RESEARCH ARTICLE

Management of Chorioamnionitis-Exposed Infants in the Newborn Nursery Using a Clinical Examination–Based Approach

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ABSTRACT

BACKGROUND: Antibiotic use in well-appearing late preterm and term chorioamnionitis-exposed (CE) infants was reduced by 88% after the adoption of a care approach that was focused on clinical monitoring in the intensive care nursery to determine the need for antibiotics. However, this approach continued to separate mothers and infants. We aimed to reduce maternal-infant separation while continuing to use a clinical examination–based approach to identify early-onset sepsis (EOS) in CE infants.

METHODS: Within a quality improvement framework, well-appearing CE infants ≥35 weeks' gestation were monitored clinically while in couplet care in the postpartum unit without laboratory testing or empirical antibiotics. Clinical monitoring included physician examination at birth and nurse examinations every 30 minutes for 2 hours and then every 4 hours until 24 hours of life. Infants who developed clinical signs of illness were further evaluated and/or treated with antibiotics. Antibiotic use, laboratory testing, and clinical outcomes were collected.

RESULTS: Among 319 initially well-appearing CE infants, 15 (4.7%) received antibiotics, 23 (7.2%) underwent laboratory testing, and 295 (92.5%) remained with their mothers in couplet care throughout the birth hospitalization. One infant had group B *Streptococcus* EOS identified and treated at 24 hours of age based on new-onset tachypnea and had an uncomplicated course.

CONCLUSIONS: Management of well-appearing CE infants by using a clinical examination–based approach during couplet care in the postpartum unit maintained low rates of laboratory testing and antibiotic use and markedly reduced mother-infant separation without adverse events. A framework for repeated clinical assessments is an essential component of identifying infants with EOS.

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Chorioamnionitis is diagnosed clinically during labor in 3% to 6% of mothers.[1–3] Concerns about the risk of early-onset sepsis (EOS) have led to recommendations of routine laboratory testing and empirical antibiotics in all chorioamnionitis-exposed (CE) infants.[4,5] However, in the current era of maternal group B *Streptococcus* (GBS) screening and intrapartum antibiotic prophylaxis (IAP), the risk of culture-positive EOS in CE late preterm and term infants is low (1–7 cases per 1000 infants) and even lower in infants who are clinically well-appearing at birth.[2,3,6,7] Consequently, empirical antibiotic approaches in CE infants result in antibiotic exposure for a high number of well-appearing, uninfected infants.[2,3,8,9] Accordingly, updated approaches to management of infants at risk for EOS have been advocated.[10–12]

In 2 recent reports, researchers used the Neonatal Sepsis Calculator (NSC), which is an EOS prediction model based on clinical examination and 5 perinatal risk factors (highest maternal temperature, GBS status, duration of rupture of membranes, and the nature and timing of IAP), to guide the need for antibiotics demonstrated >40% reductions in empirical antibiotic use.[13,14] Two groups from Italy used serial clinical examinations alone to identify EOS in at-risk infants and demonstrated significant reductions in antibiotic use.[15,16] Neither approach was associated with adverse events.

We previously implemented a care approach for well-appearing late preterm and term infants who were CE, focusing on a clinical examination to determine the need for antibiotics (phase I). The initial quality improvement (QI) effort safely led to an 88% reduction in antibiotic use.[17] However, the approach continued to separate mother and infant because infants were admitted to a level II NICU for the first 24 hours after birth. The separation of mother and infant has potential negative effects on establishment of breastfeeding, thermoregulation, and promotion of bonding.[18,19] In the second phase of our QI effort, we focused on clinically monitoring well-appearing CE infants during couplet care in the postpartum unit. Our aim was to reduce maternal-infant separation while continuing to use a clinical examination–based approach to identify infants with EOS.

METHODS

Context

Lucile Packard Children's Hospital Stanford is a freestanding, academic, tertiary care children's hospital that offers obstetric and neonatal services (~4500 deliveries annually). Newborn services include a postpartum unit providing couplet care (ie, newborn nursery), level II NICU, and level III/IV NICU.

Maternal chorioamnionitis is diagnosed by the obstetric team and is treated with intravenous broad-spectrum antibiotics. An in-house neonatal hospitalist is available 24 hours per day to attend all high-risk deliveries, including those infants who were exposed to chorioamnionitis.

Before the first phase of our QI intervention, institutional practice for well-appearing CE infants who were ≥34 weeks' gestation included admission to the level II NICU and empirical treatment with ampicillin and gentamicin. Infants had sepsis laboratory testing that included a complete blood count, serial C-reactive proteins (CRPs), and a blood culture (single aerobic tube with a minimum of 1 mL of blood). Antibiotic duration was determined by the treating physician on the basis of clinical presentation, laboratory evaluation, and blood culture results. Infants remained in the NICU for the duration of the antibiotic treatment.

Phase I Intervention (March 2015–July 2016)

A multidisciplinary team of nurses and physicians developed a management approach based on the use of serial clinical examinations to determine need for antibiotics and/or laboratory evaluation for well-appearing CE infants who were ≥34 weeks' gestation.[17] The neonatal hospitalist attended all deliveries of CE infants and provided an initial clinical assessment. Well-appearing infants remained with their mothers for skin-to-skin care for the first 2 hours after birth and were then admitted to the level II NICU for ongoing clinical monitoring. Laboratory testing and antibiotic treatment were not performed unless clinical signs of illness developed. Infants who remained well appearing during the first 24 hours after birth were transferred to couplet care in the postpartum unit. 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.

During the phase I time period, a concurrent change in practice for newborn infants admitted directly to couplet care in the postpartum unit occurred, whereby all infants received a nurse examination with vital signs every 4 hours for the first 24 hours of life, regardless of perinatal risk factors, knowing that even low-risk infants can become ill. In addition, sepsis laboratory testing was no longer routinely recommended in any well-appearing infant.

Phase II Intervention (August 2016–August 2017)

To reduce maternal-infant separation, we began to admit well-appearing CE infants who were ≥35 weeks' gestation directly to couplet care in the postpartum unit beginning in August 2016 (phase II). Our phase I experience was valuable in providing the local evidence for our approach and promoting buy-in from nurses, physicians, and obstetric and neonatal leadership. As part of phase II implementation, all postpartum nurses received in-service education on signs of EOS and the importance of repeated clinical assessments. In addition, in the month before implementation, 3 CE infants were piloted according to our phase II approach.

During the phase II approach, a neonatal hospitalist continued to attend deliveries and determine initial clinical status. A level II nursery nurse stayed with infants in the delivery room and performed serial assessments every 30 minutes for the first 2 hours after birth. Infants that remained well-appearing then stayed with their mothers for couplet care in the postpartum unit. In couplet care, infants were assigned a nurse staffing ratio of 1:3. All infants had a nurse examination with vital signs every

4 hours for the first 24 hours of life. During phase II, infants 34 weeks' gestation continued to be admitted to the level II NICU for prematurity and monitored clinically as in phase I.

In both phases, infants who were symptomatic at birth and those who developed clinical signs of illness after birth concerning for sepsis were evaluated by the physician for potential laboratory testing and antibiotic treatment. Criteria for laboratory testing, antibiotic treatment, or admission to the level II NICU for additional monitoring of symptomatic infants were left to the attending physician's discretion.

Study of the Intervention

Infants ≥34 weeks' gestation born to mothers with a diagnosis of chorioamnionitis were identified through a query of the electronic health record, and an in-depth chart review was performed. Data were maintained in Research Electronic Data Capture.[20]

Measures

Outcome measures included the percentage of infants that remained in couplet care throughout the hospitalization and the percentage that received antibiotic treatment and/or sepsis laboratory evaluation. Cases of culture-positive sepsis and culture-negative clinical sepsis (defined as a negative blood culture result and ≥5 days of antibiotics) were also evaluated. Additional collected metrics included demographic information, perinatal risk factors, birth history, exclusive breastfeeding at discharge, the infant's clinical course, and readmission within 30 days.

To examine the impact of our QI initiative, the percentage of all inborn infants ≥34 weeks' gestation at our hospital who had a sepsis laboratory evaluation (defined by measurement of CRP) or treatment with antibiotics (defined by receipt of ampicillin) within the first 3 days after birth was tracked. In addition, all cases of culture-positive EOS during the QI time period were reviewed.

To compare our approach with the published NSC, the estimated risk of EOS was calculated retrospectively for each infant at birth on the basis of perinatal risk factors and after incorporating the most severe clinical presentation during the first 24 hours after birth.[21–23]

A background EOS risk of 0.6 per 1000 was used. Infants were grouped into NSC risk categories of <0.65, 0.65 to 1.54, and >1.54 per 1000 based solely on perinatal risk factors at birth.[22] After incorporating clinical presentation into the NSC risk, the number of infants exceeding an antibiotic treatment threshold risk score of 3 per 1000 was compared with actual antibiotic use in the first 24 hours.[13]

Analysis

Categorical data were summarized as count (percent), whereas continuous data were summarized as mean (SD) or median (interquartile range). Comparisons between groups were made by using the χ^2 test or 2-sided t test for categorical and continuous data, respectively. A control chart of the percentage of infants ≥34 weeks' gestation who received ampicillin or had CRP measured during the first 3 days after birth was constructed with 3 SD control limits. A shift in the center line was considered at ≥8 consecutive points, either all above or all below the mean. In addition, an interrupted time series analysis was performed to model the level and trend of both the monthly antibiotic exposure and CRP use pre- and post-QI implementation. Autocorrelation was tested by using the Durbin–Watson statistic. Statistical significance was set at $P < .05$. Data were analyzed by using Stata 13 (Stata Corp, College Station, TX).

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

Study Population

During the phase II study period, there were 4577 live births ≥34 weeks' gestation. Of 339 CE infants, 319 infants (94.1%) were well-appearing at birth and included in the primary analysis. Thirteen infants (3.8%) who were clinically ill at birth and 7 infants (2.1%) who had a known congenital anomaly requiring NICU admission were excluded (Fig 1). Well-appearing infants at birth were similar in demographics to those excluded (Table 1), with the exception of late preterm status ($P = .002$).

Outcomes of Initially Well-Appearing CE Infants

Among 319 initially well-appearing infants born during phase II, 15 (4.7%) received antibiotics, 23 (7.2%) underwent sepsis laboratory testing, and 295 (92.5%) remained in couplet care with mother

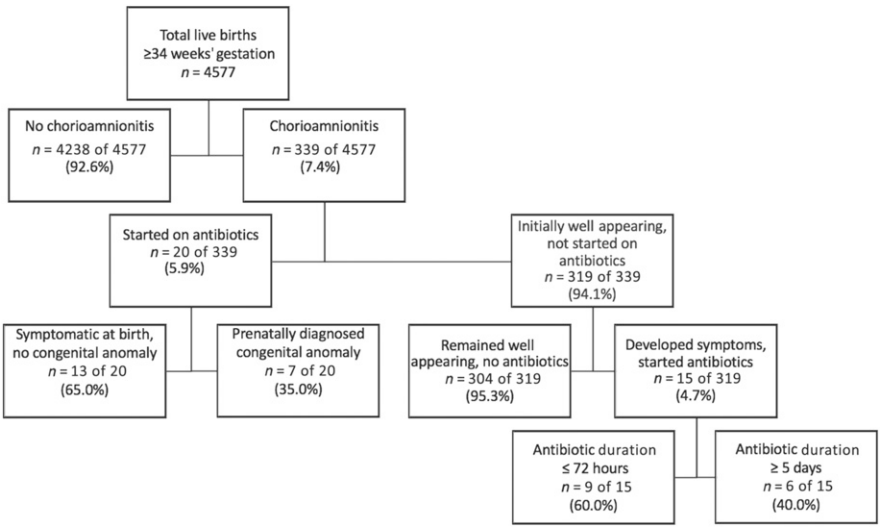

FIGURE 1 Flow diagram of infants born during the quality improvement phase II study period.

TABLE 1 Characteristics of Phase II CE Infants Categorized by Clinical Appearance at Birth

	Well Appearing ($n = 319$)	Symptomatic or Congenital Anomaly ($n = 20$)	P
Birth wt, kg	3.35 (3.06–3.66)	3.16 (2.70–3.77)	.23
Late preterm, *n* (%)	8 (2.5)	3 (15.0)	.002
Girls, *n* (%)	142 (44.5)	7 (35.0)	.41
Max maternal temperature, °C	38.4 (38.1–38.8)	38.3 (38–38.8)	.61
ROM ≥18 h, *n* (%)	81 (25.4)	6 (30.0)	.65
Maternal GBS status, *n* (%)			.11
Negative	251 (78.7)	12 (60.0)	
Positive	57 (17.9)	6 (30.0)	
Unknown	11 (3.4)	2 (10.0)	
GBS-specific intrapartum antibiotics ≥2 h before birth, *n* (%)	56 (17.6)	8 (40.0)	.13
Broad-spectrum intrapartum antibiotics ≥2 h before birth, *n* (%)	109 (34.2)	8 (40.0)	.60

All data are median (interquartile range) or number of patients (%). Max, maximum during labor; ROM, rupture of membranes.

throughout the birth hospitalization. For comparison, rates of these outcomes before and during phase I of the QI study period are shown in Table 2.

Fifteen initially well-appearing infants (4.7%) who developed signs concerning for sepsis during the birth hospitalization received sepsis laboratory testing and antibiotic treatment. Only 1 infant had culture-positive sepsis. He was born at 40 weeks' gestation to a GBS-positive mother with a maximum intrapartum temperature of 38.3°C after rupture of membranes for <1 hour. The mother did not receive intrapartum antibiotics. He developed tachypnea at 24 hours of age. At that time, the CRP was 13.6 mg/dL, the immature to total neutrophil ratio was 0.7, and the blood culture yielded GBS. Tachypnea resolved shortly after antibiotic treatment, and the subsequent course was uncomplicated.

The remaining 14 infants who received antibiotics all had negative blood culture results; 9 infants (2.8%) were treated with antibiotics for ≤72 hours and 5 infants (1.6%) for ≥5 days. According to the NSC clinical definitions, 12 had an "equivocal" presentation, whereas 2 became "clinically ill." One of the latter was found apneic and cyanotic while prone during skin-to-skin care at 31 hours of age. The infant was resuscitated, required intubation and ventilation for 5 hours, and received therapeutic hypothermia for 72 hours for neuroprotection. He remained clinically well-appearing thereafter. The event was suspected to represent a sudden unexpected postnatal collapse due to positional asphyxia,[24–26] but a full antibiotic treatment course was administered. The second clinically ill infant presented with a heart murmur in the newborn nursery and was diagnosed postnatally with moderate to severe pulmonary stenosis. After admission to the NICU, he developed apparent shock at 70 hours of age, and antibiotics were discontinued after sepsis was excluded. No infants were readmitted within our network of hospitals with culture-positive sepsis within 30 days after discharge.

Retrospectively calculated NSC risk scores at birth of <0.65, 0.65 to 1.54, and >1.54 per 1000 were seen in 72 (22.6%), 116 (36.4%), and 131 (41.1%) phase II study infants, respectively. The NSC risk score at birth in the sole case of GBS sepsis was 0.93 per 1000. After incorporating clinical presentation into the NSC risk scores for initially well-appearing CE infants from both phase I and II ($n = 596$), there was a 95% concordance between the NSC antibiotic recommendations (risk estimate >3 per 1000) and actual antibiotic use during the first 24 hours (Table 3).

TABLE 2 Antibiotics, Laboratory Testing, and Clinical Care Outcomes in Well-Appearing CE Infants

	Pre-QI[a]	Phase I $n = 277$	Phase II $n = 319$
Antibiotics, *n* (%)	All (100)	32 (11.6)	15 (4.7)
Sepsis laboratory testing, *n* (%)	All (100)	48 (17.3)	23 (7.2)
Couplet care throughout hospitalization, *n* (%)	0 (0)	0 (0)	295 (92.5)[b]
Exclusive breastfeeding at discharge, *n* (%)	—	131 (47.3)	161 (50.5)

—, not applicable.
[a] Represents historical institutional standard of care, which included empirical antibiotics, sepsis laboratory testing, and admission to level II NICU for any infant who was CE.
[b] $P < .001$ versus phase I.

Outcomes in All Infants

The percentage of all inborn infants at our hospital ≥34 weeks' gestation exposed to ampicillin (Fig 2A) decreased from 12.3% in the pre-QI period ($n = 422$ of 3434) to 5.1% in the post-QI period ($n = 627$ of 12 208; $P < .001$). Interrupted time series analysis revealed a significant change in the level of ampicillin exposure in the post-QI period (−6.6%; $P < .001$). No significant trends in ampicillin exposure within the pre-QI and post-QI period were found. CRP use in infants declined from 16.6% in the pre-QI period to 7.6% ($P < .001$) in the post-QI period (Fig 2B). A significant change in the level of CRP use was also found when using interrupted time series analysis (−7.5%; $P < .001$). No significant trends in CRP use within the pre-QI and post-QI period were found.

Over the time period of our QI effort (2015–2017), 5 infants have had culture-positive EOS among 12 901 infants ≥34 weeks gestation born at our hospital. This represents an overall EOS risk of 0.39 (95% confidence interval 0.2–0.9) per 1000 live births. In all cases, the causative organism was GBS (Supplemental Table 4).

TABLE 3 Comparison of Antibiotic Use in the First 24 Hours After Birth and the Antibiotic Treatment Recommendation of the NSC in Initially Well-Appearing CE Infants Born During Phase I and II of the QI Study Period ($N = 596$)

Antibiotics Recommended per NSC[a]	Received Antibiotics During First 24 h After Birth	
	No, *n* (%)	Yes, *n* (%)
No	538 (90.3)	5 (0.8)
Yes	25 (4.2)	28 (4.7)

[a] NSC risk score >3 per 1000 after incorporating severest clinical presentation during the first 24 h after birth.

One infant was born to a mother with chorioamnionitis (described above) and 1 was a late preterm with prolonged rupture of membranes. All 5 infants had NSC risk scores based on perinatal risk factors of <1 per 1000 and were identified based on their clinical presentation at birth (1 infant), between birth and 24 hours (2 infants), or after 24 hours of age (2 infants).

DISCUSSION

As previously reported, phase I of a hospital-wide QI effort that was focused on the use of clinical monitoring in a level II NICU to determine the need for antibiotic treatment rather than reliance on an empirical antibiotic approach resulted in an 88% reduction in antibiotic use in initially well-appearing late preterm and term CE infants. However, this phase I approach separated infants from their mothers. In phase II reported here, clinical monitoring was shifted from the level II NICU to the postpartum maternity unit and resulted in 92.5% of CE infants remaining in couplet care. The rate of antibiotic use remained low (4.7%), and no adverse clinical outcomes were identified.

EOS management ideally stratifies infants to target antibiotic use for those at highest risk. Chorioamnionitis has been identified as a major risk factor for EOS, leading to recommendations for empirical evaluation and antibiotic treatment of all CE infants.[4,5] Before phase I of our QI initiative, infants were managed accordingly at our institution. However, the strength of this association is driven largely by the high risk of EOS in extremely preterm infants born to women with chorioamnionitis.[27] In late preterm and term infants, with the widespread adoption of maternal GBS screening and IAP, the incidence of EOS is low, even in those with chorioamnionitis.[2,3,6,7,13,21] As such, our center ended a strategy of empirical evaluation and antibiotic treatment of all CE infants in early 2015.[17] The low rate of EOS among CE infants reported by others[2,3,6,7] is consistent with our observation of only 1 case of culture-positive EOS in 596 CE infants (EOS risk 1.7 [95% confidence interval 0.3–10] per 1000) since implementation of this QI project.

Because of the frequent diagnosis of chorioamnionitis during labor, management approaches in CE infants have a major impact on the rate of medical interventions in the late preterm and term population.[1–3] After our QI practice changes, reductions in laboratory testing and antibiotic exposure were evident when looking across the entire cohort of late preterm and term infants (Fig 2). Our reductions in laboratory testing and antibiotic exposure are similar to those reported after implementation of serial examinations[15] or use of the NSC[13,14] at other centers. Collectively, these experiences indicate that substantial reductions in interventions for infants traditionally deemed at high risk for EOS can be achieved without adverse events.

Our QI experience reveals the necessity for repeated clinical evaluations to ensure timely identification of infants who develop EOS. The 1 patient who had culture-positive EOS in our CE cohort was well-appearing from birth until 24 hours of age and had an NSC-estimated EOS risk of 0.93 per 1000 at birth. The other 4 patients who had culture-positive EOS in this period had not been exposed to chorioamnionitis; none had NSC risk estimates >1 per 1000 at birth and all were identified on the basis of clinical examination (one at birth). Researchers at other centers have reported similar observations.[15,16] Berardi et al[16] reported 4 cases of culture-positive EOS among 10 569 births, all of whom were identified through clinical examination in the first 6 hours of life.

In descriptions of NSC implementation, Kuzniewicz et al[13] reported 10 cases of culture-positive EOS (excluding 2 cases of apparent asymptomatic transient bacteremia) among 56 261 births. Six patients were ill at birth; the other 4 had NSC risk estimates at birth <0.3 per 1000 and developed signs of illness between 5 and 20 hours of age.[13] Dhudasia et al[14] reported 4 cases of culture-positive EOS in a cohort of 11 782 births; of these, 1 patient was ill at birth, 1 had a low NSC risk estimate (0.3 per 1000) at birth but developed signs of infection at 36 hours of age, and 2 were treated with antibiotics empirically because of elevated EOS risk estimates at birth (11.45 and 3.41 per 1000, respectively) and never developed signs of illness. These reports reveal the central role of serial clinical evaluations in identifying infected infants even when using the NSC. The large influence that clinical examination has on the NSC treatment recommendations is further highlighted in our cohort by the 95% concordance between actual antibiotic use and the antibiotic recommendations of the NSC (Table 3).

In phase II, we successfully reduced maternal-infant separation in CE infants. Potential benefits include promotion of bonding, reduced maternal stress, better thermoregulation, and establishment of breastfeeding.[18,19] The rate of exclusive breastfeeding at discharge in our CE infants (50.5%) was similar to the rate for all infants in our newborn nursery (56%) and among CE infants at another institution (46.1%),[28] but no improvement in breastfeeding was achieved between phase I and phase II of this project.

Our QI study represents the experience of a single institution and is limited by the small sample size. In addition, generalizability of our approach may be limited to hospitals that can provide similar resources for the clinical monitoring of infants. Our institution

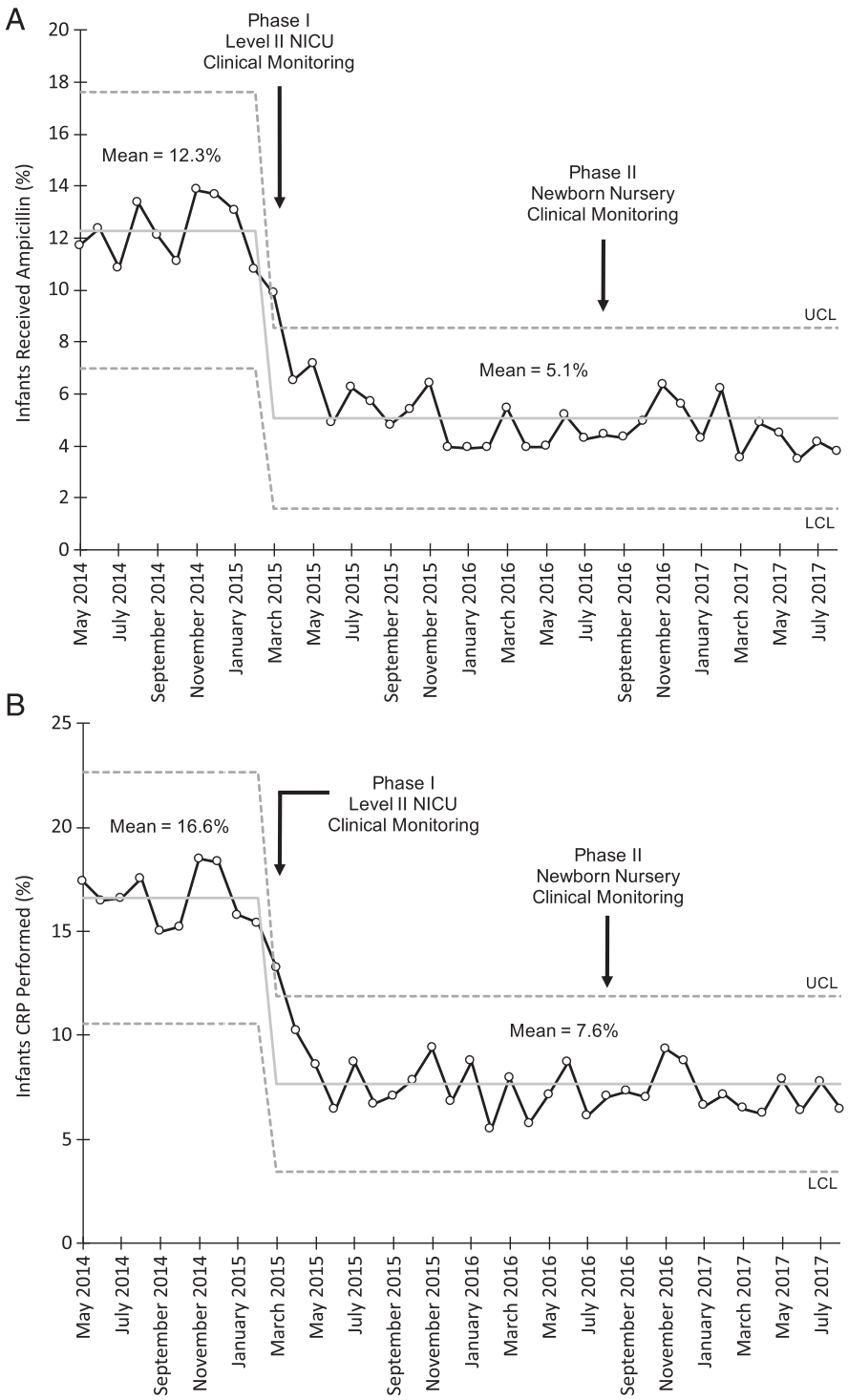

FIGURE 2 Percentage of all inborn infants ≥34 weeks' gestation who (A) received ampicillin or (B) had CRP measured during the first 3 days surrounding the practice change. The median (range) number of live births per month was 347 (303–404). UCL, upper control limit; LCL, lower control limit.

has an in-house neonatal hospitalist who attends all deliveries of CE infants and is readily available to evaluate infants if clinical signs develop. Nurse staffing ratios of 1:3 couplets in the newborn nursery for all CE infants allowed for frequent clinical assessments. We have also expanded close clinical monitoring for not only CE infants, but all infants regardless of perinatal risk factors, knowing that even infants initially deemed low risk can develop EOS. Thresholds to start antibiotics based on clinical examination were left to the discretion of the physician, potentially leading to practice variation.

The optimal approach to monitoring infants for sepsis in the neonatal period is unknown because questions remain regarding the ideal frequency of clinical assessments, duration of monitoring, and which clinical signs matter most. Neither risk factors nor physical examination at birth will identify all infants who will develop sepsis, so vigilance in the form of serial examinations is necessary for all infants no matter what ascertainment strategy is adopted.

CONCLUSIONS

Management of well-appearing CE infants by using a clinical examination–based approach during couplet care in the postpartum unit maintained low rates of sepsis laboratory testing and antibiotic use and markedly reduced mother-infant separation, without adverse events. A framework for repeated clinical assessments is an essential component of identifying infants with EOS.

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