Diagnostic performance and patient outcomes with C-reactive protein use in early-onset sepsis evaluations

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Abstract

Objectives: To determine performance of C-reactive protein (CRP) in diagnosis of early-onset sepsis (EOS), and to assess patient outcomes with and without routine use of CRP.

Study design: Retrospective cohort study of infants admitted to two neonatal intensive care units. CRP was routinely used in EOS evaluations during 2009–2014; this period was utilized to determine CRP performance at a cut-off of 10 mg/L in diagnosis of culture-confirmed EOS. Routine CRP use was discontinued during 2018–2020; outcomes among infants admitted during this period were compared with those in 2012–2014.

Results: From 2009–2014, 10,134 infants were admitted; 9,103 (89.8%) had CRP and 7,549 (74.5%) had blood culture obtained within 3 days of birth. CRP obtained ±4 hours from blood culture had a sensitivity of 41.7%, specificity 89.9% and positive likelihood ratio 4.12 in diagnosis of EOS. When obtained 24–72 hours after blood culture, sensitivity of CRP increased (89.5%), but specificity (55.7%) and positive likelihood ratio (2.02) decreased. Comparing the periods with (n=4,977) and without (n=5,135) routine use of CRP, we observed lower rates of EOS evaluation

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(74.5% vs. 50.5%), antibiotic initiation (65.0% vs. 50.8%), and antibiotic prolongation in the absence of EOS (17.3% vs. 7.2%) in the later period. Rate and timing of EOS detection, transfer to a higher level of care, and in-hospital mortality were not different between periods.

Conclusions: CRP diagnostic performance was not sufficient to guide decision-making in EOS. Discontinuation of routine CRP use was not associated with differences in patient outcomes despite lower rates of antibiotic administration.

Keywords

antibiotic stewardship; biomarker; clinical utility; newborn

C-reactive protein (CRP) is an acute phase reactant commonly used as a biomarker in evaluation for neonatal early-onset sepsis.(1–5) The clinical utility of a test can be measured using two approaches: diagnostic performance, and impact on patient outcomes.(6) Metrics for diagnostic performance include sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios, and are calculated by comparing the results of the test with a "gold standard". The gold standard used to diagnose EOS is pathogen isolation from blood or cerebrospinal fluid (CSF) culture, with or without additional clinical findings of infection.(7,8) Microbial cultures have limitations, and their use as the gold standard comparator for testing diagnostic performance of other biomarkers in neonatal sepsis has been debated.(9) The clinical utility of a test can also be measured by the extent to which its use guides decisions that improve patient outcomes, an approach that may circumvent the issue of an inadequate gold standard.(5,6) For EOS, relevant patient outcomes include early recognition of infection, prompt initiation of indicated antibiotic treatment, minimal antibiotic use among the uninfected, and reduction of mortality and morbidity. In this study, we assessed the clinical utility of CRP in the diagnosis of EOS using both the approaches – measuring diagnostic performance (Objective 1) and impact on patient outcomes with and without routine use (Objective 2), in a large cohort over a 12-year period.

Methods

This was a retrospective cohort study of all infants admitted within 3 days after birth to two neonatal intensive care units (NICUs) in the University of Pennsylvania Health System. The study centers share a common medical record system and aligned clinical practice. From 1/1/2009–12/31/2014, the centers used a categorical approach to neonatal EOS risk assessment based on previously published work, and utilized routine CRP measurement.(10) We determined the diagnostic performance of CRP in EOS for infants admitted during this time period (Objective 1). Between 2015–2017, both centers transitioned their approach of neonatal EOS risk assessment to the Neonatal Early-Onset Sepsis Calculator for term infants, and delivery criteria for preterm infants.(11,12) These new approaches did not require CRP values for decision making, and the new guideline did not incorporate its use.(13,14) By 2018, <10% of EOS evaluations included CRP measurement. To study the impact of CRP use on patient outcomes (Objective 2), comparisons were made between infants born 1/1/2012–12/31/2014 (Period 1: routine CRP use) and 1/1/2018–12/31/2020 (Period 2: minimal CRP use) (Figure 1). These time periods were selected to maximize capture of EOS cases for diagnostic performance analysis (Objective 1)

and to minimize missing data elements in comparing patient outcomes (Objective 2; discharge disposition data was missing from hospital records during 2009–2011). Patient demographics, laboratory results, and medication data were obtained from the institutional data warehouse for 2009–2014 and from electronic medical records (Epic®, Epic Systems Corporation, Verona, WI) for 2018–2020. The study was approved by the Institutional Review Board of the University of Pennsylvania with a waiver of informed consent.

Study definitions

EOS was defined as isolation of a pathogenic organism from blood and/or CSF culture obtained within 3 days after infant birth. Coagulase-negative staphylococci and other common skin commensal organisms from cultures obtained 0–3 days after birth were deemed as contaminants and included among negative cultures. Coagulase-negative staphylococci isolated from cultures obtained on day 4–7 after birth were considered pathogens if treated by the clinical team with antibiotics for 5 days. Prolonged antibiotics were defined as antibiotics administered for >2 days in the absence of pathogen isolation from blood or CSF culture.

CRP diagnostic performance—CRP testing was performed at the clinical laboratory at each site using latex particle immunoturbidimetry. We measured the diagnostic performance of CRP against the gold standard of culture-confirmed EOS. Blood culture practices for EOS at both sites included obtaining a minimum blood volume of 1 mL that was inoculated into a single pediatric aerobic blood culture bottle. An anaerobic blood culture bottle with a 1 mL inoculant was added in 2016 at one site.[15] Both CRP and blood culture results were reported in the electronic medical record system and interpreted by clinicians per standard care. We used a CRP cut-off value of 10 mg/L for the main analysis of diagnostic performance, but also analyzed diagnostic performance metrics at other thresholds that are commonly reported in the literature, ranging from 5 to 15 mg/L.[16] CRP tests that were resulted as 'quantity not sufficient' or cancelled by the laboratory were excluded from the analysis. Diagnostic performance of CRP was analyzed for tests ordered within ±4 hours of blood culture, and for tests ordered between 4–24 hours, and 24–72 hours after blood culture. If more than one CRP value was available during an analytic time frame, we chose the highest CRP value for analysis. Among infants without EOS, we compared birth characteristics, antibiotic initiation, type of antibiotics, antibiotic duration, frequency of CSF cultures in days 0–3, frequency of blood and CSF cultures in days 4–7, and hospital length of stay, between infants with CRP values above and below the cutoff value of 10 mg/L.

CRP and clinical outcomes—We defined clinically relevant patient outcomes as follows: proportions of all NICU infants from whom blood or CSF cultures were obtained on day 0–3 and 4–7 after birth; rates of positive blood or CSF cultures; time from birth to obtaining blood culture and antibiotic administration among culture-confirmed cases; rate of antibiotic initiation on day 0–3 and 4–7; duration of antibiotic use in the absence of positive cultures; hospital length of stay; transfer for higher level of NICU care in the first 7 days after birth; and all-cause in-hospital mortality overall, and in the first 7 days after birth.

Statistical analyses

We measured the diagnostic performance of CRP in EOS using sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios, and plotted receiver operating characteristic curves. Exact binomial confidence intervals for proportions were calculated by the method of Clopper & Pearson, and confidence intervals for ratios of proportions by the method of Koopman.(17,18) Associations between various characteristics and comparator groups were made using chi-squared test, Fisher's exact text, and Mann-Whitney *U* test, as appropriate. Additionally, we used statistical process control p-charts to vizualize the changes in use of CRP and pre-specified outcomes over the study periods.(19) Proportions are presented monthly for all variables except deaths, which are presented quarterly due to the rarity of this outcome. The p-charts were generated using QI Macros for Excel developed by KnowWare International, Inc, Denver, CO. All other analyses were performed using Stata version 16 (StataCorp, College Station, TX).

Results

Diagnostic performance of CRP

From 2009–2014, 10,134 infants were admitted to the study NICUs (Figure 1); characteristics of the cohort are shown in Table I (onavailable at www.jpeds.com). The median gestational age was 37 weeks (IQR 34–39), median birth weight was 2,830 grams (IQR 2,050–3,415), 5,569 (55.0%) were male, and 5,019 (49.5%) were delivered by cesarean.

A total of 7,549 (74.5%) infants had at least one blood culture obtained on day 0–3 after birth. Of them, 1,092 (14.5%) also had a CSF culture. Most blood cultures (7,083/7,549, 93.8%) were obtained within one day after birth. Among infants with a blood culture obtained on day 0–3, 41 (0.5%) were diagnosed with EOS. The most common organisms were group B *Streptococcus* (GBS, 39.0%) and *Escherichia coli* (39.0%). One infant with GBS bacteremia also had GBS isolated in the CSF. There were no infants with a positive CSF culture in the absence of a positive blood culture.

A total of 9,103 (89.8%) had one or more CRP obtained on day 0–3, and of them, 2,085 (22.9%) had at least one value 10 mg/L. Among 7,549 infants with a blood culture on day 0–3, 7,450 (98.6%) also had a CRP obtained in that timeframe. The diagnostic performance of CRP 10 mg/L in EOS is shown in Table II. With increasing duration between time when blood culture and CRP were obtained, sensitivity of CRP increased while specificity decreased. CRP obtained 4–24 hours after blood culture had the highest area under the curve on a receiver operating characteristic curve (Figure 2 available at www.jpeds.com). Alternate thresholds of CRP demonstrated similar patterns with the highest sensitivity at low cut-offs farther from time of blood culture and highest specificity for high cut-offs closer to the time of blood culture (Table III available at www.jpeds.com).

Clinical management of infants without EOS

Of the 7,508 infants without EOS, 7,410 (98.7%) had a CRP obtained on day 0–3, and of these, 1,934 (26.1%) had at least one CRP 10 mg/L. Infants with CRP 10 mg/L were

more frequently males born via vaginal delivery at higher gestational ages and with higher birth weights (Table IV). They were also more likely to be started on empiric antibiotics, receive prolonged antibiotics despite negative blood or CSF cultures, receive antibiotics other than penicillin, ampicillin, and gentamicin, have a CSF culture obtained on day 0–3 or 4–7, and have a longer hospital length of stay.

Comparing outcomes in time periods with and without routine use of CRP

We compared 4,977 infants admitted to the study sites from 2012–2014 (Period 1: routine CRP use) with 5,135 infants admitted from 2018–2020 (Period 2: minimal CRP use) (Table V). Change in CRP use and pre-specified outcomes over time are shown in Figure 3 (available at www.jpeds.com). Proportion of infants with CRP on day 0–3 decreased significantly from 89.2% in Period 1 to 7.7% in Period 2. The proportion of infants with a blood or CSF culture obtained on day 0–3 and 4–7 also decreased in Period 2. A smaller proportion of admitted infants were administered antibiotics on day 0–3 and 4–7 in Period 2 compared with Period 1. Among infants with a blood culture on day 0–3, a higher proportion of infants were started on antibiotics in Period 2 as compared with Period 1 (98.3% vs 86.1%; P<0.001). In Period 2, among infants for whom antibiotics were initiated on day 0–3, a smaller proportion of infants were administered prolonged antibiotics in the setting of negative cultures.

The incidence of EOS and of blood or CSF culture confirmed infection on day 4–7 was not different between the two periods. Among culture-confirmed infection cases, the time from birth to when blood culture was collected, and empiric antibiotics initiated, was not different between the two periods. There was no difference in the hospital length of stay between the two periods overall, or among term and preterm infants considered separately. The proportions of infants who died or were transferred for higher level of care in the first week after birth, and the proportion of infants who died any time during hospitalization was also not different between the two periods.

Discussion

In this study, we measured the clinical utility of CRP in EOS risk assessment in two ways: diagnostic performance in the detection of culture-confirmed EOS and differences in patient outcomes with and without routine use of CRP. CRP had low sensitivity when obtained within ±4 hours of a blood culture, and a modest positive likelihood ratio; with increasing time between blood culture and CRP measurement, sensitivity increased but positive likelihood ratio and specificity decreased. Overall, our results are aligned with other studies where sensitivity of CRP early in EOS evaluation varies from 30% to 74%, and increases with time.(16,20–22) These results support existing data that CRP should not be used to decide initiation of empiric antibiotics.(23) Given that sensitivity improves over the same period of time culture results are reported, we suggest that CRP has little role in early identification of infants with EOS. Nonetheless, it is possible that CRP could function to modify clinical decisions and actions in a manner that would improve patient outcomes. This hypothesis arises from the concept that recognition of the presence or absence of an inflammatory state could have clinical value, and potentially compensate for an undefined

"failure rate" of blood culture to detect true infection. In comparing 3-year periods in our centers marked by ~90% use of CRP with EOS evaluation and <10% use, we found no significant clinical harm as measured by change in time to detection of infection, time to antibiotic initiation among EOS cases, infection rates, transfer for higher level of care or in-hospital mortality in the first week after birth. Overall, we found that CRP did not improve care delivery in EOS management, but instead was associated with higher rates of diagnostic testing (blood cultures and lumbar punctures) and higher rates of antibiotic administration.

EOS evaluation is typically performed soon after birth and is based on presence of perinatal risk factors, clinical status, and results of laboratory tests.(24) Laboratory tests are expected to provide information that is additive to risk-based history and clinical status in order to improve decision making.(6) For example, microbiological cultures provide information about the causative pathogen and guide antibiotic choice. Host response inflammatory markers such as CRP can be viewed as analogues to the physical exam, where deviations from a physiological 'normal' is an indication for disease, much like an abnormal exam finding. Given that newborns can manifest abnormalities due to physiologic transition as well as due to infection, there are several decision-making points where CRP could be useful. The first scenario where CRP may influence EOS management is the identification of infants for whom empiric antibiotics should be initiated. The low sensitivity of CRP precludes withholding antibiotics based on normal results.(21,23,25–28) The opposite, however, is not true. During 2009–2014, infants in this study with an abnormal CRP obtained within one day after birth were uniformly started on antibiotics (1,357/1,437, 94.4%). Although we cannot isolate how many infants were started on antibiotics solely due to an abnormal CRP, it is possible that the CRP result influenced the decision to initiate empiric antibiotic therapy. The second scenario in which CRP may influence EOS management is the use of serial values to drive antibiotic initiation, given the rising sensitivity of CRP with increasing time from blood culture collection.(28) During 2009–2014, of the 6,868 study infants with antibiotics initiated on day 0–3 after birth, 211 infants (3.1%) had antibiotics initiated only after a new elevation in the second or third CRP value. This low fraction highlights that this information may not be useful in real-world practice. Most EOS cases become symptomatic within the first few hours to days after birth.(29) Therefore, as time from birth increases, the need for a test to determine well-being decreases.

The final scenario in which CRP may affect EOS management is the determination of duration of empiric antibiotic therapy.(28,30) This utility relies on the rising sensitivity of CRP with time from evaluation in addition to clinical context at the time of blood culture result. For example, a normal CRP may support early antibiotic discontinuation when a possible contaminant (such as Coagulase-negative staphylococci) is reported.(31) More commonly, concern for 'culture-negative' infection makes it likely that a negative culture result is considered unreliable.(28) This may be due to perceived poor sensitivity of blood cultures, lack of confidence in the technique of culture collection or other factors concerning for infection, such as severity of illness. A high CRP in such a context is often interpreted as an indicator of 'missed' infection. This use is demonstrated in our study (Table IV) where infants with a negative blood culture and an abnormal CRP were more likely to receive

prolonged antibiotics. However, the poor specificity of CRP at 24–72 hours suggests that by using this approach, a substantial proportion of infants without infection will be mislabeled. (2,5) It is also noteworthy that approximately half of the infants with an abnormal CRP did not receive prolonged antibiotics, suggesting that clinicians used information other than CRP for decision-making.

In each scenario where CRP may have altered decision making, the most important question is whether that change improved care. For instance, would the absence of a CRP result alter the frequency of prolonged antibiotic administration among infants with negative blood/CSF cultures, and in turn change outcomes? In the absence of CRP, clinicians could still decide to prolong antibiotics due to other factors; or the proportion with prolonged antibiotics may increase due to uncertainty created by not having a CRP result; or the antibiotics could be stopped. For the latter, if an infant is truly infected and partially treated, the infant may subsequently decompensate and require repeat evaluation. When we compared outcomes between time periods where CRP was, and was not, routinely used, we found that neither repeat evaluations nor adverse outcomes increased in the first week and clinicians did not continue to administer prolonged antibiotics, suggesting no apparent benefits of prolonged antibiotic courses administered during the routine CRP period.

Multiple studies report increase in procedures and antibiotic use in sepsis evaluations with CRP use.(3,4,32,33) We also found increased use of procedures and antibiotic use during the period of routine CRP use. In our study and others, discontinuation of routine CRP use was associated with reduced antibiotic use.(34) However, at our study centers, the decision to stop obtaining CRP routinely was made in conjunction with changes in how we conducted EOS evaluations.(13–15) Therefore, we cannot attribute the reduction in antibiotic use solely to discontinuation of CRP use, and instead attribute it to the change in EOS evaluations as a whole. Within this context, we found sustained compliance with eliminating routine CRP, and had no major adverse impacts. In the absence of demonstrable benefit, and with the possibility of triggering antibiotic overuse and unnecessary evaluations, we are unable to justify routine CRP use in EOS evaluations.

Our study has limitations. We chose to use a convenience sample to enhance the contrast in CRP use between the pre-post period, as observational studies may incur unmeasured confounding. There are other types of test utility that we did not measure.(6,35) For instance, even if clinicians made the same decisions, but did it more efficiently in the presence of a test, the test may prove to be useful. We did not assess clinician perspective on CRP use. Similarly, the utility is context dependent. We studied the use of CRP testing routinely applied to all evaluations. It is possible that in some patients where ambiguity is greater, new and useful knowledge can be obtained from a correctly timed CRP. Finally, we studied discontinuation of routine CRP in the setting of larger changes in EOS evaluation approach and our experience may not be generalizable to other settings where this was not done.

In this pre-post cohort analysis, initial CRP testing for EOS evaluations was not sufficiently sensitive to support decisions to withhold empiric antibiotic treatment. Although later CRP measurements were more sensitive, they were too nonspecific to support decisions

to continue treatment. Discontinuation of routine CRP use during EOS evaluation was not associated with changes in rate or promptness of EOS detection or management. Furthermore, discontinuation of routine CRP use was not associated with more serious adverse outcomes, despite an associated reduction in rates of antibiotic use. Using the aforementioned methods of test utility determination, we did not identify a clear advantage of using CRP in EOS evaluation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations:

CRP   C-reactive protein

CSF   cerebrospinal fluid

EOS   early-onset sepsis

GBS   group B *Streptococcus*

NICU   neonatal intensive care unit

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Objective 1: Measuring diagnostic performance of CRP in EOS

Objective 2: Comparing patient outcomes with and without routine CRP use

Study period 2009-2014

Admitted to NICU
Infants = 10,134

Blood culture ≤3 days
Infants = 7,549

CRP ≤3 days
Infants = 9,103

CRP obtained ±4 hours from blood culture
Infants = 4,201

CRP obtained 4-24 hours after blood culture
Infants = 6,193

CRP obtained 24-72 hours after blood culture
Infants = 1,817

Study periods 2012-2014 and 2018-2020

Admitted to NICU
Infants = 10,112

Period 1: 2012-2014
With routine CRP use
Infants = 4,977

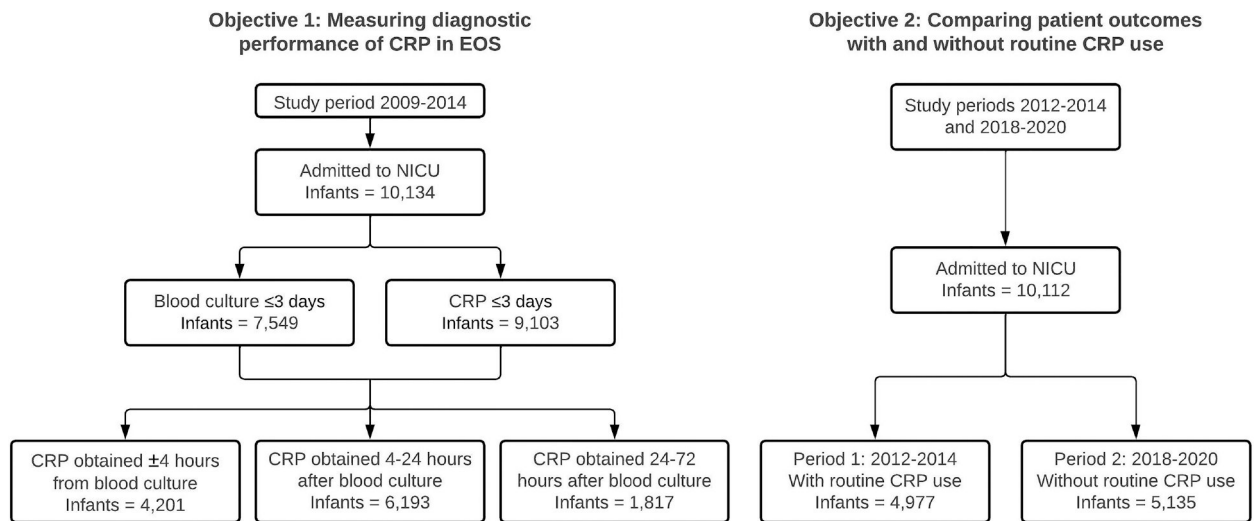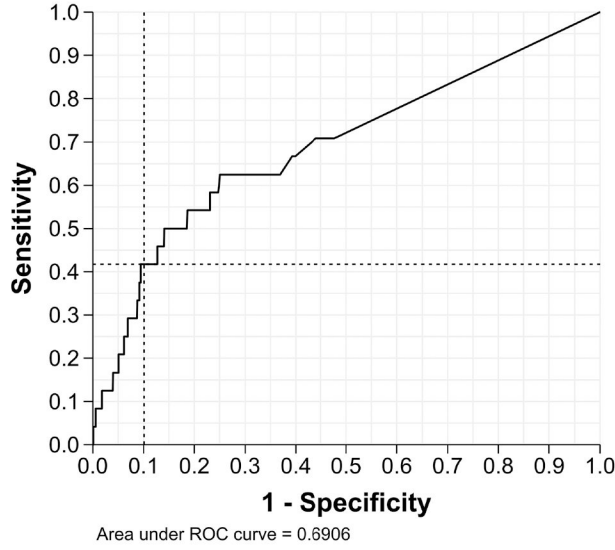Period 2: 2018-2020
Without routine CRP use
Infants = 5,135

Figure 1. Study population.

A. Derivation of cohort used in the analysis of diagnostic performance of CRP in EOS. The 3 categories of paired blood culture and CRP are not mutually exclusive – an infant could be present in more than one category if the infant had more than one CRP obtained within 72 hours of blood culture.
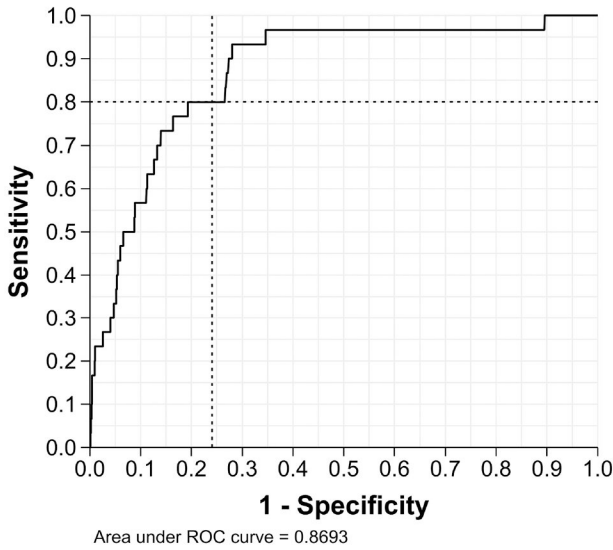
B. Derivation of cohort used in studying the impact of CRP use on clinical management and patient outcomes. Of note here, beginning in June 2016, well-appearing infants undergoing an EOS evaluation at one of the two study sites could have had blood cultures drawn and antibiotics started in the mother's room. We included these infants along with NICU admissions to allow for comparison of all infants undergoing EOS evaluations between study periods.

Abbreviations – *CRP*, C-reactive protein; *EOS*, early-onset sepsis; *NICU*, neonatal intensive care unit.

A. CRP ±4 hours from blood culture

Area under ROC curve = 0.6906

B. CRP 4-24 hours after blood culture

Area under ROC curve = 0.8693

C. CRP 24-72 hours after blood culture
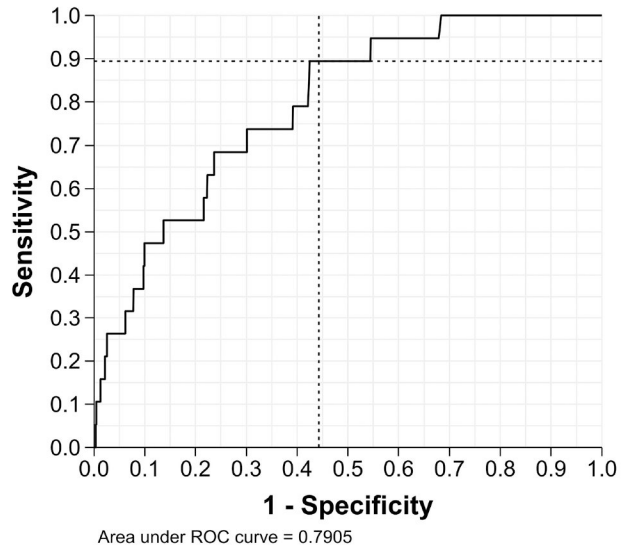

Area under ROC curve = 0.7905

Figure 2. ROC curves for CRP values in diagnosis of EOS

A. ROC curve of CRP values obtained ±4 hours from blood culture.

B. ROC curve of CRP values obtained 4–24 hours after blood culture.

C. ROC curve of CRP values obtained 24–72 after blood culture.

The dotted intersecting lines in all 3 ROC curves mark the sensitivity and 1-specificity for a CRP value of 10 mg/L. When plotting ROC curves, CRP values below the lower detection limit reported as <0.20 mg/L, were converted to 0.10 mg/L (half of the lower detection limit) and included in analysis.

Abbreviations – *CRP*, C-reactive protein; *EOS*, early-onset sepsis; *ROC*, receiver operating characteristic.
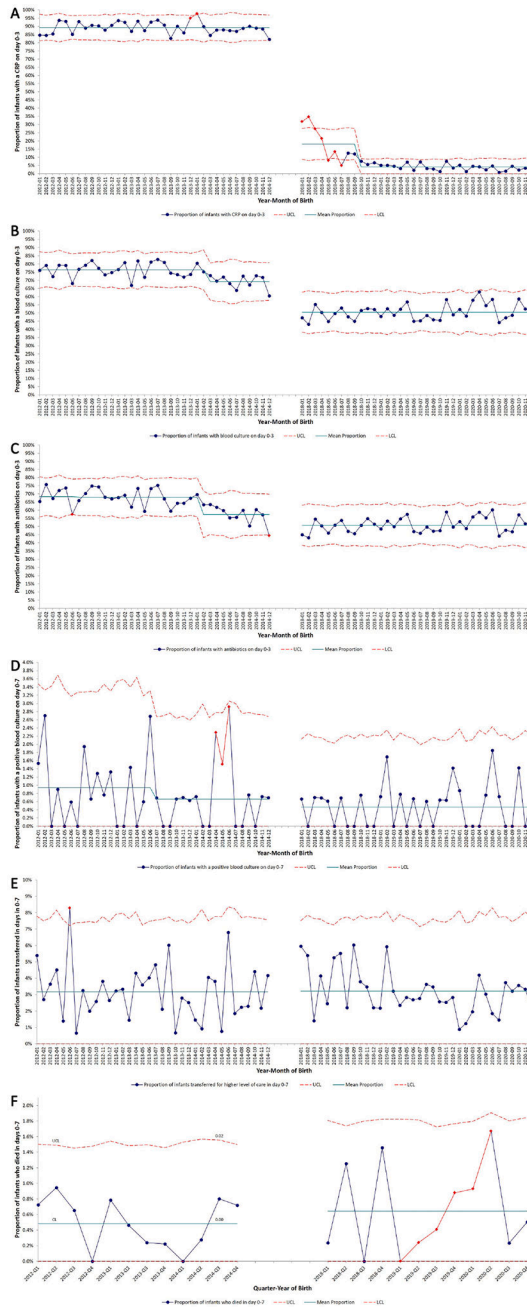
Figure 3. Statistical process control charts of infection evaluation, antibiotic use and outcomes during study Period 1 and 2.

The blue dots (●) and red diamonds (♦) represent the proportion of all NICU infants with the outcome of interest in a particular month. The results of the stability analysis are marked by red diamonds for "unstable" data points which do not follow the expected pattern. These points could be flagged for one or more of the following reasons – 1) Point above UCL or below LCL, 2) Two or more consecutive points above or below 2 standard deviations from mean, 3) Six or more consecutive points trending up or down, and 4) 15 or more consecutive points within 1 standard deviation of mean. The red dashed lines (---) represent upper and lower control limits. Special cause variation within a study period was identified when 8

consecutive data points were above or below the mean line, and the mean line subsequently adjusted.

A. SPC chart of monthly proportion of infants with at least one CRP obtained on day 0–3 over the study period.

B. SPC chart of monthly proportion of infants with blood culture obtained on day 0–3 over the study period.

C. SPC chart of monthly proportion of infants started on empiric antibiotics on day 0–3 over the study period.

D. SPC chart of monthly proportion of infants with at least one positive blood culture growing a pathogen on day 0–7 over the study period.

E. SPC chart of monthly proportion of infants transferred for higher level of care in days 0–7 over the study period.

F. SPC chart of quarterly proportion of infants who died in days 0–7 over the study period.

Abbreviations – *CRP*, C-reactive protein; *CSF* cerebrospinal fluid; *EOS*, early-onset sepsis; *LCL*, lower control limit; *NICU*, neonatal intensive care unit; *SPC*, statistical process control; *UCL*, upper control limit.

Table 1.

Characteristics and management of infants admitted to NICU from 2009–2014

Characteristics	N = 10,134
Sex (male)	5,569 (55.0)
Gestational age, wk	37 (34, 39)
Gestational age <37 wk	4,551 (44.9)
Birth weight, g	2830 (2050, 3415)
Birth weight	
<1500g	1,239 (12.2)
1500 to <2500 g	2,746 (27.1)
2500 g	6,148 (60.7)
Cesarean delivery	5,019 (49.5)
Length of stay by gestational age, d	4 (3, 15)
37 wk	3 (2, 5)
<37 wk	15 (6, 35)
Maternal race	
White/non-Hispanic	3,066 (30.3)
Black/non-Hispanic	5,475 (54.0)
Hispanic	575 (5.7)
Other/Unknown	1,018 (10.1)
Maternal age, y	28 (23, 33)
Management on day 0–3	
Blood culture obtained	7,549 (74.5)
CSF culture obtained	1,131 (11.2)
CRP obtained	9,103 (89.8)
At least one CRP 10 mg/L	2,085 (22.9)
Blood culture positive for a pathogen	41 (0.4)
HOL positive blood culture was obtained	1.4 (0.7, 2.8)
CSF culture positive for a pathogen	1 (0.1)
Antibiotics initiated	6,868 (67.8)
Antibiotics continued for >2 d	1,698 (24.7)
Management on day 4–7	
Blood culture obtained	325 (3.2)
CSF culture obtained	180 (1.8)
CRP obtained	832 (8.2)
At least one CRP 10 mg/L	172 (20.7)
Blood culture positive for pathogen	35 (0.4)
HOL positive blood culture was obtained	138.2 (107.4, 155.0)
CSF culture positive for pathogen	1 (0.0)
Antibiotics initiated	179 (1.8)

Characteristics	N = 10,134
Antibiotics continued for >2 d	78 (43.6)

Data presented as n (%) or median (Q1, Q3). Missing data – Birth weight (1), Maternal age (163). Abbreviations – *CRP*, C-reactive protein; *CSF*, cerebrospinal fluid; *HOL*, hour of life; *NICU*, neonatal intensive care unit.

Table 2.

Diagnostic Performance of CRP in EOS

	CRP ±4 hours from blood culture N = 4,201		CRP 4–24 hours after blood culture N = 6,193		CRP 24–72 hours after blood culture N = 1,817	
	Blood culture positive	Blood culture negative	Blood culture positive	Blood culture negative	Blood culture positive	Blood culture negative
CRP 10 mg/L	10	422	24	1,482	17	796
CRP <10 mg/L	14	3,755	6	4,681	2	1,002
Total	**24**	**4,177**	**30**	**6,163**	**19**	**1,798**
Diagnostic Performance Metrics						
	Value	95% CI	Value	95% CI	Value	95% CI
Sensitivity	41.7%	22.1% – 63.4%	80.0%	61.4% – 92.3%	89.5%	66.9% – 98.7%
Specificity	89.9%	88.9% – 90.8%	76.0%	74.9% – 77.0%	55.7%	53.4% – 58.0%
PPV	2.3%	1.1% – 4.2%	1.6%	1.0% – 2.4%	2.1%	1.2% – 3.3%
NPV	99.6%	99.4% – 99.8%	99.9%	99.7% – >99.9%	99.8%	99.3% – >99.9%
Positive LR	4.12	2.55 – 6.68	3.33	2.77 – 4.00	2.02	1.72 – 2.38
Negative LR	0.65	0.46 – 0.91	0.26	0.13 – 0.54	0.19	0.05 – 0.70

EOS cases did not always have a paired CRP value for each time-period. Abbreviations – *CI*, confidence interval; *CRP*, C-reactive protein; *EOS*, early-onset sepsis; *LR*, likelihood ratio; *NPV*, negative predictive value; *PPV*, positive predictive value.

Table 3.

Diagnostic accuracy of CRP in EOS for varying cut-off values and varying duration between time CRP and blood culture

CRP cut-off value	True positive	False positive	False negative	True negative	Sensitivity	Specificity	Accuracy[1]	Positive LR	Negative LR
CRP ±4 h from blood culture									
5 mg/L	12	623	12	3,554	50.0%	85.1%	84.9%	3.35	0.59
7 mg/L	10	526	14	3,651	41.7%	87.4%	87.1%	3.31	0.67
10 mg/L	10	422	14	3,755	41.7%	89.9%	89.6%	4.12	0.65
15 mg/L	7	326	17	3,851	29.2%	92.2%	91.8%	3.74	0.77
CRP 4–24 h after blood culture									
5 mg/L	29	2,209	1	3,954	96.7%	55.9%	36.1%	2.70	0.05
7 mg/L	28	1,835	2	4,328	93.3%	70.2%	70.3%	3.13	0.09
10 mg/L	24	1,482	6	4,681	80.0%	76.0%	76.0%	3.33	0.26
15 mg/L	23	1,131	7	5,032	76.7%	81.7%	81.6%	4.18	0.29
CRP 24–72 h after blood culture									
5 mg/L	18	1,084	1	714	94.7%	39.7%	40.3%	1.57	0.13
7 mg/L	17	966	2	832	89.5%	46.3%	46.7%	1.67	0.23
10 mg/L	17	796	2	1,002	89.5%	55.7%	56.1%	2.02	0.19
15 mg/L	14	593	5	1,205	73.7%	67.0%	67.1%	2.23	0.39

[1]
Accuracy calculated as $\dfrac{TP + FP}{TP + FP + TN + FN}$.

Abbreviations – *CRP*, C-reactive protein; *EOS*, early-onset sepsis; *FN*, false negative; *FP*, false positive; *LR*, likelihood ratio; *TN*, true negative; *TP*, true positive.

Table 4.

Influence of CRP measurements on management of infants without EOS

	CRP high[1] N = 1,934	CRP low[2] N = 5,476	P value
Characteristics			
Sex (male)	1,184 (61.2)	2,981 (54.4)	<0.001
Cesarean delivery	890 (46.0)	2,741 (50.1)	0.002
Gestational age, wk	39 (36, 40)	36 (33, 39)	<0.001
Birth weight, g	3250 (2550, 3640)	2680 (1931, 3330)	<0.001
Length of stay by gestational age, d			
<37 wk	38 (13, 69)	17 (8, 37)	<0.001
37 wk	4 (3, 7)	3 (2, 4)	<0.001
Management and outcomes in day 0–3			
CSF culture obtained	636 (32.9)	424 (7.7)	<0.001
CSF culture positive for a pathogen	0	0	N/A
Antibiotics initiated	1,884 (97.4)	4,777 (87.2)	<0.001
Antibiotics continued for >2 d	821 (43.6)	788 (16.5)	<0.001
Antibiotics other than penicillin, ampicillin and gentamicin given	125 (6.6)	159 (3.3)	<0.001
Vancomycin	83 (66.4)	130 (81.8)	0.003
Cephalosporins	95 (76.0)	101 (63.5)	0.02
Metronidazole	8 (6.4)	8 (5.0)	0.62
Management and outcomes in day 4–7			
Blood culture obtained	62 (3.2)	202 (3.7)	0.33
CSF culture obtained	71 (3.7)	83 (1.5)	<0.001
Blood culture positive for a pathogen	4 (0.2)	24 (0.4)	0.20
CSF culture positive for a pathogen	1 (0.1)	0	0.26

Data presented as n (%) or median (Q1, Q3). All infants in the table had a blood culture obtained in days 0–3 which was not positive for a pathogen.

[1] Includes infants who had at least one CRP value 10 mg/L in days 0–3.

[2] Includes infants with all CRP values <10 mg/L in days 0–3.

Abbreviations – *CRP*, C-reactive protein; *CSF*, cerebrospinal fluid; *EOS*, early-onset sepsis.

Table 5.

Characteristics, management, and infant outcomes during period with and without routine CRP use in EOS

	Period 1 N = 4,977	Period 2 N = 5,135	*P* value
Demographics and delivery characteristics			
Maternal age, y	29 (23, 33)	31 (26, 34)	<0.001
Race/ethnicity			<0.001
White/Non-Hispanic	1,555 (31.2)	1,786 (34.8)	
Black/Non-Hispanic	2,552 (51.3)	2,388 (46.5)	
Hispanic	297 (6.0)	400 (7.8)	
Asian/Other/Unknown	573 (11.5)	561 (10.9)	
Sex (male)	2,712 (54.5)	2,840 (55.3)	0.40
Caesarean delivery	2,519 (50.6)	2,340 (45.6)	<0.001
Gestational age, wk	37 (34, 39)	37 (34, 39)	0.06
Birth weight, g	2820 (2060, 3420)	2810 (2090, 3400)	0.99
Management in days 0–3			
Blood culture obtained	3,709 (74.5)	2,592 (50.5)	<0.001
CSF culture obtained	431 (8.7)	63 (1.2)	<0.001
CRP obtained	4,441 (89.2)	393 (7.7)	<0.001
At least one CRP 10 mg/L	984 (22.2)	190 (48.4)	<0.001
Infants with >2 CRP obtained	593 (13.4)	16 (4.1)	<0.001
Blood culture positive for a pathogen	23 (0.5)	15 (0.3)	0.16
HOL blood culture obtained, h	1.0 (0.5, 2.3)	1.2 (1.0, 5.1)	0.11
HOL antibiotics started, h	2.5 (1.6, 5.0)	2.2 (1.4, 4.5)	0.76
CSF culture positive for a pathogen	1 (0.0)	0	0.49
Antibiotics initiated in 0–3 days[1]	3,233 (65.0)	2,607 (50.8)	<0.001
Antibiotic continued for >2 d when blood/CSF cultures did not grow a pathogen[2]	548/3,170 (17.3)	183/2,532 (7.2)	<0.001
Management in days 4–7			
Blood culture obtained	146 (2.9)	109 (2.1)	0.009
CSF culture obtained	77 (1.6)	17 (0.3)	<0.001
CRP obtained	389 (7.8)	123 (2.4)	<0.001
At least one CRP 10 mg/L	79 (20.3)	46 (37.4)	<0.001
Infants with >2 CRP obtained	31 (8.0)	3 (2.4)	0.04
Blood culture positive for a pathogen	17 (0.3)	9 (0.2)	0.10
HOL blood culture obtained, h	138.2 (113.8, 155.0)	117.0 (105.4, 150.4)	0.40
HOL antibiotics started[3], h	130.0 (114.3, 162.4)	134.4 (90.5, 158.1)	0.37
CSF culture positive for a pathogen	0	2 (0.0)	0.50
New antibiotic course started in 4–7 days[4]	88 (1.8)	54 (1.1)	0.002
Antibiotic continued for >2 d when blood/CSF cultures did not grow a pathogen[2]	18/70 (25.7)	7/46 (15.2)	0.18

	Period 1 N = 4,977	Period 2 N = 5,135	*P* value
Disposition			
Length of stay by gestational age, d	4 (3, 15)	4 (3, 15)	0.84
<37 wk	15 (6, 36)	15 (6, 32)	0.37
37 wk	3 (2, 4)	3 (2, 4)	0.64
Transferred for higher level of care in 7 days after birth	158 (3.2)	165 (3.2)	0.91
Deceased in 7 days after birth	24 (0.5)	33 (0.6)	0.28
Deceased before discharge	38 (0.8)	44 (0.9)	0.60

Data presented as n (%) or median (Q1, Q3). Missing data – Maternal age (98); Sex (2); Gestational age (2).

[1]More infants may have received antibiotics than infants with blood culture because some infants were born and transferred from outside centers.

[2]The denominator includes all infants with a negative blood/CSF culture who received antibiotics in the respective time frame.

[3]Seven infants (4 in Period 1 and 3 in Period 2) with a positive blood culture in days 4–7 had antibiotics started in days 0–3 after birth; these 7 infants were excluded from comparison of HOL antibiotics started.

[4]New antibiotic course defined as new antibiotics started after a gap of >2 days from the stop date of previous antibiotic course.

Abbreviations – *CRP*, C-reactive protein; *CSF*, cerebrospinal fluid; *EOS*, early-onset sepsis; *HOL*, hour of life.