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Reduction in the use of diagnostic tests in infants with risk factors for early-onset neonatal sepsis does not delay antibiotic treatment

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THESE

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Reduction in the use of diagnostic tests in infants with risk factors for early-onset neonatal sepsis does not delay antibiotic treatment

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Summary

BACKGROUND: Despite a low positive predictive value, diagnostic tests such as complete blood count (CBC) and C-reactive protein (CRP) are commonly used to evaluate whether infants with risk factors for early-onset neonatal sepsis (EOS) should be treated with antibiotics.
STUDY DESIGN: We investigated the impact of implementing a protocol aiming at reducing the number of diagnostic tests in infants with risk factors for EOS in order to compare the diagnostic performance of repeated clinical examination with CBC and CRP measurement. The primary outcome was the time between birth and the first dose of antibiotics in infants treated for suspected EOS.
RESULTS: Among the 11,503 infants born at ≥35 weeks during the study period, 222 were treated with antibiotics for suspected EOS. The proportion of infants receiving antibiotics for suspected EOS was 2.1% and 1.7% before and after the change of protocol (p = 0.09). Reduction of diagnostic tests was associated with earlier antibiotic treatment in infants treated for suspected EOS (hazard ratio 1.58; 95% confidence interval [CI] 1.20–2.07; p <0.001), and in infants with neonatal infection (hazard ratio 2.20; 95% CI 1.19–4.06; p = 0.01). There was no difference in the duration of hospital stay nor in the proportion of infants requiring respiratory or cardiovascular support before and after the change of protocol.
CONCLUSION: Reduction of diagnostic tests such as CBC and CRP does not delay initiation of antibiotic treatment in infants with suspected EOS. The importance of clinical examination in infants with risk factors for EOS should be emphasised.

Key words: *bacterial infection; newborn infant; Group B Streptococcus; C-reactive protein; complete blood count*

Introduction

Early-onset neonatal sepsis (EOS) is associated with high mortality and morbidity [1, 2]. In consequence, antibiotics are started promptly in infants with clinical signs suggestive of bacterial infection. In asymptomatic newborns with risk factors for EOS (mother inadequately treated for colonisation with Group B Streptococcus (GBS), maternal fever, prolonged rupture of membranes, and prematurity), a complete blood count (CBC) and measurement of acute phase reactants are commonly used to decide whether antibiotics should be administered [3–5]. However, the low positive predictive value of these diagnostic tests results in administration of antibiotics to a large number of infants in whom the diagnosis of EOS will be ruled out 48–72 hours later owing to negative blood cultures, rapid clinical improvement and normalisation of diagnostic tests [6–11]. Moreover, the vast majority of infants who develop EOS become symptomatic within the first 24 hours of life [7, 8, 12, 13]. Therefore, we hypothesised that evaluating infants with risk factors for EOS by repeated clinical examination without using diagnostic blood tests does not delay initiation of antibiotics treatment. To compare the performance of repeated clinical examination with CBC and C-reactive protein (CRP) measurement, we investigated the impact of reducing diagnostic tests on the timing of initiation of antibiotic treatment in infants with suspected EOS.

Patients and methods

Patients and data collection

This historically controlled study was approved by the Institutional Review Boards of the University of Lausanne. Infants were included if they were born at the Lausanne University Hospital between December 2006 and December 2011 at a gestational age ≥35 weeks and received intravenous antibiotics during the first week of life for suspected EOS. Newborns with severe congenital malformations

and infants receiving antibiotics as prophylaxis were excluded. During the whole study period, intrapartum antibiotic prophylaxis was administered to mothers colonised with GBS as recommended by Centers for Disease Control and Prevention [14].

Two time periods were compared, before and after the change of our screening protocol for infants born with risk factors for EOS:

Period 1, December 2006 – September 2009: A CBC with manual differential count and a measurement of CRP were performed in all infants born to mothers with at least one risk factor for neonatal infection (inadequate GBS prophylaxis, rupture of membranes >18 hours [PROM], maternal fever, prematurity <37 weeks of gestation), in accordance with the 2002 guidelines of the Swiss Society of Neonatology [3]. No specific instructions were given to clinicians regarding the timing of diagnostic tests. Vital signs were checked by midwives every 4 hours during the first 24 hours and every 8 hours during the next 24 hours in all infants with risk factors for EOS.

Period 2, October 2009 – December 2011: In addition to the monitoring of vital signs by midwives, infants with risk factors for EOS were examined by paediatric residents every 8 hours during the first 24 hours. A CBC was performed only in infants exposed to maternal chorioamnionitis, defined as maternal fever >38 °C plus at least two of the following signs: maternal heart rate >100/min, foetal heart rate >160/min, uterine tenderness, purulent amniotic fluid, maternal leucocytosis 15,000/mm^3. During the two study periods, the decision to start antibiotics was at the discretion of the attending neonatologist and blood cultures were obtained only in treated patients. Blood cultures, CBCs and CRP measurements were performed during the two study periods in all treated patients to assist clinicians in determining the duration of antibiotic treatment. Lumbar punctures were performed on an individual basis and urine cultures were not part of the diagnostic workup for EOS [15].

Infants treated with antibiotics for suspected EOS during Period 1 and Period 2 were identified using the clinical information system MetaVision (iMDsoft, Massachusetts, USA) and our neonatal database. During Period 2, cases were also collected prospectively by the reporting of each infant treated with antibiotics during the first week of life. Prospective collection of cases during Period 2 showed that MetaVision effectively identified all infants treated with antibiotics for suspected EOS (no cases were missed).

Outcomes

Neonatal infection was defined as: (A) culture-proven infection (positive blood and/or cerebrospinal fluid culture) or (B) probable infection with ≥2 signs of sepsis within the first 7 days of life (temperature instability, irritability or lethargy, feeding difficulties, capillary refill >2 seconds, apnoea, tachycardia and/or tachypnoea), and elevated CRP >20 mg/l, and the decision of the attending neonatologist to treat for at least 7 days with intravenous antibiotics. Noninfected neonates were those who did not meet the above criteria. The primary outcome measure was the time between birth and the first dose of antibiotics in infants treated for suspected EOS. Secondary outcomes were the duration of the antibiotics treatment, the duration of hospital stay, and the occurrence of complications defined as requirement for catecholamine treatment, mechanical ventilation, meningitis or death. A composite variable for the occurrence of any of the above mentioned complications was also created.

Statistical analyses

Baseline clinical characteristics were described by showing the median and the first and third quartiles (Q1–Q3) for continuous variables, and numbers and percentages for categorical variables. Comparisons of continuous and categorical variables between the patients from Period 1 and Period 2 were performed using two-tailed t-tests and Pearson's Chi-squared tests (with Yates' continuity correction when required).

Survival curves were estimated using the Kaplan-Meier method. Cox regression model was fitted to study the effect of the study period on the time between birth and initiation of antibiotics. Results were expressed as hazard ratios (HRs) with their 95% confidence interval (95% CI). The level of significance was set at 0.05. Univariable analysis was performed in all treated patients, and in the subgroups of patients with or without neonatal infection. Multivariable analysis adjusted the effect of the time period for potential confounding covariables that were chosen *a priori* (gestational age, birthweight, gender, PROM, maternal colonisation with GBS, caesarean section). Only the covariables that showed a univariable association at the 0.10 level with the time between birth and the first dose of antibiotics were included in the final model. Statistical analyses were performed on the R-software version 2.14.1 (R Development Core Team, Vienna, Austria).

Results

During the whole study period, 11,613 infants were born at our institution at a gestational age ≥35 weeks. Fifty-five infants born during Period 1 and fifty-five infants born during Period 2 were excluded from the study owing to severe congenital malformations or treatment with prophylactic antibiotics. Clinical characteristics of the remaining infants born during Period 1 (n = 6183) and their mothers were similar to those of the infants born during Period 2 (n = 5,320, data not shown). Among these 11,503 infants, 222 were treated with antibiotics for suspected EOS, and there-

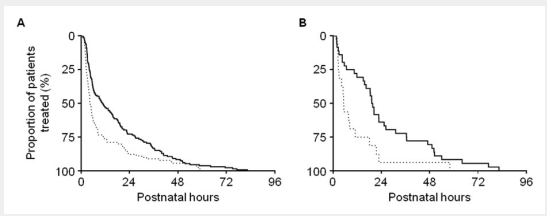

Figure 1

Kaplan-Meier estimates of the time between birth and the first dose of antibiotics in: (A) all infants treated for suspected early-onset neonatal sepsis during Period 1 (full line, n = 132) and Period 2 (dotted line, n = 90), p <0.001; (B) infants with neonatal infection during Period 1 (full line, n = 36) and Period 2 (dotted line, n = 16), p <0.001.

fore met our inclusion criteria. The proportion of infants born at a gestational age ≥35 weeks who received antibiotics for suspected EOS was 2.1% (132/6,183) during Period 1 and 1.7% (90/5,320) during Period 2 (p = 0.09).

Baseline characteristics of the included patients were similar in the two study periods (table 1). Neonatal infection (as defined in "Patients and methods") occurred in 27.3% (36/132) of the treated patients during Period 1, and 17.8% (16/90) of the treated patients during Period 2 (p = 0.10, table 2). Three patients from Period 1 had positive blood cultures growing *Escherichia coli*, *Streptococcus pneumoniae* and *Streptococcus mitis*. One patient from Period 1 had meningitis diagnosed by cerebrospinal fluid pleocytosis on two successive lumbar punctures. None of the patients from Period 2 had positive blood or cerebrospinal fluid cultures. EOS was ruled out in 72.7% (96/132) and 82.2% (74/90) of the patients treated with antibiotics during Period 1 and Period 2, respectively (p = 0.10). Therefore, one could estimate that the rate of unnecessary antibiotic treatments in infants born at a gestational age ≥35 weeks was 1.6% (96/6183) during Period 1 and 1.4% (74/5320) during Period 2 (p = 0.47).

Time between birth and the first dose of antibiotics was shorter during Period 2 (median 4.5 hours; Q1–Q3 2.6–10.9 hours) compared with Period 1 (median 10.7 hours; Q1–Q3 4.1–26.9 hours; table 2). Duration of antibiotic treatment was shorter during Period 2 (median 64.2 hours; Q1–Q3 62.3–133.3) compared with Period 1 (median 77.5 hours; Q1–Q3 64.0–158.3, p = 0.001) in all treated patients, and in noninfected patients (median 66.6 hours; Q1–Q3 62.4–127.1 during Period 1 and 64.0 hours; Q1–Q3 60.6–66.8 during Period 2, p = 0.003), but not in patients with neonatal infection (median 165.6 hours; Q1–Q3 153.8–233.0 during Period 1 and 160.4 hours; Q1–Q3 153.4–163.9 during Period 2, p = 0.38). The duration of hospital stay and the proportion of patients that required noninvasive and/or invasive ventilation and/or catecholamine treatment were similar during the two study periods for all treated patients and for patients with neonatal infection (table 2 and data not shown). One patient died during Period 1 from severe perinatal asphyxia, and no patient died during Period 2.

Survival analysis verified that infants who received antibiotics for suspected EOS were treated earlier during Period 2 than during Period 1 (HR 1.58; 95% CI, 1.20–2.07; p <0.001, fig. 1A). The difference between the two periods was even more marked in the subgroup of patients with neonatal infection (HR 2.20; 95% CI, 1.19–4.06; p = 0.01, fig. 1B). There was also a significant, but less marked, difference in the timing of initiation of antibiotic treatment in the subgroup of noninfected patients (HR 1.38; 95% CI, 1.02–1.87; p = 0.04). In univariable analysis performed on all treated patients, antibiotics were started earlier in patients with a lower gestational age and birthweight (p <0.05, table 3). A trend towards a correlation between PROM and the timing of antibiotic treatment was observed (p = 0.065), whereas no such association was found for the other tested covariables (gender, maternal colonisation with GBS and mode of delivery). Multivariable analysis adjusted for birthweight, gestational age and PROM confirmed the earlier initiation of antibiotic treatment during Period 2 compared with Period 1 (HR 1.56; 95% CI, 1.17–2.07; p = 0.002, table 3).

The proportion of patients who had clinical signs suggesting EOS when the decision was made to start antibiotics was 96.2% (127/132) during Period 1 and 97.8% (88/90) during Period 2 (p = 0.79). The number of CRP measurementss and CBCs performed at our maternity clinic was 26.8 and 51.3 per 100 live births during Period 1 and 2.3 and 36.1 per 100 live births during Period 2 (p <0.0001). CBCs and CRP measurements were performed in all patients who received antibiotics during Period 1 at a median postnatal age of 2.4 hours (Q1–Q3 1.3–7.6). During Period 2, CBCs and CRP levels were obtained prior to the start of antibiotics in 8/90 patients that received antibiotics, at a median postnatal age of 7.0 hours (Q1–Q3 4.6–12.0). Excluding these 8 patients from analysis lead to a median time between birth and the first dose of antibiotics of 4.2 hours (Q1–Q3 2.5–8.0) during Period 2, which is shorter than in Period 1 (p <0.001).

Discussion

Reduction in the use of diagnostic tests in term and late-preterm infants with risk factors for EOS did not delay the initiation of antibiotic treatment. On the contrary, it resulted in earlier treatment in all the patients treated for infection and in the subgroups of patients with and without neonatal infection. Indeed, after the introduction of a protocol that limited the number of diagnostic tests and im-

Table 1: Baseline characteristics of the newborn infants treated with antibiotics for suspected early-onset neonatal sepsis.

Study group	Period 1 (n = 132)	Period 2 (n = 90)	p-value
Caesarean section, n (%)	62 (47.0)	46 (51.1)	0.54
PROM, n (%)	18 (13.6)	16 (18.2)	0.36
Positive maternal GBS status, n (%)	27 (23.3)	20 (26.7)	0.60
Product of multiple gestation, n (%)	7 (5.3)	6 (6.7)	0.67
Female gender, n (%)	63 (47.7)	47 (52.2)	0.51
Median gestational age, weeks (Q1-Q3)	39.1 (37.1–40.2)	39.2 (37.1–40.5)	0.52
Median birthweight, grams (Q1-Q3)	3'220 (2760–3660)	3'100 (2630–3540)	0.27
Median umbilical artery pH (Q1-Q3)	7.23 (7.17–7.29)	7.25 (7.15–7.30)	0.90
Median umbilical vein pH (Q1-Q3)	7.32 (7.27–7.36)	7.33 (7.28–7.36)	0.42
Median 1 min Apgar score (Q1-Q3)	8 (4–9)	8 (6–9)	0.41
Median 5 min Apgar score (Q1-Q3)	9 (7–10)	9 (8–9)	0.62
Median 10 min Apgar score (Q1-Q3)	9 (8–10)	9 (8–10)	0.72

GBS = group B streptococcus; PROM = premature rupture of membranes, Q1 = first quartile; Q3 = third quartile

plemented repeated clinical evaluations, we observed a reduction of over 6 hours in the median time between birth and the first dose of antibiotics in treated patients compared with the period preceding the change in the protocol. Most importantly, the impact of the change of protocol on shortening the time to initiate antibiotic treatment was even stronger in patients with neonatal infection. Antibiotics were started earlier in infants with a lower gestational age and/or birthweight, and in infants born after PROM. Yet, after adjustment for these variables, the change of protocol was still associated with earlier antibiotic treatment. These findings are clinically significant. Indeed, a delay in administration of antibiotics of more than one hour is associated with an increased mortality in adults with sepsis [16, 17]. The majority of newborns who die from sepsis die during the first 72 hours due to overwhelming infection, emphasising the crucial importance of early antibiotic treatment [1, 18].

Despite the low positive predictive value of CBC and CRP, it is tempting for clinicians to order these easily available tests to decide whether or not to start antibiotics in asymptomatic infants with risk factors for EOS [6–10]. This approach is supported by the 2012 guidelines of the American Academy of Pediatrics who recommend performing a CBC and measuring CRP between 6 and 12 hours postnatally in asymptomatic infants born in the context of inadequate GBS prophylaxis, PROM or chorioamnionitis [4]. This recommendation is based on data indicating that the information provided by the diagnostic tests increases with postnatal age [6, 9]. However, the majority of infants who develop EOS are symptomatic before 12 hours of life [12, 13, 19]. Therefore, a CBC and a CRP measurement at 6–12 hours postnatally may not identify infants with EOS before development of symptoms. Performing diagnostic tests in the large population of infants with risk factors for EOS generates significant costs and leads to a number of painful procedures [20]. In the present study, early detection and prompt initiation of antibiotic treatment was achieved in infants with neonatal infection by careful clinical observation of newborns with risk factors, without performing adjunct laboratory tests.

Reduction in the use of diagnostic tests in infants with risk factors for EOS led to a slight but nonsignificant decrease in the proportion of infants who received antibiotics. Overall, the proportion of infants who received intravenous antibiotics for suspected EOS was two-fold lower in our patient population compared with previously reported data [7, 21]. No change in the rate of inappropriate antibiotic treatment was observed between the two study periods. There was no difference in the incidence of complications and outcome of infants with neonatal infection between the two study periods. The duration of antibiotic treatment was shorter during Period 2, most likely due to an earlier discontinuation of antibiotic treatment in noninfected infants during Period 2 compared with Period 1. Following implementation of the Protocol used during Period 2, we observed a 91% reduction in the number of CRPs measured at our maternity clinic, which indicates good adherence to the protocol. The reduction in the number of CBCs was only 30%, due to the fact that most CBCs were obtained for the workup of hyperbilirubinaemia.

The strengths of our study include the use of a clinical information system that allows reliable identification of patients and accurate determination of the time between birth and the first dose of antibiotics, a simple design with the use of clearly defined criteria to diagnose neonatal infection, and highly significant results. Our study has several limitations. First, it is an observational study. Although

Table 2: Clinical characteristics of the newborn infants treated with antibiotics.

	Period 1 (n = 132)	Period 2 (n = 90)	p-value
Median time between birth and the first dose of antibiotics, hours (Q1-Q3)	10.7 (4.1–26.9)	4.5 (2.6–10.9)	0.002
Median duration of antibiotic treatment, hours (Q1-Q3)	77.5 (64.0–158.3)	64.2 (62.3–133.3)	0.001
Median duration of hospital stay, days (Q1-Q3)	7.0 (5.0–9.0)	6.0 (4.0–8.0)	0.77
Patients with neonatal infection, n (%)	36 (27.3)	16 (17.8)	0.70
Noninfected neonates, n (%)	96 (72.7)	74 (82.2)	0.10
Catecholamine treatment, n (%)	6 (4.5)	5 (5.6)	0.98
Mechanical ventilation, n (%)	13 (9.8)	8 (8.9)	0.81
Noninvasive ventilation, n (%)	57 (43.2)	49 (54.4)	0.81
Meningitis, n (%)	1 (0.76)	0	0.85
Mortality, n (%)	1 (0.76)	0	0.85
Any complication*	8 (6.1)	5 (5.6)	0.89

* Requirement for catecholamine treatment and/or mechanical ventilation, meningitis or death
Q1 = first quartile; Q3 = third quartile

Table 3: Uni- and multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) for the time between birth and the first dose of antibiotics according to the time period, gestational age, birthweight and premature rupture of membranes (PROM).

		Univariable analysis			Multivariable analysis		
Covariable	**Level**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Time period	1	1			1		
	2	1.58	1.20–2.07	<0.001	1.56	1.17–2.07	0.002
Gestational age	+1GA wk	0.91	0.84–0.97	0.005	0.92	0.84–1.01	0.089
Birthweight	+1g	0.99	0.99–0.99	0.002	0.99	0.99–1.00	0.418
PROM	No	1			1		
	Yes	1.41	0.98–2.06	0.065	1.33	0.91–1.93	0.136

treatment strategies in general remained stable in our unit during the whole study period, we cannot rule out that some variations in clinical practice might have influenced our results. Similar clinical characteristics of patients treated for suspected EOS during the two study periods and multivariable analysis of potential confounders reduce the potential bias induced by the study design. Second, it is a historically controlled study planned to assess the safety of the protocol used during Period 2. Being part of a study could have influenced the clinical assessment by residents. Third, the majority of infants treated during Period 1 had a first CBC and CRP measurement performed before 6 hours of life. Obtaining CBCs and CRPs before 6 hours of life is likely to increase the proportion of falsely reassuring results compared with later time points [6, 9]. During Period 2, deciding whether or not to start antibiotics on the basis of clinical examination and risk factors alone lead to treatment of 56% of patients with neonatal infection before 6 hours of life and 75% before 12 hours. There is no evidence from clinical studies that performing a CBC and/or a CRP at 6–12 hours would have led to earlier treatment. Another limitation is the low incidence of culture-proven sepsis in our patients (0.26‰ in our study vs 0.4‰–0.9‰ in recent studies on term and late preterm infants [1, 22]). However, culture-proven sepsis represents only a proportion of the total cases of EOS [7, 10, 19]. Gestational age characteristics and several aspects of perinatal care may have contributed to a low incidence of culture-proven sepsis in our population.

In conclusion, reduction in the use of diagnostic tests such as CBC and CRP does not delay initiation of antibiotic treatment in newborns with suspected EOS. On the contrary, it results in earlier treatment in infants with suspected EOS and in infants with neonatal infection. The importance of repeated clinical examination in infants with risk factors for EOS should be emphasised.

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Figures (large format)

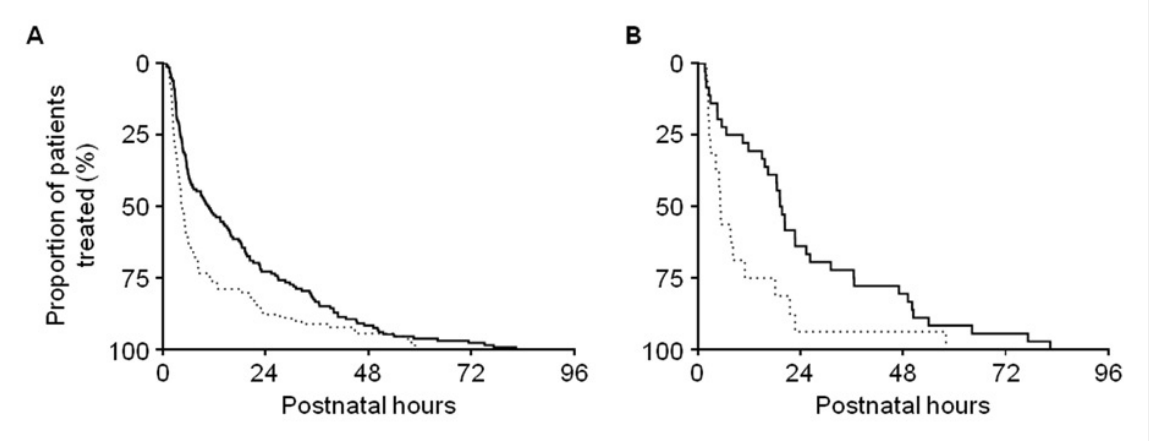

Figure 1

Kaplan-Meier estimates of the time between birth and the first dose of antibiotics in: (A) all infants treated for suspected early-onset neonatal sepsis during Period 1 (full line, n = 132) and Period 2 (dotted line, n = 90), p <0.001; (B) infants with neonatal infection during Period 1 (full line, n = 36) and Period 2 (dotted line, n = 16), p <0.001.