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REGULAR ARTICLE

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Multicentre study found that adherence to national antibiotic recommendations for neonatal early-onset sepsis was low

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Abstract

Aim: Our aim was to evaluate adherence to the Dutch neonatal early-onset sepsis (EOS) guidelines, adapted from UK guidance. We also looked at the effect on antibiotic recommendations and duration.

Method: This was a multicentre, prospective observational cross-sectional study carried out in seven hospitals in the Netherlands between 1 September 2018 and 1 November 2019. We enrolled 1024 neonates born at 32 weeks of gestation or later if they demonstrated at least one EOS risk factor or clinical signs of infection.

Results: The Dutch guidelines recommended antibiotic treatment for 438/1024 (42.8%) of the neonates designated at risk, but only 186/438 (42.5%) received antibiotics. The guidelines advised withholding antibiotics for 586/1024 (57.2%) of neonates and in 570/586 (97.3%) cases the clinicians adhered to this recommendation. Blood cultures were obtained for 182/186 (97.8%) infants who started antibiotics and only four were positive, for group B streptococci. Antibiotic treatment was continued for more than 3 days in 56/178 (31.5%) neonates, despite a negative blood culture.

Conclusion: Low adherence to the Dutch guidelines meant that the majority of neonates did not receive the antibiotic treatment that was recommended, while some antibiotic use was prolonged despite negative blood cultures. The guidelines need to be revised.

KEYWORDS

adherence, antibiotic treatment, early-onset sepsis, guidelines, neonates

Abbreviations: CRP, C-reactive protein; EOS, early-onset sepsis; GBS, group B Streptococcus; NICE, National Institute for Health and Care Excellence.

1 | INTRODUCTION

Neonatal early-onset sepsis (EOS) is defined as suspected when an untested systemic infection occurs within the first 72 hours after birth[1] and proven if it is confirmed by a positive blood or cerebrospinal fluid culture.[2-4] The incidence of proven EOS is approximately 0.5-2.0 cases per 1000 live newborn infants,[7,8] whereas the incidence of suspected EOS is estimated to be much higher. One study found that six to 16 times more infants receive antibiotics for sepsis than the actual number with a positive blood culture.[1] Difficulties in ascertaining EOS have led to many neonates receiving potentially harmful antibiotic treatment, even though they did not have EOS.[5,6]

Guidelines have been published to provide evidence-based support to prevent, recognise and optimise the diagnosis and treatment of EOS.[7-10] These contain three general approaches to identifying neonates at increased risk of EOS: a categorical risk factor assessment, a multivariate risk assessment and a risk assessment primarily based on the newborn infant's clinical condition.[10,11] The Dutch guidelines, which follow the categorical risk factor approach, have been adapted from guidelines produced by the National Institute for Health and Care Excellence (NICE). This is the organisation that advises the UK National Health Service.[8,9] The Dutch guidelines are a simplified version of NICE's categorical assessment. They provide eight maternal and 15 neonatal risk factors, which are each categorised as red flags for major criteria or non-red flags for minor criteria. These are used to guide decisions about whether to start or withhold antibiotic treatment[8] (Table S1). In accordance with the NICE guidelines, the Dutch guidelines also advise clinicians about discontinuing antibiotic treatment if the patient has a negative blood culture result.[9]

A number of papers have discussed adherence to the NICE guidelines in clinical practice and have debated whether they are appropriate.[5,12-14] That is why we decided to prospectively examine the use of the Dutch guidelines in clinical practice. The primary aim of this study was to evaluate whether clinicians adhered to the antibiotic recommendations of the guidelines. The secondary aim was to determine the duration of, and the reasons for, continuing antibiotic treatment when patients had a negative blood culture.

Keynotes

- We evaluated clinical adherence to the antibiotic recommendations of the Dutch adaption of the National Institute for Health and Clinical Excellence guidelines for neonates at risk of early-onset sepsis.
- Adherence to the guidelines was low, due to withholding antibiotics against the recommendations and continuing antibiotic treatment despite negative blood cultures.
- The current guidelines need to be revised or replaced by a new strategy to improve antibiotic prescribing.

2 | METHODS

2.1 | Study design and setting

This was a prospective multicentre observational study that collected data from seven non-academic hospitals in the Netherlands from 1 September 2018 to 1 November 2019. The hospitals were the Dijklander Hospital in Hoorn, Juliana Children's Hospital in The Hague, Isala in Zwolle, Martini Hospital in Groningen, Spaarne Hospital in Hoofddorp, Tergooi in Blaricum and Zaans Medical Centre in Zaandam. The participating centres provide different levels of care, up to level II special care for stable or moderately ill neonates,[15] and their annual birth rates range between 1200 and 4000 births per year. They were selected because they were part of a paediatric research network. All the hospitals used the Dutch national guideline to guide antibiotic use in neonates at risk for EOS during the study period.

2.2 | Study participants

Neonates born at 32 weeks of gestational age or later were eligible if their clinical condition indicated they could have suspected EOS. The indications were at least one EOS risk factor or clinical sign of infection in the first 72 hours of life (Table S1). There were no other inclusion or exclusion criteria.

2.3 | Study protocol

The Dutch guidelines are a simplified form of the NICE guidelines, and they use eight maternal, and 15 neonatal, risk factors, each categorised as either red flag or non-red flag (Table S1).[8,9] These criteria provide clinicians with guidance on how to manage suspected EOS in infants of more than 31 weeks of gestation. Briefly, antibiotic treatment is recommended if there is at least one red flag present and, or, two or more non-red flags (Figure S1). The Dutch guidelines advise clinicians to take a blood culture before they start antibiotic treatment or obtain a C-reactive protein (CRP) level, and to continue antibiotic treatment for at least 36-48 hours. This timescale is based on the time it takes to ascertain a positive blood culture.[9] The guidelines advise repeating the CRP 24-36 hours after the start of antibiotic treatment. Clinicians can consider antibiotic treatment after 36 hours in certain circumstances. These are if there is a negative blood culture, the initial clinical suspicion of infection was not strong, the neonate's clinical condition is reassuring, with no clinical indicators of possible infection, and the CRP concentrations are repeatedly below <10 mg/L.[9]

An observation period of at least 12 hours is recommended in the presence of one non-red flag, and this could relate to the risk factors that could affect the mother or the neonate. Antibiotic treatment is recommended if an infection is suspected during this observation.

TABLE 1 Clinical characteristics, presence of red flags and non-red flags and treatment characteristics for the study population

Characteristics	Overall (n = 1024)	AB treated (n = 186)	No AB (n = 838)
Male sex, n (%)	581 (56.7%)	112 (60.2%)	469 (56.0%)
Gestational age, mean (SD) weeks	38.7 (2.3)	37.6 (3.0)	38.9 (2.1)
Major criteria that indicated the need to start antibiotics			
Red flags: any maternal risk factors	26 (2.5%)	12 (6.5%)	14 (1.7%)
Red flags: any infant clinical indicators	41 (4.0%)	33 (17.7%)	8 (1.0%)
Red flags: any maternal risk factor or infant clinical indicators	3 (0.3%)	3 (1.6%)	0 (0%)
Minor criteria that indicated the need to start antibiotics			
Red flags: none. Non-red flags: at least two maternal risk factors and no infant clinical indicators	133 (13.0%)	22 (11.8%)	111 (13.2%)
Red flags: none. Non-red flags: at least two infant clinical indicators and no maternal risk factors	22 (2.1%)	17 (9.1%)	5 (0.6%)
Red flags: none. Non-red flags: at least one maternal risk factor and at least one clinical infant indicator	213 (20.8%)	83 (44.6%)	130 (15.5%)
No recommendations to start antibiotics			
Red flags: none. Non-red flags: one maternal risk factors and no infant clinical indicators	518 (50.6%)	5 (2.7%)	513 (61.2%)
Red flags: none. Non-red flags: one infant clinical indicator and no maternal risk factors	27 (2.6%)	9 (4.8%)	18 (2.1%)
Red flags: none. Non-red flags: no maternal risk factors and no infant clinical indicators	41 (4.0%)	2 (1.1%)	39 (4.7%)
Blood culture results			
Blood culture obtained	182 (17.8%)	182 (97.8%)	0 (0%)
Blood culture positive	4 (0.4%)	4 (2.2%)	—
Blood culture negative	178 (17.4%)	178 (97.8%)	—
Antibiotic treatment			
Any antibiotics	186 (18.2%)	186 (100%)	0 (0%)
Antibiotics < 48 h	6 (0.6%)	6 (3.2%)	—
Antibiotics 48-72 h	117 (11.4%)	117 (62.9%)	—
Antibiotics 4-6 d	8 (0.8%)	8 (4.3%)	—
Antibiotics ≥ 7 d	55 (5.4%)	55 (29.6%)	—
Antibiotics > 3 d with a negative blood culture	56 (5.5%)	56 (31.5%)	—

Note: Results are presented as numbers (%) for all categories except gestational age.
Abbreviation: SD, standard deviation.

When all possible flags are absent, no antibiotic treatment is recommended, and the neonate should be discharged to normal maternity care.

2.4 | Data collection

Data on the maternal risk factors, which were recorded by obstetricians in the electronic health records, were collected by the attending paediatric clinicians at time of inclusion. This was done by using a clinical report form. The data that were collected on the neonates included information on red flags and the results of the physical examination performed by a paediatric resident or paediatrician. After the clinical evaluation, the potential management options included discharging the neonate, clinical observation for at least 12 hours or starting antibiotic treatment. If antibiotic treatment was started, additional data on the use of antibiotics, namely the start and duration and the results of laboratory tests on blood culture and CRP levels, were collected. If there was a negative blood culture, but antibiotic treatment was continued, the clinician reported the reason for this. The potential reasons were the clinical condition of the neonate at the start of antibiotic treatment, the clinical course of the neonate while medical staff waited for the blood culture results and the results of laboratory tests. Castor Electronic Data Capture, version 1.4 (Ciwit BV), was used to process all the clinical report forms.

2.5 | Data analysis

Adherence to the guidelines was defined as starting antibiotic treatment in accordance with the guidelines if there was at least one red flag and, or, two or more non-red flags were present. It also included withholding antibiotic treatment, in accordance with the guidelines, if a maximum of one non-red flag was present. Non-adherence to the guidelines was if those conditions did not exist (Table 1). To ensure that the data on adherence were as accurate as possible, the clinicians were not asked to report whether their actions were in accordance with the guidelines or not. This was retrospectively determined by comparing the reported clinical findings to the guidelines and was carried out by an independent single research fellow who was not one of the attending physicians.

2.6 | Statistical methods

SPSS Statistics, version 26.0 (IBM Corp.), was used for the statistical analysis. Categorical variables were analysed using Pearson's chi-square test or Fisher's exact test when the expected frequencies were low. An alpha value of $<.05$ was considered statistically significant for all of the comparisons.

2.7 | Ethical standards

The study was approved by the Medical Ethics Review Committee for Zwolle (number 180220), and written, informed consent was provided by the patients' caregivers. The study was not subject to the Medical Research Involving Human Subjects Act, because no interventions were performed and only data were collected.

3 | RESULTS

During the study period, 1028 eligible neonates were identified and included in the study. Of those, four (0.4%) were excluded because incomplete data meant that we could not determine adherence to the antibiotic guidance (Figure 1). The final cohort was 56.7% male, and they had a mean gestational age of 38.7 ± 2.3 at birth. Of these 186 (18.2%) were prescribed antibiotics and 838 were not. The mean gestational age of those in the antibiotics group was slightly younger (37.6 ± 3.0 versus 38.9 ± 2.1 weeks), and there were more boys in that group (60.2% versus 56.0%). The clinical characteristics of the study population and data on antibiotic treatment are reported in Table 1.

3.1 | Adherence regarding starting treatment

The Dutch guidelines recommended antibiotic treatment for 438/1024 (42.8%) of the at-risk neonates (Figure 1). However, only 186/438 (42.5%) of the study cohort received antibiotics and they were prescribed in line with the guidance in 170/438 (38.8%) cases.

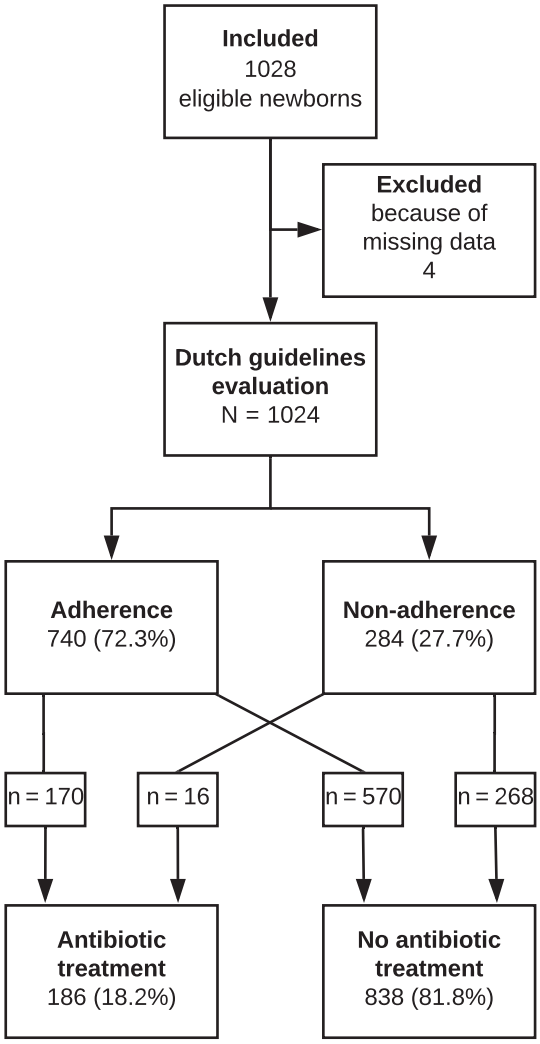

FIGURE 1 Flow chart of study population. Flow chart of at-risk neonates included in the study, showing what the rates would have been if clinicians had followed the recommendations in the Dutch guidelines and the actual treatment they provided in clinical practice

We compared the adherence group and the non-adherence group and found that three of the eight maternal risk factors were significantly more frequent in the non-adherence group. These were as follows: known positive GBS colonisation, prolonged rupture of membranes of over 24 hours and preterm birth. In the other five cases, the maternal risk factors were more frequent in the adherence group. We also found that 10 of the 15 neonatal risk factors were more common in the adherence group and in seven categories this reached statistical significance. These included respiratory distress at any time, respiratory distress that started more than four hours after birth, need for mechanical ventilation at term age and the same need in a preterm neonate. They also included altered behaviour in terms of responsiveness or muscle tone, apnoea and bradycardia and hypoxia (Table 2).

TABLE 2 Neonates qualifying for antibiotics according to the guidelines: Comparison between adherence and non-adherence to the guidelines by clinicians

	Adherence	Non-adherence	*P* value
Total (n)	170	268	N/A
Maternal risk factors			
Parenteral antibiotic treatment	9 (5.3%)	13 (4.9%)	.836
Suspected or confirmed infection in sibling from multiple pregnancy	6 (3.5%)	2 (0.7%)	.060
Invasive GBS in previous neonate born to mother	3 (1.8%)	6 (2.2%)	1.000
GBS colonisation	22 (12.9%)	66 (24.6%)	.003
Prelabour rupture of membranes for >24 h in a term birth[a]	39 (23.2%)	109 (40.8%)	<.001
Preterm birth following spontaneous labour	69 (40.6%)	84 (31.3%)	.048
Rupture of membranes for >18 h in a preterm birth[b]	41 (24.3%)	53 (19.8%)	.267
Intrapartum fever >38°C or suspected or confirmed chorioamnionitis[b]	61 (35.9%)	98 (36.7%)	.862
Neonatal risk factors			
Respiratory distress starting more than 4 h after birth	33 (19.4%)	8 (3.0%)	<.001
Neonatal epileptic seizures	0 (0%)	0 (0%)	—
Need for mechanical ventilation in a term neonate	6 (3.5%)	0 (0%)	.003
Signs of shock	2 (1.2%)	0 (0%)	.150
Altered behaviour with regard to responsiveness or muscle tone	22 (12.9%)	8 (3.0%)	<.001
Feeding difficulties	14 (8.2%)	13 (4.9%)	.151
Apnoea and bradycardia	15 (8.8%)	2 (0.7%)	<.001
Signs of respiratory distress	115 (67.6%)	86 (32.1%)	<.001
Hypoxia	33 (19.4%)	10 (3.7%)	<.001
Neonatal encephalopathy	0 (0%)	1 (0.4%)	1.000
Need for cardiopulmonary resuscitation	3 (1.8%)	1 (0.4%)	.304
Need for mechanical ventilation in a preterm neonate	6 (3.5%)	0 (0%)	.003
Persistent pulmonary hypertension	1 (0.6%)	0 (0%)	.388
Unexplained temperature abnormality	32 (18.8%)	48 (17.9%)	.810
Local signs of infection	1 (0.6%)	2 (0.7%)	1.000

Note: Risk factors summarised for clarity. More detailed descriptions are available in Table S1.

Abbreviation: GBS, group B Streptococcus.

[a]Three missing.

[b]One missing.

The guidelines also advised withholding antibiotics from 586/1024 (57.2%) of the neonates and the clinicians followed this recommendation in 570/586 (97.3%) cases.

3.2 | Duration of antibiotics

In total, 186/1024 (18.2%) of the cohort received antibiotics. Blood cultures were determined in 182/186 (97.8%) of the treated neonates, and 178/182 (97.8%) were negative. All four neonates with culture-proven EOS were infected with GBS. Prolonged antibiotic treatment of more than three days, despite a negative blood culture, was observed in 56/178 (31.5%) infants, and 49/56 (87.5%) of these received at least seven days of antibiotic treatment. The reasons given for continuing this treatment were sustained clinical suspected infection in 39/56 (69.6%), increasing CRP levels in 22/56 (39.3%) and the clinical course of the neonate in 1/56 (1.8%). The serial CRP levels are presented in Table 3.

4 | DISCUSSION

This study showed that the adherence to the Dutch guidelines was low, mainly as a result of withholding antibiotics against the recommendations in the guidelines. Once antibiotic treatment was started, it was continued in one-third of the neonates, despite a negative blood culture. Strict adherence to the guideline would have reduced the amount of unnecessary antibiotics.

To our knowledge, this study provides the first large, multicentre analysis of adherence to the Dutch EOS guidelines, which are based on the UK NICE guidelines. It provides essential data that responds to calls for more re-evaluation and better tailored consensus guidelines

TABLE 3 Comparison of C-reactive protein levels (mg/L) in neonates treated with antibiotics, broken down by adherence and non-adherence to the guidelines by clinicians

	Adherence	Non-adherence	*P* value
Total	(n = 170)	(n = 16)	N/A
1st CRP level (mg/L), median (IQR)	0.9 (0.9-3.0)[a]	0.9 (0.9-4.4)[b]	.572
2nd CRP level (mg/L), median (IQR)	4.1 (1.0-17.0)[c]	6.0 (2.0-31.5)[d]	.551
Prolonged antibiotics	(n = 50)	(n = 6)	N/A
1st CRP level (mg/L), median (IQR)	2.0 (0.9-21.5)	0.9 (0.9-56.5)[b]	.950
2nd CRP level (mg/L), median (IQR)	20.0 (6.0-50.0)[e]	39.0 (7.0-54.5)[b]	.398

Abbreviation: CRP, C-reactive protein; IQR, interquartile range.

[a]Five missing.

[b]One missing.

[c]31 missing.

[d]Four missing.

[e]Three missing.

for the use of antibiotics for suspected EOS. Studies have reported on compliance to the NICE guidelines, with regard to the use of laboratory investigations, and these have suggesting variations in adherence with recommended practice.[12,13] A study of all live births of at least 34 weeks of gestation at eight hospitals in Wales showed that 576/3593 (16%) received antibiotics when clinicians followed the NICE guidelines for EOS.[5] This was significantly higher than other European antibiotic treatment rates (2%-8%).[16-19] Our results suggest that strict adherence to the Dutch guidelines would also have led to increased rates of antibiotic treatment.

Alternative approaches to the categorical risk factor approach of the Dutch and NICE guidelines exist, and these can lead to less unnecessary use of antibiotics. For example, multivariate risk assessments using the EOS calculator appeared to result in significantly fewer neonates born after at least 34 weeks of gestation being started on antibiotic treatment for EOS, without obvious safety concerns.[5,20] Data on adherence to the EOS calculator approach have been scarce, but one implementation study reported 91% adherence, suggesting a higher level of agreement between the calculator and clinical judgement. The use of serial physical examinations may lead to even lower rates of antibiotic treatment, similar to the EOS calculator.[10,18,21-23] For example, one study found that using serial physical examinations to guide empiric antibiotic treatment in term neonates with suspected EOS more than halved the burden of antibiotic exposure. It achieved this without delaying providing antibiotic treatment for infected neonates or increasing the sepsis-related mortality rates.[19] Remarkable, the already low baseline antibiotic treatment exposure rate of 2.9% was decreased to 1.3% in the post-implementation period.

We observed that antibiotic treatment was continued for more than two days for the majority of the neonates who received treatment and for more than three days in nearly a third, despite negative blood cultures and reassuring CRP levels. This was not in line with the recommendations in the Dutch guidelines. Prolonged antibiotic treatment has been reported to be a common problem in low-risk EOS situations.[24,25] Various reasons have contributed to continued antibiotic treatment, despite negative cultures, such as concern about the sensitivity of blood cultures.[26] We found that CRP levels were a common argument for continuing treatment. This reasoning could be considered unsound, because the positive predictive value of serial CRP levels was still very low, in contrast to the high negative predictive value.[10] In the future, other biomarkers, such as procalcitonin, may be helpful in encouraging clinicians to discontinue antibiotic treatment at an early stage.[27]

The Dutch guidelines contain 23 risk factors (Table S1), and six of these hardly ever occurred in clinical practice in this cohort. This raises the question about how much risk factors add value to the guidelines. We found that the presence of three objective maternal risk factors was significantly more associated with non-adherence, namely known positive GBS colonisation, prolonged rupture of membranes exceeding 24 hours and preterm birth. Meanwhile, the presence of more subjective neonatal risk factors was significantly more associated with adherence. This suggests that clinicians mostly depended on their own clinical assessments. These findings, along with poor adherence, highlight important discrepancies between the current Dutch guidelines and the clinical judgement or intuition of healthcare professionals. In general, the results of our study emphasise the importance of carrying out clinical evaluations of guidelines after they have been implemented to see whether theory translates into practice in real-life settings.

Our study had some limitations. First, the physicians selected the patients who were included and collected the data and this may have resulted in selection bias. It is possible that patients were more likely to be included if they had more symptoms or risk factors and this may have affected our estimated adherence to the guidelines. Second, although this was purely an observational study, the systematic data collection, and comparison with the guidelines, may have increased the physicians' adherence to the guidelines. This could have led to an overestimation of adherence in these real-life settings. Finally, this study observed the use of adapted Dutch guidelines and not the original NICE version and

this may have limited the generalisation of our findings. Overall, and despite these limitations, this study provides the first large, multicentre analysis of adherence to management based on the Dutch adaption of the NICE guidelines. It provides essential data to help answer current calls for more re-evaluation, and better tailored, consensus guidelines for the use of antibiotics for suspected EOS.[28]

5 | CONCLUSION

We observed low adherence to the Dutch guidelines when it came to prescribing antibiotics for infants with EOS. This meant that patients received less antibiotic treatment than recommended and there was prolonged use in patients with negative blood cultures. Strict adherence to the guidelines would have resulted in more neonates being exposed to antibiotic treatment. In order to prevent unnecessary antibiotic treatment, we advocate that the current Dutch guidelines need to be revised or replaced by a new strategy.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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