Sustainability of a Clinical Examination-Based Approach for Ascertainment of Early-Onset Sepsis in Late Preterm and Term Neonates

Adam Frymoyer, MD[1], Neha S. Joshi, MD[1], Jessica M. Allan, MD[2], Ronald S. Cohen, MD[1], Janelle L. Aby, MD[1], Juliann L. Kim, MD[2], William E. Benitz, MD[1], and Arun Gupta, MD[1]

We demonstrated the sustained impact over a 5-year period of a clinical examination-based approach to identification of early-onset sepsis in late preterm and term neonates at our hospital. To date, more than 20 000 neonates have been safely managed using this approach, resulting in a 63% reduction in antibiotic use. *(J Pediatr 2020;225:263-8).*

Owing in large part to the implementation of effective obstetrical measures over the past 2 decades, including universal maternal group B *Streptococcus* (GBS) screening and intrapartum antibiotic treatment strategies,[1,2] the incidence of culture-positive early-onset sepsis (EOS) in late preterm and term neonates at ≥35 weeks gestation is now low (0.2-0.4 cases per 1000 neonates).[3-5] To align our treatment approach for EOS with this contemporary epidemiology, our institution advanced a local antimicrobial stewardship effort within a quality improvement (QI) framework aimed at reducing unnecessary laboratory testing and antibiotic exposure in initially well-appearing late preterm and term neonates. The EOS ascertainment approach centers on use of the clinical examination to determine the need for laboratory testing and/or antibiotic treatment in neonates. In those who remain well-appearing, empiric laboratory testing and/or antibiotics are not recommended, irrespective of risk factors present at birth.

During the first 30 months after implementation of our clinical examination-based approach, laboratory testing and antibiotic use in late preterm and term neonates born at our hospital decreased by >50%, and no adverse outcomes occurred.[6,7]

Achieving sustainability of a QI intervention is essential for continued benefit of an approach to patients in clinical care.[8] Often after initial successes, attention can shift, and old practices can creep back into care. Therefore, ongoing evaluation is necessary to demonstrate sustained impact and safety. The objective of this QI report is to evaluate the sustainability of our EOS approach in maintaining a safe reduction in laboratory testing and antibiotic use within a framework of routine newborn care.

CBC	Complete blood count
CRP	C-reactive protein
CSF	Cerebrospinal fluid
EOS	Early-onset sepsis
GBS	Group B *Streptococcus*
NICU	Neonatal intensive care unit
QI	Quality improvement

Methods

Lucile Packard Children's Hospital at Stanford is a freestanding, tertiary-care children's hospital with approximately 4500 deliveries annually. Routine newborn care includes couplet care for the mother and neonate with both rooming together in the postpartum unit (ie, newborn nursery). A level II-IV neonatal intensive care unit (NICU) is located adjacent to the postpartum unit. An in-house neonatal hospitalist is available 24 hours per day to attend all high-risk deliveries and evaluate neonates as needed.

Before the implementation of our QI initiative, our institutional practice for EOS was similar to the 2010 Centers for Disease Control and Prevention guidelines and included sepsis laboratory testing and empiric treatment with ampicillin and gentamicin for all chorioamnionitis-exposed neonates. Neonates with other perinatal risk factors (ie, prolonged rupture of membranes, preterm premature rupture of membranes, GBS colonization without appropriate intrapartum antibiotic prophylaxis) routinely had a complete blood count with differential (CBC) and serial C-reactive protein (CRP) testing performed.

Intervention

We previously described phase 1 (March 2015 to July 2016) and phase 2 (August 2016 to August 2017) of our QI initiative using an updated approach for EOS at our hospital.[6,7] Here we report our ongoing experience during a sustainability phase (September 2017 to December 2019). No changes in our clinical approach occurred in the sustainability phase. Supported by our accumulated experience over 30 months in phases 1 and 2, chorioamnionitis-exposed neonates were no longer individually tracked as a subpopulation for the sustainability phase.

From the [1]Department of Pediatrics, Stanford University, Stanford, CA and [2]Palo Alto Medical Foundation, Palo Alto, CA

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In brief, we implemented a clinical examination-based approach for the identification of EOS in late preterm and preterm neonates. As part of this approach, neonates who were well-appearing at birth remained with their mother, regardless of perinatal risk factors. Enhanced clinical monitoring was performed in all neonates and included vital signs and clinical nursing assessments with documentation in the electronic health record at 0, 30, 60, 90, and 120 minutes and then every 4 hours for the first 24 hours after birth. After 24 hours of age, vital signs and clinical nurse assessments were performed every 8 hours until discharge. Nurse staffing ratios for all neonates in couplet care in the postpartum unit were 1:3. For neonates born to mothers diagnosed with chorioamnionitis, the initial clinical assessment was performed by a neonatal hospitalist at time of delivery. A level II nurse then stayed with chorioamnionitis-exposed neonates in the delivery room to provide continued clinical assessments over the first 2 hours after birth.

In phase 1 of our QI initiative, chorioamnionitis-exposed neonates were initially admitted to the level II NICU for clinical monitoring over the first 24 hours after birth. If they remained well-appearing, they were then transferred to couplet care in the postpartum unit. In phase 2, chorioamnionitis-exposed neonates who were well-appearing were no longer admitted to the level II NICU and instead remained with their mothers in couplet care for the entire hospitalization. Timing of discharge from the newborn nursery was determined by the treating physician, and no minimum length of stay was stipulated within the QI approach.

In all phases of the QI initiative, antibiotic treatment was not recommended unless a neonate was clinically ill at birth or subsequently developed clinical signs of illness concerning for sepsis. Although an emphasis was placed on general well-being, pallor/perfusion, and respiratory status, no formal criteria or "trigger" was applied, and the decision to start antibiotic treatment was left to the treating physician. Laboratory testing for sepsis was recommended only once antibiotic treatment was started, and the routine use of sepsis laboratory testing to "screen" neonates was discouraged. Lumbar puncture for cerebrospinal fluid (CSF) studies and culture were not performed routinely during evaluation for EOS unless neurologic signs were present (eg, mental status changes, seizures) at the time of presentation or unless the blood culture became positive.

Study of the Intervention and Analysis

We identified and tracked neonates at ≥35 weeks of gestation born at our hospital through a query of the electronic health record. This gestational age represents the population eligible for admission to couplet care in the postpartum unit if clinically well. Outcome measures included the percentage of neonates who had sepsis laboratory evaluation (defined by measurement of CRP) or antibiotic treatment (defined by receipt of ampicillin) within the first 3 days after birth. Control charts for each measure were constructed with control limits of 3 SD. To test for a process change after implementation of the QI initiative, a special cause shift in the center line shift was considered at ≥8 consecutive points either all above or all below the mean of the pre-QI implementation period. If a process change was detected, a new center line and control limits were calculated for the post-QI implementation period.

Comparisons between the pre-QI and post-QI implementation periods in overall antibiotic treatment and CRP testing were made using the χ^2 test. In addition, interrupted time series analyses were performed to model the level and trend in monthly antibiotic exposure and CRP before and after implementation of the QI initiative. Autocorrelation was tested using the Durbin-Watson statistic. To assess for safety, clinical outcomes of all cases of culture-positive EOS in neonates born at our hospital during the post-QI period were reviewed. In addition, neonates readmitted within the first 7 days after birth who had a positive blood culture with a pathogenic bacterial species were queried. Statistical significance was set at $P < .05$. Data were analyzed using Stata 13 (StataCorp, College Station, Texas).

This project was reviewed by the local Institutional Review Board and determined to be a local QI project that did not meet the definition of human subjects research.

Results

Since the start of our QI practice change in March 2015, a total of 20 394 neonates at ≥35 weeks of gestation were born at our hospital and followed using a clinical examination-based approach for EOS. The percentage of neonates exposed to ampicillin (**Figure**, A) decreased from 11.1% in the pre-QI period (373 of 3355) to 4.1% in the QI period (837 of 20 394; $P < .001$). The use of ampicillin during the sustainability phase of the QI period (3.7%; 370 of 9886) was lower than that in phase I (4.8%; 289 of 6022; $P = .001$) but similar to that in phase II (4.0%; 178 of 4486; $P = .5$).

Interrupted time series analysis also showed a significant change in the level of ampicillin exposure in the QI period compared with the pre-QI period (−6.6%; 95% CI, −8.1% to −5.2%; $P < .001$). A small downward trend in antibiotic exposure was found during the QI period (−0.038% per month; 95% CI, −0.057% to −0.018%; $P < .001$). There was no significant trend in ampicillin exposure during the pre-QI period.

CRP testing declined from 15.3% in the pre-QI period to 6.3% in the post-QI period ($P < .001$) (**Figure**, B). Interrupted time series analysis similarly showed a significant decrease in the level of CRP testing in the QI period (−7.7%; 95% CI, −9.8% to −5.6%; $P < .001$). A small downward trend in CRP testing was seen during the QI period (−0.046% per month; 95% CI, −0.072% to −0.020%; $P < .001$). No significant trend in CRP testing was seen during the pre-QI period.

Since initiation of the QI practice change, 7 neonates at ≥35 weeks of gestation born at our hospital have had culture-positive EOS (**Table**). This represents an overall

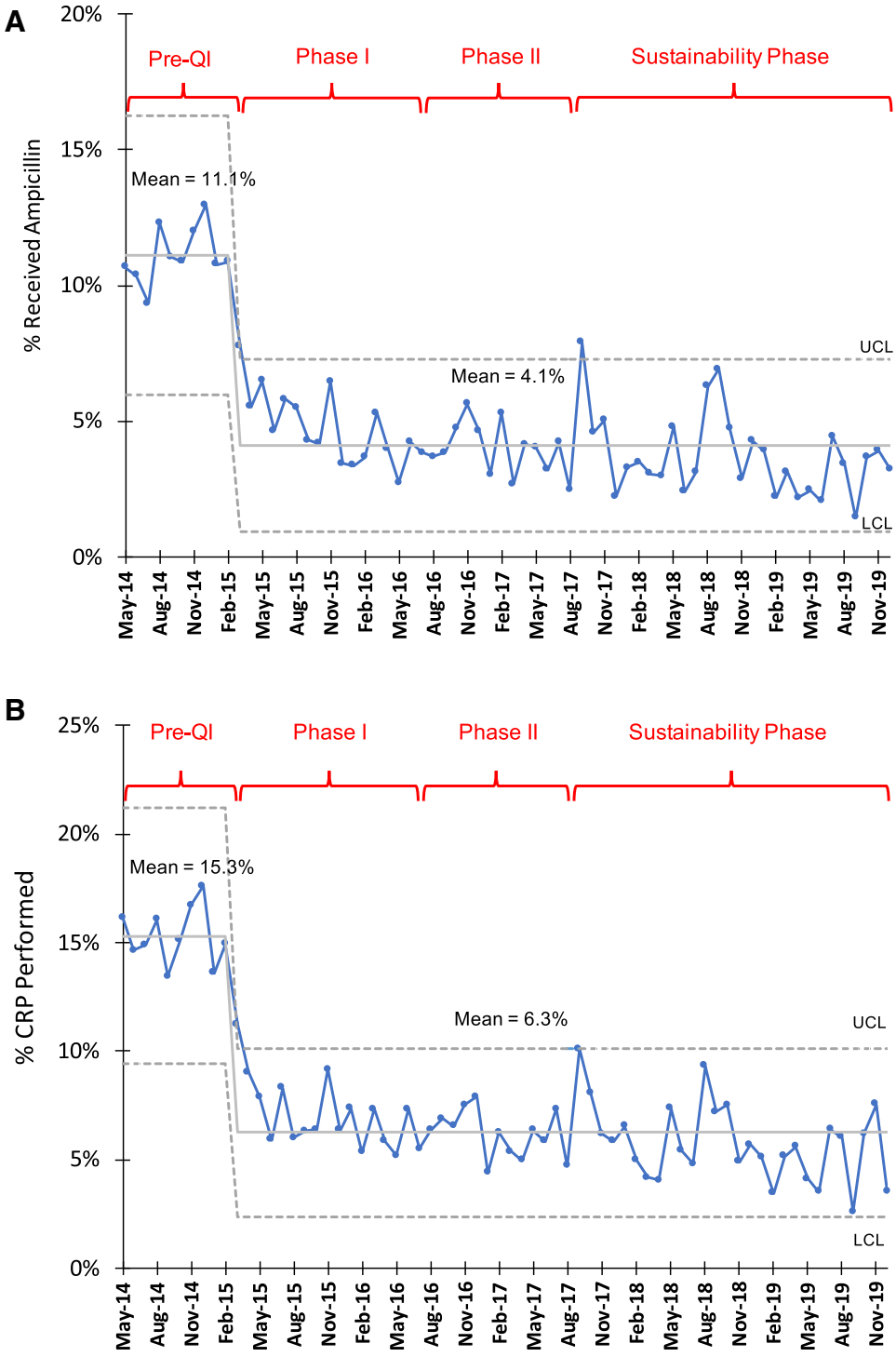

Figure. Control chart of the monthly percentage of neonates born at ≥35 weeks of gestation or later who **A,** received ampicillin or **B,** had CRP testing during the first 3 days after birth before and after implementation of clinical examination-based approach for EOS ascertainment. *UCL*, upper control limit; *LCL*, lower control limit.

EOS risk in this population of 0.34 (95% CI, 0.33-0.35) per 1000 live births at our hospital. In neonates with culture-positive EOS, clinical signs of illness developed at birth (2 neonates), between birth and 6 hours (2 neonates), at 24 hours (1 neonate), or after 24 hours of age (2 neonates). No neonate with culture-positive EOS died, required mechanical ventilation, or required inotropic support. In 6 neonates, the causative organism was GBS, including 2 who were born to mothers known to be colonized with GBS, neither of whom had received adequate antibiotic

Table. Cases of EOS in all neonates ≥35 weeks of gestation born since the QI practice change (2015-2019)

Risk factors	Clinical signs	Age at presentation, h	Highest I:T ratio	Highest CRP, md/dL	NSC score, risk factors only	NSC score after clinical exam*	Organism
Gestational age: 35 wk Maternal T_{max}: 37.0 °C ROM: 27 h GBS status: negative Intrapartum antibiotics: none	Respiratory distress requiring CPAP	Birth	0.71	9.6	0.98	20.4	GBS
Gestational age: 39 wk Maternal T_{max}: 39.5 °C ROM: 2.75 h GBS status: positive Intrapartum antibiotic: ampicillin 2.8 h	Respiratory distress requiring CPAP	Birth	0.65	4.2	3.33	66.1	GBS
Gestational age: 39 wk Maternal T_{max}: 37.2 °C ROM: 17 h GBS status: negative Intrapartum antibiotic: none	Respiratory distress requiring CPAP	0.5	0.9	6.8	0.2	4.17	CSF *S parasanguinus* and *S mitis*†
Gestational age: 39 wk Maternal T_{max}: 37.2 °C ROM: 3.5 h GBS status: negative Intrapartum antibiotic: none	Respiratory distress requiring CPAP	6	0.17	4.4	0.16	3.31	GBS
Gestational age: 40 wk Maternal T_{max}: 38.3 °C ROM: 0.4 h GBS status: positive Intrapartum antibiotic: none	New-onset tachypnea	24	0.6	13.6	0.93	4.63	GBS
Gestational age: 39 wk Maternal T_{max}: 37.0 °C ROM: 5.5 h GBS status: unknown Intrapartum antibiotic: none	Seizures	36	0.83	19.0	0.14	0.06	GBS‡
Gestational age: 37 wk Maternal T_{max}: 37.2 °C ROM: 17 h GBS status: unknown Intrapartum antibiotic: none	Fever	64	0.28	8.8	0.39	0.16	GBS§

CPAP, continuous positive airway pressure; *Maternal T_{max}*, highest maternal temperature during labor; *NSC*, Kaiser Neonatal Sepsis Risk Calculator risk score per 1000 live births; *ROM*, rupture of membranes duration.

The study cohort comprised 20 394 births at ≥35 weeks gestation.

*Most severe clinical presentation in first 24 hours after birth.

†Blood culture was negative. The 2 organisms in this case were detected only in liquid broth medium in "very rare numbers," the neonate never had neurologic signs, and CSF studies were reassuring: white blood cell count, 9 cells/mm^3; red blood cell count, 2585 cells/mm^3; protein, 108 mg/dL; glucose, 69 mg/dL.

‡This neonate also grew GBS from CSF culture.

§Probable central line infection. Neonate born to poorly controlled mother with diabetes and required central line placement at 24 hours for intravenous dextrose. Initial CRP was 0.7 md/dL at 23 hours and 1.0 md/dL at 39 hours. New-onset fever at 64 hours of age with central line in place prompting sepsis laboratories and antibiotics.

prophylaxis due to precipitous labor. The non-GBS case was a neonate with a CSF culture growing both *Streptococcus parasanguinus* and *Streptococcus mitis*; the blood culture was sterile. The 2 organisms in this case were detected only in liquid broth medium in "very rare numbers." The neonate had no neurologic signs, and CSF studies were reassuring (**Table**). An indication for lumbar puncture was not apparent, and the case might have been spurious. Two neonates were born to mothers with fever during labor and diagnosed with maternal chorioamnionitis. Retrospectively applying the published Neonatal Sepsis Calculator[3] and using a baseline incidence of 0.6 per 1000, 6 of 7 neonates had a low risk score (<1 per 1000) based on perinatal risk factors alone. The 1 neonate with an elevated risk score (3.3 per 1000) based only on perinatal risk factors was also sick at birth and needed continuous positive airway pressure.

Two neonates readmitted within 7 days after birth had positive blood cultures. One neonate had *Escherichia coli* urosepsis presenting at 6 days of age with poor feeding. The second presented at 6 days of age with hypothermia and had a positive blood culture for *viridans* group *Streptococcus*. The isolate was considered a contaminant by the treating team (time to positivity 30 hours, anaerobic culture negative, and normal CBC and serial CRP), and antibiotics were stopped after 2 days.

Both neonates were term-born to GBS-negative mothers who did not have a fever or chorioamnionitis during labor and were well-appearing throughout the birth hospitalization.

Discussion

Here we describe the ongoing impact of a clinical examination-based approach for EOS management in late preterm and term neonates at our hospital. Over a period of almost 5 years, implementation of this approach has reduced the use of antibiotics by 63% and reduced sepsis laboratory testing by 59%. The change in practice has been sustained with continuing low rates of antibiotic use and sepsis laboratory testing over the most recent ~30 months of evaluation. The current report adds to previous accounts[6,7] of our QI efforts by demonstrating the sustainability and safety of a clinical examination-based approach in clinical care.

There is growing evidence demonstrating the clinical utility and safety of using the clinical examination to guide EOS risk assessment in neonates. Two separate investigations in Italy have reported on the regional implementation of a clinical examination-based approach, with more than 270 000+ neonates at risk for EOS followed.[4,9,10] No significant delays in care or adverse outcomes have been reported. With an additional ~10 000 neonates from the present study, we have now treated more than 20 000 neonates at our institution using a clinical examination-based approach with no adverse clinical outcomes. The 2018 American Academy of Pediatrics guidelines on EOS management in late preterm and term neonates now recognizes a clinical examination-based approach as one of 3 options for identifying infected neonates.[11]

Many neonates with EOS will not be identified based solely on traditional perinatal risk factors or clinical status at birth. As part of the Italian experience, Berardi et al reported that >40% (47 of 108) of EOS cases occurred in neonates without any traditional risk factors, and most of these low-risk neonates did not have clinical signs of illness at birth.[9] Even when perinatal risk factors are optimally interpreted using the multivariate approach of the Neonatal Early-Onset Sepsis Calculator, nearly 40% (20 of 51) of EOS cases had neither a qualifying risk estimate (risk >1 per 1000) nor clinical signs of illness at birth.[3] Our experience is in line with these reports. Of our 7 neonates with EOS, 4 were well-appearing at birth, all of whom had a Neonatal Early-Onset Sepsis Calculator score of <1 per 1000 based on perinatal risk factors. Accordingly, we have implemented a broad safety net as part of our center's clinical examination-based approach, with enhanced monitoring (vital signs and clinical nurse assessment every 4 hours for the first 24 hours then every 8 hours until discharge) for all neonates regardless of risk factors. Systems of newborn care to promote repeated clinical assessments will be an essential component of any center's successful EOS approach, including those using the Neonatal Early-Onset Sepsis Calculator.

Owing to their poor positive predictive value,[11] CBC and CRP tests were no longer routinely recommended as part of our clinical examination-based approach to assess EOS risk and determine the need for starting antibiotics. As a result, a large reduction in CRP testing was observed at our hospital in the post-QI period. Nonetheless, CRP testing remained higher than antibiotic use in the post-QI period, suggesting that some clinicians may have continued to perform such testing to "screen" for infection. Similarly, for the 7 neonates with EOS, CBC and CRP analyses were performed after the onset of clinical signs of illness but before the initiation of antibiotics in 2 neonates and thus might have factored into the decision to start antibiotics. Both cases occurred in the second year of the QI project, when comfort was still being gained without the use of laboratory testing. We were unable to evaluate for which other specific clinical scenarios or populations (ie, NICU admissions) laboratory testing was performed.

No apparent adverse clinical outcomes or safety signals occurred in neonates with EOS during the post-QI period. Two of the 7 neonates with EOS presented after 24 hours of age and would not have been identified at birth by any current approach recommended in the American Academy of Pediatrics guidelines, highlighting the importance of ongoing clinical vigilance throughout the newborn period. The duration for which neonates should be monitored in the hospital before qualifying for discharge is not known, and any early discharge will need to carefully consider the risk of sepsis in the neonate along with the family's medical literacy and access to medical care. Excluding 1 likely spuriously positive blood culture, 1 neonate (5 per 100 000 live births) in the post-QI period was readmitted in the first 7 days after birth for culture-positive urosepsis. We did not have comparative data from the pre-QI period, but the rate of readmission was low and comparable with a previous report.[3] Although most neonates born at our hospital would be readmitted to our hospital for any problems in the newborn period, we cannot exclude readmission to other hospitals in the area.

Our EOS approach leveraged the unique care system and resources at our center and represents only one potential way to set up a clinical examination-based strategy. The optimal strategy in terms of frequency and timing of assessments, who performs the assessments, what clinical signs to prioritize, and availability of in-house physicians remain to be established. In addition, local obstetric care practices and background incidence of EOS are important components of any approach. For example, the centers that have implemented a clinical examination-based approach all use universal maternal GBS screening and intrapartum antibiotic prophylaxis, with resulting low background rates of EOS.[9] Each center will need to consider its unique care setup, resource allocation, and patient population to individualize its approach to identifying EOS. The experiences described to date can serve as a starting framework.

In summary, a clinical examination-based approach for the management of EOS in late preterm and term neonates has been a sustainable and safe strategy at our hospital, resulting in reduced sepsis laboratory testing and antibiotic use. Any successful approach for EOS will require systems of care that enable repeated clinical assessments in neonates. ■

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Reprint requests: Adam Frymoyer, MD, Department of Pediatrics, Stanford University, 750 Welch Rd, Suite 315, Palo Alto, CA 94304. E-mail: frymoyer@stanford.edu

Data Statement

Data sharing statement available at www.jpeds.com.

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