegian

Paediatric Association has suggested the following criteria for the diagnosis: (a) clinical signs of infection, (b) maximum CRP > 30 mg/L, (c) ≥5 days of antibiotic treatment and (d) exclusion of other explanations for the clinical picture. The arbitrarily chosen CRP cut-off at 30 mg/L has later been supported by CRP analyses in healthy infants.[14] We analysed antibiotic treatment duration in all infants in the pre- and post-implementation period, and focused on three groups: infants commenced on antibiotics but not diagnosed with sepsis, infants diagnosed with sepsis and all infants treated with antibiotics in the first week of life. Trends in overall antibiotic use in the three study hospitals versus the other 18 Norwegian hospitals with a neonatal unit were compared using an already established benchmarking parameter from the NNN; mean days of antibiotic therapy among admitted infants during the first two weeks of life.

Continuous variables are presented as median with interquartile range (IQR). Data were compared between groups using non-parametric tests for continuous variables and chi-square for categorical variables. P-values were 2-sided, and P < .05 was considered statistically significant. We present survival curves for duration of antibiotic therapy before and after the CPG implementation. Statistical analyses were performed with IBM SPSS 25 for Mac (IBM Corporation) and Stata (V145, StataCorp).

3 | RESULTS

There were 11,477 and 10,790 live infants ≥ 34+0 weeks of gestation born before and after guideline implementation, respectively, in the well-defined catchment areas of the three participating NICUs.

TABLE 1 Background data on all neonates ≥ 34+0 weeks of gestation who received IV antibiotics in the three participating neonatal intensive care units

	Pre-implementation (n = 11,477)	Post-implementation (n = 10,790)	P value
Any antibiotic treatment, n (%)	284 (2.5)	195 (1.8)	.001
Hospital, Antibiotic therapy/no. of newborns (%)			
AHUS	122/5807 (2.1)	79/5303 (1.5)	.016
OHT	111/3596 (3.1)	83/3596 (2.3)	.042
UNN	51/2074 (2.5)	33/1891 (1.8)	.12
Diagnosis, n (%)			
No sepsis	120 (42)	105 (54)	.015
Culture-negative sepsis	161 (57)	88 (45)	
Culture-positive sepsis	3 (1.1)	2 (1.0)	
Birthweight (grams), mean (SD)	3650 (682)	3642 (629)	.90
Gestational age (weeks), median (IQR)	40 (39-41)	40 (38-41)	.56
Caesarean delivery, n (%)	85 (30)	36 (18)	.005
Respiratory support at start/during infection, n (%)			
No	189 (67)	113 (58)	
CPAP/nHFT	78 (28)	72 (37)	
Ventilator	16 (6)	10 (5)	.10

Abbreviations: AHUS, Akershus University Hospital; CPAP, continuous positive airway pressure; IQR, interquartile range; nHFT, nasal high-flow therapy; OHT, Ostfold Hospital Trust; SD, standard deviation; UNN, University Hospital of North Norway.

Background data on patients admitted to the three NICUs and receiving antibiotic therapy are presented in Table 1. Three positive blood cultures were identified before (two viridans group streptococci and one *Escherichia coli*) and two positive blood cultures after (one *Staphylococcus aureus* and one viridans group streptococci) guideline implementation. Antibiotic treatment duration and proportion of infants receiving antibiotics before and after guideline implementation are presented in Table 2.

The treatment duration for infants without sepsis did not change appreciably (Table 2). In infants without a sepsis diagnosis at discharge, antibiotic treatment had been continued beyond 48 hours in 49% before vs. 44% after the CPG (P = .65), but the treatment duration varied substantially between the three NICUs. After guideline implementation, the treatment duration for all infants, including those diagnosed with sepsis, was reduced (Table 2). Moreover, a lower proportion of infants were commenced on antibiotics (Table 1). Overall, there was a 37% reduction in antibiotic days from 11.4 to 7.2/100 near-term and term infants. Figure 1 shows that antibiotic treatment duration was reduced more after guideline implementation in the two units using PCT versus the one not using PCT (P = .001).

Table 3 shows infection biomarkers in infants diagnosed with sepsis (P36.9) and those not diagnosed with sepsis. There were marked differences between the two groups. No patients were re-hospitalised with relapse within 14 days, or developed relevant sequelae or complications before or after guideline implementation.

There was a general trend in Norwegian NICUs to use less antibiotics during 2016-2017, the period of this QI project (Figure 2). However, in 2017 after implementing the QI project there was a markedly larger reduction in antibiotic use in the three study hospitals than in the other 18 Norwegian hospitals reporting data to the NNN.

4 | DISCUSSION

There is a wide variation in antibiotic use, both within countries and globally, but with little difference in infection-attributable morbidity and mortality.[2,8,15] This may indicate an overuse of antibiotics in some NICUs and countries resulting in potentially adverse short- and long-term consequences for the health of individual infants.[4,16,17] In our QI project, the primary goal was to reduce the duration of antibiotic therapy in infants commenced on antibiotics, but who later did not have clear evidence of a bacterial infection, one of the top five items in the Choosing Wisely campaign for newborn medicine.[5] We did not achieve our primary goal, but median treatment duration before and after intervention in our study was 49 and 48 hours, respectively, half of the 96 hours observed in the nationwide Norwegian study 2009-2011.[8] We also observed reductions in overall antibiotic use, including > 1/3 reduction in antibiotic days per 100 live-born infants. Despite the common CPG and beneficial outcomes associated with the QI project, large differences persisted between the three participating NICUs.

An ASO policy to ensure continuation of antibiotics only in infants considered to benefit from further therapy is more common in North America than Europe.[10,11] In our QI project, the implementation of ASO was challenging, both in the units using manual drug prescription and in the unit using computerised prescription. This indicates that establishing the ASO as a routine policy requires stewardship, in addition to more in-depth education of NICU staff.

In the two units using PCT to guide treatment discontinuation, the treatment duration in infants not diagnosed with sepsis was shorter than in the unit not using PCT. One of these units (OHT) had a reduction in both the proportion of neonates started on antibiotic treatment and the duration of treatment. The second unit (UNN)

TABLE 2 Antibiotic duration (hours) for different conditions and hospitals before and after implementation of a joint clinical practice guideline

	Pre-implementation	N (%)	Post-implementation	N (%)	P value
Antibiotic duration (hours) —All treated					
Ahus	120 (84-155)	122 (2.1)	120 (72-144)	79 (1.5)	.24
OHT	112 (60-136)	111 (3.1)	96 (47-120)	83 (2.3)	.03
UNN	60 (24-98)	51 (2.5)	36 (24-72)	33 (1.8)	.21
Total	108 (60-144)	284 (2.5)	96 (48-120)	195 (1.8)	.013
Antibiotic duration (hours) —No sepsis					
Ahus	72 (45-108)	39/122 (32)	72 (48-96)	37/79 (47)	.67
OHT	48 (36-106)	47/111 (42)	47 (36-60)	40/83 (48)	.19
UNN	43 (24-60)	34/51 (67)	36 (24-72)	28/33 (85)	.98
Total	49 (31-84)	120/284 (42)	48 (36-72)	105/195 (54)	.68
Antibiotic duration (hours)—Sepsis					
Ahus	132 (108-156)	83/122	120 (120-168)	42/79 (53)	.71
OHT	120 (108-148)	64/111	120 (108-122)	43/83 (52)	.42
UNN	108 (96-120)	17/51	108 (84-108)	5/33 (15)	.43
Total	120 (108-155)	164/284	120 (108-144)	90/195 (46)	.73

Note: All data are median (interquartile range).

Abbreviations: AHUS, Akershus University Hospital; OHT, Ostfold Hospital Trust; UNN, University Hospital of North Norway.
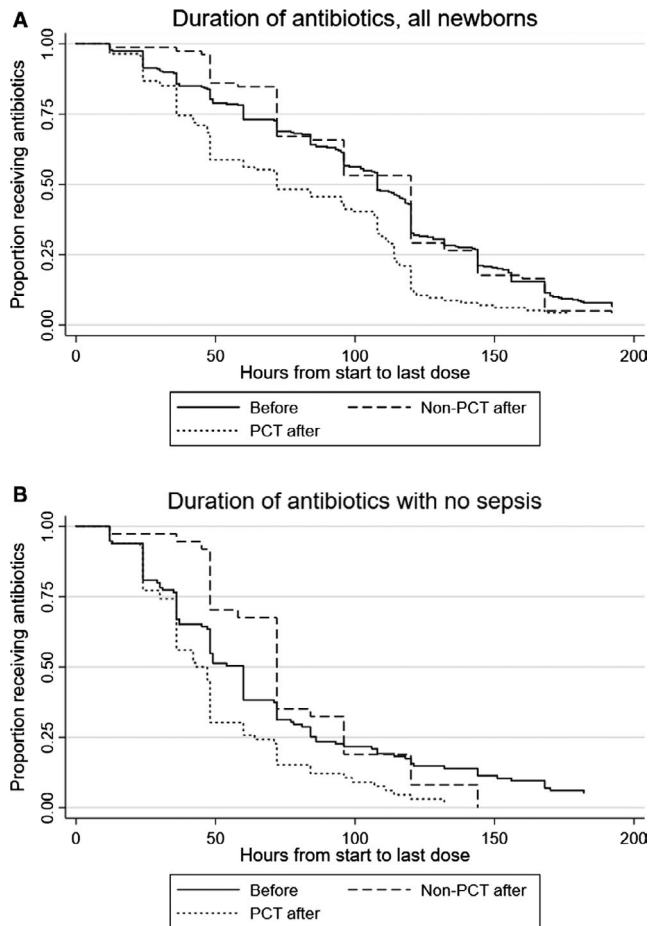
FIGURE 1 (A) Duration of antibiotic therapy before and after implementing procalcitonin (PCT) as part of the clinical practice guideline—all newborns treated with antibiotics. (B): Duration of antibiotic therapy before and after implementing procalcitonin (PCT) as part of the clinical practice guideline—newborns without sepsis

had neither a reduction in the proportion started on treatment, nor treatment duration, but this unit was nearly fully adhering to the main elements in the CPG before the QI project. This unit also had a significantly lower proportion of infants diagnosed with P36.9 among all infants commenced on antibiotics (15%) compared with the two other units who diagnosed 47%-48% of all infants commenced on antibiotics with P36.9. Our data indicate a considerable variation between the three hospitals regarding diagnostic regiments in suspected EOS. We believe that the policies and level of training are comparable between the centres, but that implementation of international recommendations may depend on local champions and the size of the unit. The combination of a unit head with research focuses on neonatal infections, and a lower number of patients and staff at UNN might have been facilitating factors in the earlier acquisition and implementation of international recommendations for treatment discontinuation.[6,7]

Our data may support that use of PCT can contribute to a reduction in antibiotic therapy duration as was observed in the large NeoPINS,[9] but the low number of infants included in our study limits the conclusions that can be drawn.

Overall, fewer infants were commenced on antibiotic therapy and the duration of therapy for all infants commenced on therapy was shorter. The reduced proportion of neonates who was commenced on antibiotic treatment was an unintended effect of the project, and it was specifically not included as an aim in the QI project as it would have required a more thorough safety assessment. We can only speculate that an increased attention to unnecessary antibiotic use and its potential adverse effects in neonates, a fact recognised as a major health problem over the last 5-10 years,[18] may have contributed to this surprising result. None of the participating NICUs used the neonatal early-onset sepsis calculator (NEOSC) and the main indications to start therapy were clinical symptoms in conjunction with abnormal biomarkers. The proportion of infants exposed to antibiotic therapy after implementing the new CPG was only 1.8%. This is in line with data from a large Swiss neonatal unit where the rate of antibiotic use went down to 1.7% by focusing on clinical assessment rather than laboratory tests.[19] Our overall antibiotic prescription rate is lower than that reported in the largest study evaluating the effects of the NEOSC where still 2.6% of all term and late preterm infants were treated with antibiotics during the first 24 hours of life.[20]

TABLE 3 Laboratory analyses for CRP and PCT in newborns with and without infectious diagnosis

	Sepsis**	No sepsis	P value*
CRP initial, n = 467	30 (3-55)	5 (1-16)	<.001
CRP max 0-48 hours, n = 468	50 (32-70)	14 (4-28)	<.001
PCT initial, n = 89	12 (5-29)	3 (1-15)	.005
PCT max 24-36 hours, n = 64	10 (4-27)	2 (1-6)	<.001

Note: All data are median (interquartile range).
CRP; C-reactive protein, mg/L; PCT; procalcitonin, μg/L.
*Wilcoxon rank-sum test.
**In the sepsis group, there were five patients with culture-proven infection; Viridans group streptococci (n = 3), *Staphylococcus aureus* (n = 1) and *Escherichia coli* (n = 1). CRP ranged from 46 to 189 mg/L for this group. PCT was only taken in the infant with *S aureus* sepsis and was 1.49 μg/L.
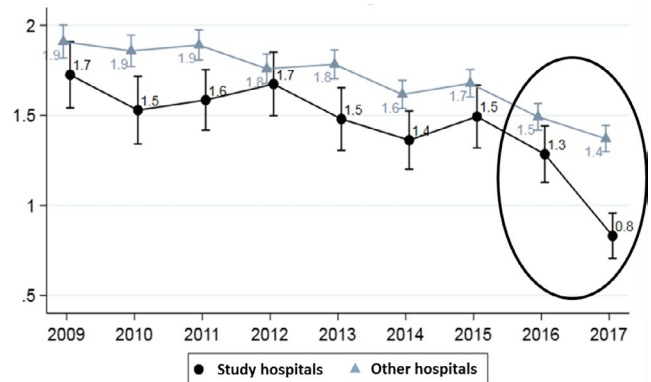

FIGURE 2 Trends in overall antibiotic use among infants ≥ 34+0 weeks in the three study hospitals 2009-2017 compared with trends in the other hospitals in the Norwegian neonatal network. Data presented as mean (95% confidence interval) days of antibiotic therapy among all infants admitted to the neonatal unit during the first two weeks of life

Our study has limitations. We have not established a causal link between the new CPG and the decrease in antibiotic use. The observed reduction may mainly be due to the educational component of the QI project. Although we assessed a population of more than 20,000 infants, the number of patients in our study was too low to conclude that the overall reduction in antibiotic use was safe. Given the low incidence of EOS, much larger studies are needed to be confident about safety measures. It was still reassuring that the overall reduction in antibiotic use was not associated with adverse events. Strengths of the study include the well-defined catchment area of the participating hospitals leading to population-based data and the development of a 'modern' CPG based on recent evidence, initiatives and guidelines.

5 | CONCLUSION

In this QI project, we did not observe a significant reduction in antibiotic therapy duration in infants commenced on antibiotic therapy for suspected EOS, which was later not confirmed. However, through a relatively simple intervention, overall antibiotic use was reduced without seemingly affecting safety. The educational part of the QI project may have had the most important impact, but we speculate that PCT analysis may aid in recognising not-infected infants where antibiotics may be stopped safely. An interesting finding was that some differences between the units persisted, possibly reflecting that it takes time to change established antimicrobial stewardship cultures. Further multicentre and national QI long-term initiatives are needed to reduce unwarranted variation in practice.

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