

Antibiotic treatment of Chorioamnionitis-Exposed Neonates Based Only on Signs of Infection

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Abstract:

Introduction: Decisions about the management of infants exposed to maternal chorioamnionitis are often based on estimates of the risk of infection determined by a neonatal early onset sepsis risk calculator (NEOSC). Such management, however, results in drawing blood from and starting intravenous lines on many healthy infants. In some institutions, it also results in separating them from their families for treatment in the neonatal intensive care unit (NICU). Our practice for many years has been to do laboratory studies and give antibiotics to chorioamnionitis-exposed (CE) infants only if they show signs of infection. Using this approach, we have evaluated and treated far fewer infants than we would have if we had used the NEOSC. We reviewed our experience over five years to document the differences in patient management and to identify adverse outcomes in these infants.

Methods: Charts of CE infants ≥ 35 weeks EGA (estimated gestational age) were reviewed over a 5-year period in 2012 when our institution converted to electronic medical records. Data collected included vital signs, laboratory results, NICU admission, antibiotic treatment, and hospital readmission during the first week after discharge. Their mothers' charts were reviewed for data needed to complete the NEOSC. The number of infants who underwent laboratory evaluations and treatment with antibiotics was compared to the number who would have had such evaluations and treatment according to NEOSC recommendations.

Results: We treated 126 (16%) of 768 CE infants with antibiotics vs. 216 (28%) who would have been treated according to the NEOSC recommendations. Another 17 patients had blood cultures but were not treated with antibiotics. None of the untreated infants became ill, had positive blood cultures, were admitted to the NICU, or were readmitted to the hospital within the first week after discharge.

Conclusion:

CE infants were managed safely in our institution based only on clinical signs of infection. If multicenter studies corroborate our experience, revised recommendations could markedly reduce the number of CE infants evaluated and treated with antibiotics.

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Infants born to mothers with intra-amnionic infection or inflammation or both, "Triple I," (formerly referred to as chorioamnionitis) are at increased risk of early-onset sepsis (EOS) (1). Prior to 2018, the Center for Disease Control (CDC) and American Academy of Pediatrics Committee on Fetus and Newborn (AAP/COFN) recommended that these chorioamnionitis-exposed (CE) infants be treated with antibiotics for 48 hours after a limited evaluation, including blood culture and complete blood count (CBC) (2). These recommendations were updated in 2018(3) and included the option of managing these patients based on the Neonatal Early-Onset Sepsis Risk Calculator (NEOSC) (4).

Despite the pre-2018 recommendations of the CDC and AAP CE, infants at our institution during that era were not evaluated with laboratory studies or treated with antibiotics unless they showed clinical signs of sepsis. We report our experience with this approach for five years, from 2012, when we converted to the electronic medical record (EMR), until 2018. We describe how these patients were managed and how they would have been managed based on NEOSC recommendations. Our objectives were: 1. to compare the numbers of CE infants ≥ 35 weeks estimated gestational age (EGA) who were subjected to laboratory evaluation and antibiotic treatment using our approach based on clinical signs only with those who would have been evaluated and treated according to the NEOSC recommendations, and 2. to identify adverse outcomes in CE infants in our institution who were not evaluated and treated. To our knowledge, no published reports describe this type of hands-off management of asymptomatic CE infants.

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Methods:

Selection criteria and study period

Charts of all women who delivered liveborn infants at ≥ 35 weeks EGA from when the EMR was implemented in July 2012 until January 2018 were reviewed. Those containing CPT codes for chorioamnionitis or intrapartum fever were searched, and our study population consisted of those with a clinical diagnosis of chorioamnionitis or a documented intrapartum temperature elevation of $\geq 100.4^\circ\text{F}$.

Data collection and monitoring

Data was entered into a deidentified electronic case report form by a clinical research associate with the supervision of one of the authors to assure adherence to the protocol, accuracy, and privacy in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines and HIPAA Regulations. The Cone Health Institutional Review Board reviewed the protocol, which determined an exempt status.

Maternal and infant data needed to complete the NEOSC was collected. Maternal data included the EGA, the mother's highest antepartum temperature, duration of rupture of membranes, Group B Streptococcus (GBS) status, and type and timing of intrapartum antibiotics given. Neonatal data included the vital signs, laboratory results including CBCs, procalcitonin (used at our institution as an inflammatory marker), blood and cerebrospinal fluid cultures, admission to the Neonatal Intensive Care Unit (NICU), treatment with antibiotics, length of stay, and hospital readmission within the first week after discharge.

Patient stratification and management

Symptomatic infants. Infants were identified as symptomatic if they met any of the following criteria:

1. Need for supplemental oxygen or any respiratory support lasting more than 30 minutes after birth
2. Persistent respiratory distress (even without the need for supplemental oxygen)
3. Persistent abnormal vital signs (heart rate ≥ 160 , respiratory rate ≥ 60 , or temperature $\geq 100.4^{\circ}\text{F}$ or $< 97^{\circ}\text{F}$)
4. Non-specific signs of infection were noted by attending providers, e.g., poor color/perfusion, lethargy, and irritability.

The NEOSC would have classified these "symptomatic" infants as either having "clinical illness" or as being "equivocal." They were admitted to the NICU for further observation. They underwent laboratory evaluations, including blood cultures and CBCs, and, in most cases, were treated with at least a short course of antibiotics.

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Asymptomatic infants. Infants who met none of those criteria were defined as asymptomatic. They did not undergo any laboratory evaluation, regardless of NEOSC score, and they roomed in with their mothers in the mother-baby unit. They received routine care, including a full assessment within 2 hours of birth by a nurse who had reviewed the mother's prenatal record and delivery in-

formation. Vital signs were performed at 30 minutes and 1 and 2 hours of age. If vital signs were outside normal ranges they were repeated every 1 – 2 hours until stable. Attending providers were notified of abnormal vital signs or other concerns at any time.

NEOSC scores. Data collected from maternal records was entered into the "Scenario" fields of the NEOSC to assess the sepsis risk. The CDC national incidence of early-onset sepsis (0.5/1000 live births) was used as the baseline. Data from the neonatal records was used to determine EOS risk after clinical exam based on assessment as well appearing, equivocal, or clinical illness.

Statistical analysis

Our analytical approach to these data was descriptive. We used a Fisher's exact test to compare the recommendations made by the NEOSC to our clinical results (Table). We report the odds ratios and the p values in the Table. All statistical analyses were performed using JMP 11 (SAS Institute, Cary, NC).

Results:

Sample

29,830 infants ≥ 35 weeks EGA were born during the study period, of which 768 (3%) met our selection criteria. Of these 768 infants, 533 (69%) of their mothers received antibiotics before delivery, and 171 (22%) were GBS positive. The median gestational age was 40 weeks (10-90th percentile was 38-41 weeks); 14 patients (1.8%) were late preterm (35 – 36 6/7 weeks EGA) with the remainder ≥ 37 weeks; median birth weight was 3405 grams (10-90th percentile was 2854-4074 grams). The median 5-minute Apgar score was 9 (10-90th percentile was 7-9).

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Outcomes

Of the 768 infants enrolled in our study, 126 (16%) were identified as symptomatic. They were admitted to the NICU and treated with antibiotics because of clinical illness. Another 17 patients had blood cultures but were not treated with antibiotics. The remaining 642 patients were not symptomatic and received routine care in the mother-baby unit (i.e., no blood cultures or laboratory studies). None had a later onset of illness, received antibiotics, were admitted to the NICU, or had prolonged length of stay. None were readmitted to our hospital within one week after discharge.

NEOSC recommendations

Sepsis risk scores were calculated using the NEOSC for 764 of the 768 infants (data were unavailable to calculate scores in 4 patients). In 216 patients (28%), the NEOSC recommended empiric antibiotics; for another 102 (13%), the recommendation was to

obtain blood cultures and watch closely. For two infants (0.3%), it was to “strongly consider” starting empiric antibiotics. The calculator recommended no culture or antibiotics for the other 444 infants (58%).

Comparison of management (Table)

If we had followed the NEOSC recommendations, we would have treated 90 patients with antibiotics and done blood cultures on 102 patients. None of those 192 patients experienced adverse outcomes.

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Discussion:

This review expands on our previously reported experience using clinical signs alone managing CE infants from 2009 – 2012, in which none of 182 asymptomatic patients had positive blood cultures, significant morbidity, or needed readmission after hospital discharge (5). Recent reports have described limited testing and treatment of CE newborns using the NEOSC. Money et al. (6) confirmed that NEOSC would reduce antibiotic use from essentially all (99.7%) CE infants to only 2.5%. Multiple other studies (7-9) described approaches that reduced the use of antibiotics but, as opposed to our practice, subjected many to laboratory testing. Joshi et al. (10) suggested that treatment based primarily on clinical signs of illness might necessitate changes in the surveillance of at-risk infants to ensure their safety. We have not implemented cautionary measures for asymptomatic CE infants; they receive routine care and monitoring like the non-CE infants in the mother-baby unit.

As noted by Hooven and Polin (11), many studies indicate that laboratory evaluations of well-appearing CE infants may not be helpful and may have adverse effects, including interference with breastfeeding (12). A 2016 AAP policy statement (13) underscores gaps in knowledge of the effects of pain in neonates but notes that “repeated painful exposures have the potential for deleterious consequences.” Franck et al. (14) surveyed parents at 11 NICUs in the United Kingdom and the United States and reported that they were affected emotionally by their infants’ pain and worried about long-term effects on their relationships.

If this can be done safely, there are many reasons to avoid antibiotic exposure. Antibiotic exposure is associated with health problems in later childhood, including obesity (15-17), wheezing, (18) allergic rhinitis (19), and asthma (20, 21). Also, of course, it increases hospital costs. Gong (22) showed savings of about \$4000/patient when treatment was reduced by using the NEOSC versus adherence to the former CDC/AAP guidelines. Length of stay is undoubtedly reduced by avoiding antibiotic treatment, but we could not measure this since we did not have a comparison group of treated asymptomatic patients.

The safety of approaches restricting evaluation and treatment is difficult to establish since EOS is uncommon, even in CE infants. Using a higher baseline EOS incidence (4/1000 versus 0.5/1000) captured all cases of culture-positive EOS in the study of Sloane et al. (23) but required culturing almost all CE infants and treating three times as many. The multicenter study by Wortham et al. (24) documented an incidence of EOS of about 0.1%, 60% of which occurred in CE infants. They estimated that 60 to 1400 infants would be evaluated and treated for each infected infant. Assuming (hypothetically) that all EOS infants were born to mothers with chorioamnionitis and that 20% of them died, we estimated a sample size of 16,000 to prove perfect safety of our approach in the prevention of death due to EOS. Any single-center study would, therefore, face sample-size limitations.

Also, our outcomes may not be universally applicable since ours is a single-center study. Our careful observation of the routine, low-risk newborn population provides a safety net for untreated infants, which may not be the case in other institutions. Finally, it may be that there were infants readmitted to other institutions for sepsis-related complications, but this is unlikely since our institution has the only pediatric emergency department within 30 miles, and most of our patients are local.

Conclusions:

Most (84%) of the 768 CE infants at our institution were managed without laboratory evaluation and antibiotic treatment, and no adverse outcomes were seen. Using the NEOSC would have resulted in significantly greater numbers of infants being cultured and treated. If adequately powered multicenter studies corroborated our results, widespread practice changes could save many at-risk but healthy infants from unnecessary, costly, and detrimental procedures.

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Virginia Wimmer Thompson extracted data from the EMRs of patient dyads and entered it into the electronic case report forms.

Statement of Ethics:

This study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines and HIPAA Regulations. The Cone Health Institutional Review Board reviewed the protocol, which determined an exempt status.

Data availability statement

Deidentified individual participant data (including data dictionaries) will be made available in addition to study protocols, the statistical analysis plan, and the informed consent form. The data will be available upon publication to researchers who provide a methodologically sound proposal for achieving the approved proposal's goals. Proposals should be submitted to john.wimmer@conehealth.com.

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