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Safety of physical examination alone for managing well-appearing neonates ≥ 35 weeks’ gestation at risk for early-onset sepsis
Safety of physical examination alone for managing well-appearing neonates 
≥ 35 weeks’ gestation at risk for early-onset sepsis

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Short Title: The management of neonates at-risk for early-onset sepsis

Key words: Group B streptococcus, Neonatal sepsis, Management, Intrapartum antibiotic prophylaxis, Prevention

Abbreviations:

EOS - early-onset sepsis
PEA - physical examination alone
WAARNs - well-appearing at-risk newborns
ABSTRACT

OBJECTIVE: published data to support recommendations for prevention and management of well-appearing at-risk newborns (WAARNs) for early-onset sepsis (EOS) are limited.

METHODS: retrospective cohort study comparing 2 different strategies for managing WAARNs (≥35 weeks’ gestation) during a 6-year period (Period 1, 2005-2007; Period 2, 2009-2011).

WAARNs were defined as healthy-appearing neonates evaluated because of risk factors for EOS. Laboratory evaluation plus simplified physical examination (Period 1) was compared with physical examination alone (PEA, Period 2). The use of antibiotics, the length of stay, the timeliness of diagnosis and the risk of falling ill immediately after hospital discharge in both periods were also compared.

RESULTS: WAARNs receiving empirical antibiotics were 14/500 (Period 1) and 3/500 (Period 2, p=0.01). Median length of stay was 4 (Period 1) and 3 days (Period 2, p=0.04).

Symptoms of EOS were earlier than laboratory evaluation results in 42/44 neonates. Severe disease was diagnosed within 6 hours of life in all neonates. No WAARNs presented with EOS following hospital discharge.

CONCLUSIONS: WAARNs managed through PEA received less unnecessary antibiotics and had a shorter length of stay. They had no increased risk of severe complications or increased risk of becoming ill following hospital discharge.
Introduction

Early-onset sepsis is typically defined as sepsis occurring within the first 3 or 7 days after birth. Seven days is typically used for group B streptococcus, a leading cause of EOS in newborn infants (1). Prevention guidelines as well as obstetrical and neonatal care have reduced the incidence of both group B streptococcus-specific (2) and overall EOS (3,4). In the United States, overall incidence has recently declined to 0.8-1.0 cases/1000 live births (2-4). However, sepsis remains a major cause of mortality and morbidity in the newborn. Initial symptoms of sepsis are often subtle, but the clinical course may be fulminant (1).

Up to ~10-15% of all newborn babies are evaluated to rule out EOS (5,6). However, the sensitivity of blood cultures following intrapartum antibiotic prophylaxis is low (7), as is the positive predictive value of a complete blood count in well-appearing at-risk newborns (WAARNs) (8). A complete blood count provides more information about the risk of sepsis after the first 4 hours following birth (9). C-reactive-protein is one of the standard parameters in the workup of neonatal sepsis. However, limitations of C-reactive-protein include low sensitivity during the early phases of sepsis and raised values in many non-infectious diseases (10). More promising markers are expensive and unavailable in most centers. Consequently, EOS evaluation remains a subject of significant controversy.

As clinical signs are a sensitive indicator of neonatal sepsis (11), the 2010 revised Centers for Disease Control and Prevention guidelines recommend observation alone instead of laboratory evaluation plus observation for full-term WAARNs whose mother has <18 hours of membrane rupture and received inadequate intrapartum antibiotic prophylaxis. However, the algorithm for neonatal management includes the option of performing a limited diagnostic evaluation at age 6–12 hours (2).

There is no consensus for this recommendation. In 2013, the American Academy of Pediatrics (Committee on the Fetus and Newborn) recommended observation for 48 hours without further testing or cultures in WAARNs (≥ 37 weeks’ gestation) in cases of inadequate intrapartum
antibiotic prophylaxis and membrane rupture >18 hours (12). The discordance in the algorithms has prompted questions by the paediatric community as to which recommendations to follow.

We recently reported that infants with ≥35 weeks’ gestation at risk of group B streptococcus EOS can be safely managed with physical examination alone (PEA) (13). However, we did not assess the effectiveness of this strategy for all cases of EOS, its impact on the number of antibiotic treatments or length of stay. Furthermore, there is a concern that neonates may fall ill after hospital discharge if not duly evaluated. Current data concerning PEA in WAARNs are limited and further data supporting this strategy should be considered.

The purpose of this study was i) to assess whether PEA leads to a timely diagnosis of proven/suspected EOS in neonates with ≥35 weeks’ gestation and ii) whether PEA affected rates of unnecessary antibiotics and length of stay or increased the risk of falling ill after hospital discharge.
Methods

Study design: this is a retrospective cohort study of infants delivered at Modena University Hospital (Italy), a high volume tertiary care centre with approximately 3500 live births/yr. The project was approved by the local ethical committee (N°125/11)

The Modena University Hospital advocates a strategy of recto-vaginal culture screening at 35-37 weeks of gestation. Women with prenatal group B streptococcus colonization are given intrapartum antibiotic prophylaxis. Furthermore, intrapartum antibiotic prophylaxis is administered to women with unknown group B streptococcus status and risk factors, such as group B streptococcus bacteriuria identified during the current pregnancy, a previous group B streptococcus-infected newborn, preterm birth (<37 weeks’ gestation), rupture of membrane ≥18 hours, or intrapartum fever ≥38° C (a surrogate for chorioamnionitis).(2) Full maternal data (gestational age, mode of delivery, group B streptococcus status, risk factors for EOS, duration of intrapartum antibiotic prophylaxis) is routinely recorded in neonatal charts.

Management of WAARNs ≥35 weeks gestation: in Period 1 (2005 to 2007) a laboratory evaluation was recommended at age 6-12 hours for neonates born to mothers with intrapartum fever or neonates receiving inadequate intrapartum antibiotic prophylaxis (14). Empirical antibiotics were given routinely to neonates born to mothers with intrapartum fever or neonates with abnormal laboratory evaluation.

In Period 2 (2009 to 2011) PEA became the standard of care (13) Laboratory evaluation was recommended only in a few WAARNs (neonates born to mothers with intrapartum fever or neonates with at least 2 risk factors receiving inadequate intrapartum antibiotic prophylaxis). PEA is performed by midwives within 2 hours of birth, and then by nurses and clinicians in turn. Each examiner fills in and signs a standardized form (detailed general wellbeing, skin colour including perfusion, and the presence of respiratory signs) at standard intervals (at age 3-6-12-18-36-48 hours). A baby with any symptom of possible sepsis is immediately referred to a neonatal care specialist.
Comparison of screening practices: compliance with the maternal prevention strategy, rates of laboratory evaluations and antibiotic treatments were compared by reviewing medical records of 1000 neonatal births (≥35 weeks gestation). In order to ensure a representative sample of the broad population of neonatal births in the two study periods, we performed a random selection of neonatal charts, 500 from Period 1 and 500 from Period 2.

Live births occurring during 2008 were excluded, because the neonatal management approach changed in that year.

Three investigators (S.F, V.P. and C.R.) abstracted information from neonatal records. Standardized forms were used to collect data (antenatal screening, gestational age, ethnicity, mode of delivery, hours since membrane rupture, intrapartum antibiotics, Apgar score, sex, birth weight, health status, laboratory evaluation, length of stay).

Cases of EOS: with the aim of confirming whether PEA leads to a timely diagnosis, we i) searched the laboratory database for pathogens yielded in blood or cerebrospinal fluid cultures during both study periods and ii) we reviewed the medical records of neonates with International Code of Diagnosis (Version:2010) of EOS at discharge from hospital (sepsis, 038.0, 038.4, 038.9, 038.42, 995.91, 995.92, 771.81; bacterial meningitis, 320.0-9; pneumonia and additional infections, 482.0-9, 041.02, 941.19, 041.4, 599.0). Charts of sick neonates readmitted to our Unit within 7 days of birth with a code diagnosis of sepsis were also abstracted from our registry and were reviewed.

All neonates were analysed by comparing their ages at the first suspicion of sepsis (based on symptoms and/or abnormal laboratory evaluation results). Since sepsis presenting after the age of 3 days may be the result of horizontal transmission, and as we wished to assess the long-term effects of PEA, neonates presenting with illness from 0 to 72 and from 73 to 168 hours were analyzed separately.

Definitions: Culture proven early-onset sepsis is defined as isolation of a pathogen from a normally sterile body site (blood or cerebrospinal fluid) within 7 days of birth and clinical signs and symptoms consistent with sepsis.(1)
Suspected early-onset sepsis is defined as the presence of clinical signs and symptoms consistent with sepsis (see reference 1), plus abnormal complete blood count and/or an elevated C-reactive-protein level in the absence of a positive blood culture.

Well-appearing status, refers to cases in which EOS evaluation is performed only in the presence of risk factors, without clinical symptoms of sepsis.

At-risk newborn is defined as an infant whose mother is group B streptococcus colonized or has risk factors for EOS.

Severe disease is any of the following: death, meningitis, seizures, brain lesions at discharge from hospital, need for catecholamine support or mechanical ventilation.

Statistical analysis: A calculation was made of the sample size needed to detect a difference between neonatal management approaches: assuming that at least 4% and 1% of WAARNs underwent laboratory evaluation in Period 1 and Period 2, respectively, with alpha = 0.05 and a power of 80%, the required sample was determined as 489 births in Period 1 and 489 births in Period 2.

Statistical analysis was performed using the $\chi^2$ test and Mann-Whitney test for independent samples, when appropriate. A p value <.05 was used as a threshold for statistical significance.
Results

During the 6-year study period there were 20,401 live births (9832 live births in Period 1; and 10569 in Period 2), of which 19,504 (95.6%) with ≥35 weeks’ gestation.

Comparison of screening practices: Eleven records were incomplete and were excluded; 1000 neonatal medical records randomly selected were abstracted and reviewed. Table I compares the characteristics of 500 records from Period 1 and 500 records from Period 2. Antenatal screening and recto-vaginal cultures increased significantly in Period 2.

Table II compares laboratory evaluations and antibiotic treatments. With respect to Period 1, in Period 2 the rates of laboratory evaluations significantly decreased in WAARNs. Fewer WAARNs received empirical antibiotics and the length of stay was significantly shorter.

Forty-six neonates in Period 2 underwent PEA; among them 2 had signs of illness within 6 hours of birth. Sepsis was ruled out in both neonates.

Neonates with a code diagnosis of EOS. Among the 19,504 babies with 35 or more weeks’ gestation, 93 were diagnosed with EOS. Two of the 93 neonates (1 in Period 1 and 1 in Period 2) presented with symptoms at age 73 to 168 hours; neither was classified as at-risk. Eleven of the 93 neonates (8 in Period 1 and 3 in period 2) had no apparent signs of illness and cultures were sterile. Their diagnoses of infection were based on abnormal results of tests performed to rule out sepsis in WAARNs.

Among the remaining 80 neonates with symptoms within 72 hours of birth, 44 were at risk and 36 had no identifiable risk factor.

Eight out of 36 neonates without risk factors (4 in period 1 and 4 in period 2) had culture-proven sepsis (group B streptococcus, n=2; Staphylococcus aureus, n=3; Escherichia coli, n=2; Listeria monocytogenes, n=1).
**At-risk neonates with EOS:** Each at-risk neonate was analysed in terms of age at the first suspicion of sepsis (based on symptoms and/or abnormal laboratory evaluation results). Results were informative before the presentation of symptoms of EOS only for 2 out of 44 at-risk neonates. Age at the first suspicion of sepsis did not change between Period 1 (median 2 hours, range 0-36, IQ 0.0-7.0) and Period 2 (median 0, range 0-60, IQ 0.0-2.0, p 0.40).

Figure 1 details the 44 at-risk neonates with early presentation of symptoms (≤72 hours) according to age at presentation and intrapartum antibiotic prophylaxis exposure. Severe disease (n= 9) presented within 6 hours of life in all cases. Eight neonates (4 in Period 1 and 4 in Period 2) had culture-proven EOS.

**Positive blood cultures in WAARNs:** During the study period, there were moreover 26 positive blood cultures in WAARNs (coagulase-negative Staphylococci, n=23; Brevibacterium spp, n=2; Flavobacterium/ Chryseobacterium spp, n=1). Among them, 21 occurred in Period 1 and 5 in Period 2. None of the 26 neonates had symptoms within the first week of life. C-reactive-protein and complete blood count yielded normal results and isolates were considered as probable contaminants. These positive cultures were not included among true cases of EOS.
Discussion

Neonatal EOS has become a low-incidence disease. However, pediatricians are frequently faced with the challenge of evaluating and managing WAARNs born to mothers with inadequate intrapartum antibiotic prophylaxis. Algorithms based on risk-factor threshold values may result in large numbers of uninfected newborns being evaluated and treated with empiric antibiotics, leading to maternal/infant separation and unnecessary antibiotic exposure. The recent literature underlines that up to 50% of neonates evaluated for sepsis are treated with antibiotics, even if only few are subsequently proven to have had an infection (5,6). Antibiotic exposure may lead to the selection of resistant organisms, or may induce changes in the gut flora composition resulting in long-term effects (15-17).

Given these concerns, data supporting safe alternative strategies for managing at-risk neonates should be considered. Because information is limited, the American Academy of Pediatrics urges that data be provided to support recommendations for prevention and management of neonates at risk of EOS (12).

Cantoni and co-workers (18) evaluated a cohort of 15239 full-term neonates, of whom 3092 were at risk. They demonstrated that laboratory tests plus standardized physical examination offered no advantage over standardized PEA. This latter strategy was also associated with fewer infants treated with antibiotics. However, they excluded preterm neonates from their analysis; furthermore, the only outcome data provided by the authors concerned respiratory support, which is only a rough outcome measure.

We recently reviewed cases of culture-proven group B streptococcus -specific EOS in Emilia-Romagna (13), an Italian region with active group B streptococcus surveillance (19). Infants with \( \geq 35 \) weeks’ gestation were diagnosed in a timely manner through PEA. This threshold of gestational age was used because signs of sepsis are quite similar in preterm (35-36 weeks’ gestation) and full-term neonates.
What is left unanswered in both studies is whether neonates have an increased risk of falling ill following hospital discharge due to the failure to perform laboratory evaluation in the first days of life.

In the current study, the group B streptococcus prevention strategy had been implemented progressively over time. The rates of antenatal screening and recto-vaginal cultures increased significantly in Period 2.

Approximately 45% of neonates with a diagnosis of EOS in both study periods were not at risk, consequently they had received no intrapartum antibiotic prophylaxis.

In both periods most diagnoses of EOS were initially based on an evaluation of symptoms, as most neonates with EOS and all neonates with severe disease became ill within 6 hours of birth. The clinical yield of laboratory testing performed at age 6-12 hours was negligible.

There was no evidence that neonates undergoing PEA in period 2 had an increased risk of falling ill immediately after hospital discharge. Furthermore, significantly fewer WAARNs had laboratory evaluations, contaminants in blood cultures, or received empirical antibiotics. Consequently they had a shorter length of stay.

This study has some limitations. Firstly, our results may not be generalizable to centres that cannot perform frequent clinical evaluations of neonates in the first hours of life.

In addition, this is an observational, retrospective study, and the cases of EOS were checked through the diagnosis code. Consequently, some cases of suspected EOS in both periods may have been missed. Furthermore, we could not exclude that some neonates discharged home were readmitted elsewhere. However, Modena University Hospital is a reference hospital for the entire province that receives the vast majority of neonates.

Despite these limitations our findings show that WAARNs need to be observed closely during the first few hours of life for having a timely diagnosis of EOS.
Declaration of Interest statement

The authors report no declarations of interest.
References:


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Table I: Demographics from the random sample of 1000 birth records

<table>
<thead>
<tr>
<th></th>
<th>Mothers</th>
<th>Period 1</th>
<th>Period 2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=500)</td>
<td>(N=500)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antenatal screening, n (%)</td>
<td></td>
<td>450 (90.0)</td>
<td>471 (94.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>GBS culture-positive, n (%)</td>
<td>104 (23.1)</td>
<td>122 (25.9)</td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>Rectovaginal specimens, n (%) °</td>
<td>318 (85.0)</td>
<td>476 (99.0)</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mothers with risk factor, n (%)</td>
<td>75 (15.0)</td>
<td>79 (15.8)</td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>GBS bacteriuria during pregnancy, n (%)</td>
<td>10 (2.0)</td>
<td>9 (1.8)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Previous infant with GBS disease, n (%)</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Preterm delivery (35 to 36 weeks’ gestation), n (%)</td>
<td>20 (4.0)</td>
<td>24 (4.8)</td>
<td></td>
<td>0.64</td>
</tr>
<tr>
<td>Intrapartum fever ≥ 38°C, n (%)</td>
<td>4 (0.8)</td>
<td>6 (1.2)</td>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td>Membrane rupture ≥ 18 hours, n (%)</td>
<td>44 (8.8)</td>
<td>45 (9.0)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Vaginal delivery, n (%)</td>
<td>361 (72.2)</td>
<td>368 (73.6)</td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>IAP administration, n (%)</td>
<td>132 (26.4)</td>
<td>148 (29.6)</td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>IAP administration in culture-positive women, n (%) †</td>
<td>85 (90.4)</td>
<td>103 (94.5)</td>
<td></td>
<td>0.40</td>
</tr>
<tr>
<td>Gestational age, weeks, median (IQ)</td>
<td>39 (38-40)</td>
<td>39 (38-40)</td>
<td></td>
<td>0.84</td>
</tr>
<tr>
<td>Birth weight, g, median (IQ)</td>
<td>3350 (3030-3650)</td>
<td>3315 (3057-3625)</td>
<td></td>
<td>0.55</td>
</tr>
</tbody>
</table>

IAP, Intrapartum antibiotic prophylaxis; GBS, group B streptococcus; IAP, intrapartum antibiotic prophylaxis; IQ, interquartile range 25th - 75th

° information on specimen (whether vaginal or recto-vaginal) was not available in 126 and 19 cases (period 1 and period 2 respectively); % rates include only women with known information.

† women with planned caesarean section were excluded from calculation.
Table II: Random sample of 1000 birth records: laboratory evaluations, empirical antibiotics and length of stay

<table>
<thead>
<tr>
<th>Newborns</th>
<th>Period 1 (n=500)</th>
<th>Period 2 (n=500)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory evaluations, n (%)</td>
<td>83 (16.6)</td>
<td>23 (4.6)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Laboratory evaluations in WAARNs ¶</td>
<td>58 (11.6)</td>
<td>8 (1.6)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Empirical antibiotics</td>
<td>14 (2.8)</td>
<td>3 (0.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Laboratory evaluations in neonates with signs of sepsis</td>
<td>25 (5.0)</td>
<td>15 (3.0)</td>
<td>0.15</td>
</tr>
<tr>
<td>Suspected sepsis</td>
<td>5 (1.0)</td>
<td>2 (0.4)</td>
<td>0.45</td>
</tr>
<tr>
<td>Culture-proven sepsis</td>
<td>1 (0.2)</td>
<td>0</td>
<td>0.48</td>
</tr>
<tr>
<td>Non-septic neonates †</td>
<td>19 (3.8)</td>
<td>13 (2.6)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

At-risk neonates, length of stay, median (IQ), days ° 4 (3-4) 3 (3-4) 0.04

WAARNs, well-appearing at-risk neonates; IQ, interquartile range 25th-75th

¶ includes blood culture, C-reactive protein test and complete blood count (white blood cell with differential and platelet count)

† In these neonates sepsis was ruled out. Their diagnoses were: respiratory disease (14 cases in Period 1 and 8 in Period 2); heart disease (2 cases in Period 1 and 2 cases in Period 2); metabolic disease (1 case in Period 1 and 2 cases in Period 2) and neurological disorder (2 cases in Period 1 and 1 case in Period 2)

° Length of stay was calculated on the basis of the date of birth and the date of hospital discharge.
<table>
<thead>
<tr>
<th></th>
<th>Period 1 (n=19)</th>
<th>Period 2 (n=25)</th>
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<tbody>
<tr>
<td><strong>Age at presentation of symptoms</strong></td>
<td>≤ 6 hours</td>
<td>≤ 6 hours</td>
</tr>
<tr>
<td></td>
<td>&gt; 6 hours</td>
<td>&gt; 6 hours</td>
</tr>
<tr>
<td><strong>35-36 weeks’ gestation</strong></td>
<td>Non-severe disease</td>
<td>Non-severe disease</td>
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<td>□  □ a</td>
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<tr>
<td><strong>Severe disease</strong></td>
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<td>□ □ □ □</td>
<td>□ □ □ □ □ □ a</td>
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<tr>
<td><strong>Full-term neonates</strong></td>
<td>Non-severe disease</td>
<td>Non-severe disease</td>
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<tr>
<td><strong>Severe disease</strong></td>
<td>□</td>
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</table>
Figure 1 – At-risk neonates (≥ 35 weeks’ gestation) presenting with sepsis within 72 hours of birth: comparison between Period 1 (n=19) and Period 2 (n=25)

Figure 1 legend - Open squares indicate neonates without intrapartum antibiotic prophylaxis exposure. Half-solid squares indicate neonates exposed to inadequate intrapartum antibiotic prophylaxis. Solid squares indicate neonates with adequate intrapartum antibiotic prophylaxis.

Letters in superscript next to 8 squares show the infants with culture-proven sepsis:

a: Group B streptococcus (n=5)
b: Staphylococcus aureus (n=2)
c: Listeria monocytogenes (n=1)