Early onset sepsis in Suriname

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Association between Early Onset Sepsis Calculator and Infection Parameters for Newborns with Suspected Early Onset Sepsis

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ABSTRACT

Context

Early onset sepsis (EOS) remains an important clinical problem with significant antibiotic overtreatment as a result of poor specificity of clinical and infection parameters. Quantitative risk stratification models such as the EOS calculator are promising, but it is unclear how these models relate to infection parameters in the first 72 hours of life.

Aim

To evaluate the hypothesis that higher EOS calculator results are associated with (serial) laboratory infection parameters, in particular an increase in CRP within 24-48 hours, and low leukocyte counts.

Design and Methods

EOS risk estimates were determined for infants born ≥ 34 weeks of gestation who were started on antibiotic treatment for suspected EOS within 72 hours after birth. EOS risk estimates were retrospectively compared to (changes in) available laboratory infection parameters including C-reactive protein (CRP), leukocyte and thrombocyte count.

Statistical Analysis Used

Spearman's rho rank correlations coefficient was used when testing for correlations between continuous parameters. Kruskal-Wallis and Mann-Whitney U tests were applied to differences between stratified risk groups.

Results

EOS risk was not correlated with changes in infection parameters. We found negative correlations between both EOS risk and CRP level and leukocyte count within 6 hours of the start of antibiotics, as well as CRP level between 6-24 hours after start of treatment.

Conclusions

In contrast to our hypothesis, high EOS risk at birth was consistently correlated with lower CRP and leukocyte counts within 24 hours after the start of antibiotics, but not with infection parameters after 24 hours. Further interpretation of infection parameters during sepsis calculator use needs to be elucidated.

Key Messages

The sepsis calculator is neither associated with changes in CRP level, nor leukocyte or thrombocyte count in newborns with suspected early onset sepsis.

INTRODUCTION

Early onset neonatal sepsis (EOS) remains an important clinical problem in neonatal care. Due to poor specificity of clinical findings and limited usability of available infection biomarkers, there is significant over-treatment with antibiotics in the first 72 hours of life of newborns with suspected EOS [1]. In an attempt to overcome this problem a quantitative risk stratification strategy based on objective maternal risk factors and neonatal clinical findings has been developed [2]. This model, hereafter referred to as the EOS calculator, provides a quantitative estimation of EOS risk along with a recommendation on the use of antibiotics, and is available online. Two retrospective studies revealed that application of the sepsis calculator may significantly reduce antibiotic therapy and thus use of the EOS calculator may become more common in clinical practice [3,4].

Despite this promising potential, it is currently unclear how the EOS calculator estimated risk and recommendations relate to infection parameters in the first 72 hours of life. Serial values in C-reactive protein (CRP) and leukocyte count are still commonly used as arguments for the start and duration of antibiotic therapy [1,5]. For this study, our aim was to evaluate the hypothesis that higher EOS calculator results are associated with (serial) laboratory infection parameters. As EOS is associated with elevated CRP and a lower leukocyte count [5,6] we particularly hypothesized high EOS risk estimate to be associated with an increase in CRP within 24-48 hours, and low leukocyte counts

SUBJECTS AND METHODS

Study Design

Data from a previously established retrospective birth cohort were used for analysis [4]. The study included all newborns born ≥34 weeks of gestation, who were started on antibiotic treatment for suspected EOS within 72 hours after birth, in Tergooi Hospital, Blaricum, The Netherlands, during 2014. Exclusion criteria were major congenital anomalies, including chromosomal, and prophylactic treatment with antibiotics. The study was approved by the Scientific Review Committee of Tergooi Hospital.

Data Collection

Maternal and neonatal clinical data were derived from hospital records. Local protocol required routine infection parameter testing in newborns treated for clinically suspected EOS at start of antibiotic therapy, and follow-up testing at 12-24 hours and/or 24-72 hours after the start of antibiotic treatment. Infection parameter results were derived from electronic laboratory records.

EOS Calculator Risk Estimates and Stratification

EOS risk estimates were determined using the online calculator as provided by Escobar et al., through http://newbornsepsiscalculator.org [2,7]. These estimates represent the estimated incidence of EOS per 1000 live births, and were calculated individually for each newborn in the study. The resultant sepsis risk was categorized into three levels; <0.65 (low risk), 0.65-1.54

(intermediate risk), and >1.54 (high risk) per 1000 live births. In addition to using EOS calculator risk estimate as continuous variables, we used these groups for stratified analysis.

Delta Variables

Since specifically serial values in infection parameters are used to guide clinical decisions [8] we calculated delta variables when serial values were available. For delta variables, we calculated absolute differences between values derived from initial blood draw (0-6 hours after start of treatment) and follow-up values 24 hours after start of treatment. Values derived between 6-24 hours were used as follow-up values if values >24 hours were unavailable.

Statistical Analysis

All data were statistically analyzed using R (version 3.2.1) (http://www.r-project.org). Distributions of continuous variables were visualized using kernel density plots. Spearman's rho rank correlations coefficient was used when testing for correlations between EOS risk estimates and infection parameters (continuous variables not normally distributed). Kruskal-Wallis and Mann-Whitney U tests were applied to determine significance of differences between EOS stratified risk groups.

RESULTS

After exclusion of three newborns with insufficient clinical information to estimate EOS risk, data from 108 newborns were used for analysis (Table 1).

CRP

We found negative correlations between EOS risk estimations and CRP levels within 6 hours and between 6 and 24 hours after the start of antibiotics (Spearman's rho -0.45 and -0.24, respectively). This was confirmed by EOS stratified group analysis, where the high EOS risk group was associated with lower CRP levels (<1 versus 11.5 mg/l, $p<0.05$, Table 1). EOS risk estimate was not correlated with change in CRP as determined by the delta CRP variable based on serial CRP values.

Leukocytes and Thrombocytes

EOS risk estimate was not correlated with changes in serial leukocytes count. Lower leukocyte counts within 6 hours after the start of antibiotics were associated with higher EOS risk estimations (Spearman's rho -0.30). Leukocyte count within 6 hours after start of antibiotics was lower in the high-risk group compared to the intermediate/low risk group ($p<0.05$) (Table 1). There were no correlations between EOS risk and (serial) thrombocyte counts.

DISCUSSION

In contrast to our hypothesis, we did not find any correlations between EOS risk and changes in serial CRP or serial leukocyte or trombocyte counts. We observed negative correlations between EOS risk estimate and CRP level and leukocyte count within 6 hours of start of antibiotics, as well

Table 1. Infection parameters and correlation results among total and stratified risk group analysis.

EOS risk group		Overall (n=108)			Stratified risk group analysis: Low (n=41)	Intermediate (n=10)	High (n=57)
Infection parameter		**Median (IQR)**	**n (%)**	**Spearman's rho**		**Median (IQR)[4]**	
CRP	<6 h	<1 (13)	100 (93.6)	-0.45[3]	11.5(25)	<1(8)	<1(3)[3]
(median, mg/l)	6-24 h	7 (23)	82 (75.9)	-0.24[1]	11.5(25)	2(8)	5(20)
	>24 h	5.5 (17)	58 (53.7)	-0.01	7(15)	3(20)	5(26)
	Delta	4 (19)	96 (88.9)	-0.08	6 (18)	2(21)	4(19)
Leukocytes	<6 h	16.4 (9)	102 (94.4)	-0.30[2]	20.6(11)	15.3(20)	15.3(9)[2]
(median, x10^9/L)	6-24 h	16.5 (10)	70 (64.8)	-0.13	16.6(11)	26.2(15)	14.4(10)
	>24 h	13.1 (7)	53 (49.1)	-0.19	15.0(5)	14.3(16)	11.4(6)
	Delta	3.7 (6)	85 (78.7)	-0.18	4.7(9)	8.1(8)	2.9(5)
Trombocytes	<6 h	219 (87)	94 (87.0)	0.04	224(112)	217(93)	215(92)
(median, x10^9/L)	6-24 h	214 (113)	67 (62.0)	0.11	208(159)	233(91)	208(113)
	>24 h	245 (106)	49 (45.4)	0.01	241(169)	280(80)	243(105)
	Delta	27 (39)	77 (71.3)	0.09	25(57)	32(24)	27(39)

Statistically significant results marked in bold; [1]P<0.05, [2]P<0.01, [3]P<0.001.

[4] Mann-Whitney U test, high versus low/intermediate risk group. EOS risk; early onset sepsis risk as calculated with sepsis calculator.

as CRP level between 6-24 hours after start of treatment. Analyzing differences between EOS stratified risk groups, comparable results within 6 hours of start of treatment were found.

In the high-risk group single point measurement CRP levels were in the normal range at start of antibiotic therapy, which was started shortly after birth. This can be explained by the fact that CRP levels represent endogenous neonatal synthesis, rise above 5 mg/l by 6-8 hours and peak around 24-48 hours [9,10]. Negative correlation between high EOS risk and CRP levels at the start of antibiotic treatment may be explained by the fact that high-risk newborns started with antibiotic treatment shortly after birth, before endogenous synthesis of CRP occurred. Furthermore, this may also explain the significant differences of CRP levels of <1 mg/l in high-risk group versus 11.5 mg/l in the low-risk group at the start of antibiotics (P<0.05). In contrast to the high-risk group, antibiotic therapy was mostly started 12 hours after birth in the low risk group of our population [4].

Remarkably, CRP levels did not clearly increase in the high-risk group, as CPR level after 24-48h was not significantly raised compared to low and intermediate risk groups. This appears to contrast with studies confirming that the sensitivity of CRP increases substantially with serial determinations of CRP 24-48h after the onset of symptoms [9]. However, although EOS-risk is correlated with infection, still the majority of the newborns in this group had negative blood cultures, corresponding with persistent low CRP levels. In addition, given the half-life of CRP (19 hours) and clinical studies showing CRP levels decreasing after 16 hours in response to successful antibiotic therapy, it is well possible that CRP-levels have returned to normal range within 24-48

hours in infected children in the high-risk group, as this group was generally started on antibiotics within shortly after birth [9,11].

From a clinical point of view these findings underline the puzzling nature of EOS clinical management, with high EOS risk associated with low CRP levels. In the high-risk group, based on objective maternal factors and newborn clinical evaluation, antibiotic therapy is started and continued for 7 days. In this group, (serial) CRP measurement is not of additional value to discontinue antibiotic therapy in case of negative blood cultures. In the low EOS risk group, however, serial CRP may serve to discontinue antibiotic treatment after 3 days, given the negative predictive value of serial low CRP levels [10].

The correlation between higher EOS risk estimates and lower leukocyte counts within 6 hours after start of antibiotics corresponds with published findings showing lower leukocyte counts being associated with EOS [6]. It should be noted however, that low leukocyte counts are rare – reflected in a modest difference in absolute leukocyte count between the high-risk group and overall median (15.3 vs 16.4 x10^9/L). Therefore, leukocyte counts are likely to be of limited clinical value in EOS diagnostics. Finally, (changes) in thrombocyte counts were, in line with published literature, not related to EOS risk. Thus we do not recommend the use of thrombocyte counts to guide clinical decisions regarding antibiotics for EOS, regardless of estimated EOS risk.

Limitations of this study include its retrospective nature and selection bias for determination of infection parameters. However, given the high percentage of available results within 6 hours of start of antibiotics, we think this bias is limited for the correlations we found. Our sample size is limited, but given the consistent results among correlation and stratified group level analysis, we do not expect different results with a larger sample size.

In conclusion, EOS remains an important clinical problem with significant antibiotic overtreatment as a result of poor clinical and infection parameters. In newborns treated for EOS, risk estimates are neither associated with changes in CRP level, nor leukocyte or thrombocyte count. If more widespread use of the sepsis calculator is expected, the interpretation of common infection parameters in the context of EOS risk needs to be further elucidated.

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