Chorioamnionitis and Management of Asymptomatic Infants ≥35 Weeks Without Empiric Antibiotics

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abstract

BACKGROUND AND OBJECTIVE: Management of asymptomatic infants ≥35 weeks' gestation born to mothers with chorioamnionitis remains controversial, with many clinicians considering the need for changes to the current guidelines. The study objective was to evaluate the outcomes of asymptomatic chorioamnionitis-exposed neonates without the use of immediate empirical antibiotics.

METHODS: A retrospective data review was conducted from May 2008 to December 2014, including asymptomatic infants ≥35 weeks' gestation with a maternal diagnosis of clinical chorioamnionitis.

RESULTS: A total of 240 asymptomatic infants with chorioamnionitis exposure were identified. The majority of asymptomatic chorioamnionitis-exposed infants, 162 (67.5%), remained well in the mother-infant unit with a median stay of 2 days. There were 78 (32.5%) infants admitted to the NICU and exposed to antibiotics due to abnormal laboratory data or development of clinical symptoms. Of those infants admitted to the NICU, 19 (24%) received antibiotics for <72 hours, 47 (60%) were treated for culture-negative clinical sepsis, and 12 (15%) for culture-positive sepsis, with a median NICU stay of 7 days.

CONCLUSIONS: Nonroutine use of empirical antibiotics in asymptomatic newborns ≥35 weeks' gestation with maternal chorioamninonitis prevented NICU admission in two-thirds of these infants. This prevented unnecessary antibiotic exposure, increased hospitalization costs, and disruption of mother-infant bonding and breastfeeding. Laboratory evaluation and clinical observation without immediate antibiotic administration may be incorporated into a management approach in asymptomatic chorioamnionitis-exposed neonates. Additional studies are needed to establish the safety of this approach.

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WHAT'S KNOWN ON THIS SUBJECT: Current guidelines recommend empirical antibiotic treatment of all infants exposed to maternal chorioamnionitis regardless of clinical symptoms. Many clinicians are now advocating for change in this management approach in asymptomatic well-appearing infants.

WHAT THIS STUDY ADDS: This study presents a management strategy that eliminates immediate empirical antibiotic therapy for asymptomatic chorioamnionitis-exposed infants ≥35 weeks' gestation. Intensive care admission, disruption in mother-infant bonding, antibiotic exposure, and increased hospitalization costs were avoided in a majority of infants.

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Clinical chorioamnionitis is a complication of pregnancy defined as infection and inflammation of fetal membranes. Chorioamnionitis is reported in 3% to 10% of term pregnancies[1] and has historically caused concern for neonatal early-onset sepsis (EOS).[2] Chorioamnionitis is a clinical challenge that lacks a consistent approach to diagnosis and can be highly variable in practice. Isolated maternal fever, caused by infectious and noninfectious[3,4] sources, may be the only diagnostic trigger. Clinical suspicion is often formed with only 1 sign or symptom that may not indicate a true intrauterine infection. Efforts are being made to improve the diagnostic accuracy and management of maternal chorioamnionitis.[4] Once chorioamnionitis is diagnosed, however, it significantly impacts the subsequent management of the newborn.

Rates of neonatal EOS have dramatically declined since the introduction of maternal intrapartum antibiotic prophylaxis (IAP).[5,6] Chorioamnionitis is a previously identified risk factor for EOS,[7] but rates remain low even in chorioamnionitis-exposed infants.[1,2,8] Despite low risks, current recommendations from the American Academy of Pediatrics (AAP) and the Centers for Disease Control and Prevention (CDC)[9,10] advocate a limited laboratory evaluation and immediate empirical antibiotic therapy in all chorioamnionitis-exposed infants. Diagnosis of maternal clinical chorioamnionitis at some institutions involves neonatal admission to intensive care to administer intravenous antibiotics. This management interferes with mother-infant bonding and successful breastfeeding, prolongs the length of stay, and increases overall health care costs. These infants are exposed to broad-spectrum antibiotics that have potential adverse effects.[11–13]

Controversy exists regarding the management of asymptomatic newborns as a result of inconsistencies in chorioamnionitis diagnosis and its impact on neonates in an era of low EOS risk. The lack of consensus has led to variability in the use of empirical antibiotics in newborns at risk for EOS both nationally and internationally.[14] Recent studies reveal only a minority of institutions continue to strictly follow recommended AAP/CDC guidelines to administer prophylactic antibiotics.[15] Research and discussion point toward the need to abandon previous guidelines to treat all well-appearing chorioamnionitis-exposed infants and instead evaluate alternative approaches.[16,17]

At LAC+USC Medical Center, it has been the guideline to complete a laboratory evaluation in asymptomatic newborn infants ≥35 weeks' gestation born to mothers with clinical chorioamnionitis without administration of empirical antibiotics.[18] The objective of this study was to evaluate clinical outcomes of asymptomatic chorioamnionitis-exposed late preterm and term infants by using our alternative guideline.

METHODS

Study Design

This retrospective cohort study included infants and mothers who delivered at LAC+USC between May 1, 2008 and December 31, 2014. The Institutional Review Board at LAC+USC approved the study. Newborns ≥35 weeks' gestational age born with a maternal diagnosis of chorioamnionitis were identified from paper medical records. Infant and mother were included if the chart had a documented diagnosis of chorioamnionitis made at the discretion of the obstetrician before or up to 4 hours after delivery[4] and the mother received intravenous antibiotic treatment accordingly after diagnosis. Obstetrical diagnosis was based on the presence of maternal fever plus additional criteria, including maternal leukocytosis, maternal or fetal tachycardia, uterine tenderness, or purulent amniotic fluid. Infants included were initially asymptomatic at birth and admitted to the mother-infant unit. Infants were excluded if they were immediately admitted to the NICU or had missing medical records.

Data Collection

Data were extracted from paper charts, the maternal database (QuadraMed Affinity, version GM12 Dev-3, Reston, VA), and the neonatal database (Neonatal Information System, Medical Data Systems, version 3 and 5, Rosemont, PA). Data collected included maternal age, race, mode of delivery, duration of rupture of membranes, highest maternal temperature, maternal group B *Streptococcus* (GBS) status, and use of intrapartum antibiotics. Neonatal demographics extracted were gestational age, birth weight, and Apgar scores. Laboratory data collected included complete blood count (CBC) with manual differential count, high-sensitivity C-reactive protein (hsCRP; mg/dL), blood culture, and cerebrospinal fluid (CSF) analysis. Placental pathology reports and neonatal clinical outcomes were recorded.

Management of Asymptomatic Neonates ≥35 Weeks' Gestational Age

All infants ≥35 weeks' gestation born with chorioamnionitis exposure with any signs or symptoms of sepsis were immediately transferred to the NICU for antibiotic therapy. Asymptomatic infants were observed with usual care in the mother-infant unit, including routine examinations and vital signs every 4 hours, with a NICU clinician immediately alerted for changes in clinical status. Serial laboratory data were obtained. Empirical antibiotics were not

administered. Initial blood culture, CBC, and hsCRP were obtained between birth and 6 hours of life. Repeat CBC and hsCRP were collected at 12 to 24 hours and at 24 to 48 hours of life. The hsCRP was measured by using immune turbidimetric assay with a threshold of 10 mg/dL (Roche Diagnostics, Indianapolis, IN). Based on updated institution guidelines, asymptomatic infants with normal laboratory studies (a white blood cell [WBC] count of 5 000–30 000 mm^{-1}, band counts of <10%, and hsCRP of <10 mg/dL) are observed for signs and symptoms of sepsis for 48 hours. Asymptomatic infants with ≥1 of 5 laboratory criteria (a WBC count of >30 000 mm^{-1} or <5000 mm^{-1}, band counts of >24%, hsCRP of >10 mg/dL, and/or positive blood cultures) were transferred to the NICU, and antibiotic therapy was initiated.[18] The immature neutrophil to total neutrophil ratio was not used because our laboratory reports only band count range, and an accurate ratio cannot be calculated. Lumbar puncture was performed for clinical sepsis, a positive blood culture, or persistent laboratory abnormalities. A decision was made at the discretion of the attending neonatologist to treat with antibiotics beyond 48 hours if clinical symptoms persisted or if laboratory data remained abnormal.

Data Analysis

Nominal variables were presented as percentages and continuous data as means and SDs or median and 25th to 75th percentiles, depending on distribution normality. Categorical variables were compared between groups with the χ^2 test. Differences in continuous variables were compared by 2-tailed Student's *t* tests or Mann–Whitney *U* test where appropriate. Logistic regression was used to assess the association between histologic chorioamnionitis (HCA) and NICU admission. The result was presented as an odds ratio with 95% confidence interval. Data were analyzed by using Stata Statistical Software: Release 14 (Stata Corp, College Station, TX). Statistical significance was set at $P < .05$.

RESULTS

Maternal and Neonatal Demographics

A total of 5637 infants were born ≥35 weeks' gestation during the study period with 364 infants exposed to maternal chorioamnionitis (6.5%). There were 122 chorioamnionitis-exposed infants requiring direct NICU admission who were excluded from the study (Fig 1) with 110 (90%) infants admitted with a diagnosis of rule out sepsis. Twelve infants were directly admitted for reasons unrelated to sepsis. Clinical symptoms were documented in 55 (45%) of the 122 infants directly admitted. Respiratory distress was the prominent symptom in 52 (95%) of these symptomatic infants. Antibiotic exposure was documented in 106 (87%) of the 122 directly admitted infants.

There were 242 asymptomatic chorioamnionitis-exposed infants ≥35 weeks' gestation admitted to the mother-infant unit who qualified for this study. Only 240 infants were included in the analysis because 2 had no available laboratory information. Due to abnormal laboratory data, a positive blood culture, or the onset of clinical signs of sepsis, 78 (32.5%) infants were subsequently admitted to the NICU, and 162 (67.5%) infants remained well with a routine newborn course in the mother-infant unit (Fig 1). Infants did notsignificantly differ in birth weight, gestational age, sex, or Apgar scores between NICU-admitted and nonadmitted infants. Maternal GBS status was positive in 34 (14%) mothers. GBS-positive mothers were started on IAP as soon as possible, and 29 of 34 (85%) received

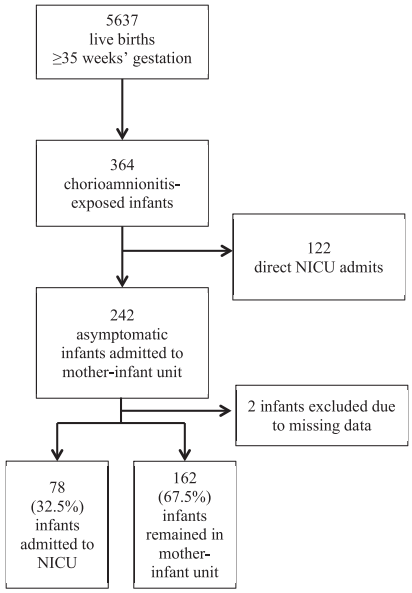

FIGURE 1
Outline of the study population.

treatment ≥4 hours before delivery. All mothers with chorioamnionitis had documented treatment with antibiotics accordingly; however, only half of the mothers, 121 (50%), received antibiotics ≥4 hours before delivery. There were no significant differences in maternal age, race, mode of delivery, hours of membrane rupture, GBS status, or exposure to intrapartum antibiotics between infants requiring NICU admission and those that did not (Table 1). The highest recorded maternal temperatures ranged from 98.5 to 103.2°F. Twenty-five mothers (10%) received a diagnosis of clinical chorioamnionitis without documentation of a fever, with the highest recorded temperatures <100.4°F. The mean maximum temperature was significantly higher in mothers of neonates requiring NICU admission compared with those not admitted (101.2°F vs 100.9°F; $P = .04$). With the exception of fever, additional criteria for the diagnosis of chorioamnionitis were only documented positive in a minority of mothers, including maternal leukocytosis (38%), maternal tachycardia (37%), or fetal tachycardia (33%). Only 4 mothers

had documentation of uterine tenderness, and only 1 with foul smelling fluid.

There were 223 infants with available placental pathology reports. HCA was demonstrated in 52% (115/223) of chorioamnionitis-exposed infants. The diagnosis of HCA was significantly higher in infants requiring NICU admission (64% vs 46%; odds ratio, 2.1; 95% confidence interval, 1.18–3.75; $P = .011$) (Table 1). Positive blood cultures did not differ between infants with HCA and those without (3 of 108 [3%] vs 9 of 105 [9%], $P = .08$).

TABLE 1 Maternal and Neonatal Demographics

	NICU Admissions, $N = 78$	Nonadmissions, $N = 162$	P
Birth weight, g[a]	3425 (±399)	3414 (±410)	.84
Gestational age, wk[a]	39.6 (±1.3)	39.3 (±1.3)	.15
Girl	41 (53%)	87 (54%)	.86
Apgar 1 min[b]	8 (8–9)	9 (9–9)	.46
Apgar 5 min[b]	9 (9–9)	9 (9–9)	.65
Maternal age[a]	24.6 (±6)	25.1 (±6)	.49
Hispanic race	69 (88%)	136 (84%)	.69
Cesarean delivery	16 (21%)	51 (31%)	.076
Rupture of membrane, h[b]	10 (6–18)	10 (6–16)	.66
GBS-positive	8 (10%)	26 (16%)	.25
Tmax (°F)	101.2 (±0.8)	100.9 (±0.8)	.04
HCA	46/72 (64%)	69/151 (46%)	.011
Maternal antibiotics before delivery[c]	38 (49%)	83 (52%)	.68

Tmax, maximum maternal temperature.
[a] Mean (±SD).
[b] Median (25th–75th percentile).
[c] More than 4 h before delivery.

TABLE 2 Neonatal Laboratory Data

	NICU Admissions, $N = 78$	Nonadmissions, $N = 162$	P
WBC count[a]			
Birth–12 h	20.7 (±7.9)	19.4 (±5.5)	.19
12–24 h	23.6 (±7.4)	20.7 (±5.2)	.036
24–48 h	18.4 (±5.6)	16.5 (±4.3)	.013
hsCRP (mg/dL)[b]			
Birth–12 h	0.3 (0.2–1.8)	0.2(0.2–0.4)	<.001
12–24 h	12.05 (2.3–30.1)	2.2 (0.8–4.9)	<.001
24–48 h	13.5 (3.2–25.6)	2 (0.8–4.6)	<.001

[a] Mean (±SD).
[b] Median (25th–75th percentile).

Indication for NICU Admission

Newborn infants were admitted to the NICU with abnormal laboratory values or signs and symptoms of sepsis at a mean postnatal age of 22 ± 12 hours. A significant difference was seen between infants requiring NICU admission and those that did not in the median values of hsCRP obtained at all time points and the mean WBC count by 12 to 24 hours and 24 to 48 hours of life (Table 2). There was no significant difference in laboratory data between infants with bacteremia and those without (data not shown).

From the infants admitted to the NICU, 59 of 78 (76%) remained clinically asymptomatic and were admitted due to abnormal laboratory results. The other 19 infants (24%) developed clinical symptoms of sepsis, respiratory distress being the most frequent presenting symptom, occurring in 9 infants (12%) (Table 3). Fourteen of the admitted infants had positive blood cultures, of which 2 were considered contaminants (*Staphylococcus* and mixed flora). Only 2 of 12 infants with a true-positive blood culture presented signs and symptoms of clinical sepsis, with the remaining 10 infants asymptomatic at the time of admission. These 10 infants were admitted after their blood cultures were reported positive between 7 and 25 hours of life. The 12 true-positive blood cultures included 7 with *Enterococcus* (58%) and 5 with *Escherichia coli* (42%). Six of the 7 *Enterococcus* species were faecalis and 1 was faecium. Only 3 mothers of these 12 culture-positive infants received antibiotic treatment >4 hours before delivery, and thus the majority of infants unlikely benefited significantly from antibiotic exposure. Of the admitted infants, 32 of 78 (41%) had a lumbar puncture performed. CSF analysis was normal in 30 infants. Two infants were treated with antibiotics for 14 days for presumed meningitis related to uninterpretable CSF analysis after traumatic lumbar punctures (Table 3).

Antibiotic Therapy and Length of Stay

Of the 240 asymptomatic chorioamnionitis-exposed infants, 78 (32.5%) were admitted to the NICU and treated with antibiotics for suspected sepsis. The majority of these infants, 59 (76%), were treated with antibiotics for >72 hours, with a median of 7 days of treatment (Table 3). Admitted infants required a median hospital stay of 7 days compared with a median of 2 days for nonadmitted infants ($P < .001$). None of the NICU-admitted infants were able to exclusively breastfeed. Only 85% of admitted infants received any breast milk compared with 94% of infants remaining in the mother-infant unit ($P = .032$). There were no deaths or morbidities identified in any infant during the study period. No infant was readmitted to our institution for sepsis after discharge.

DISCUSSION

The aim of this study was to present outcomes at a single institution for asymptomatic

TABLE 3 Neonatal Outcomes for NICU Admissions

	NICU Admissions ($N = 78$), *n* (%)
Asymptomatic	59 (76)
Elevated hsCRP	21 (27)
Elevated WBC/bandemia	10 (13)
Elevated hsCRP/elevated WBC/bandemia	16 (21)
Positive blood culture	12 (15)
Presenting clinical symptom	19 (24)
Respiratory distress	9 (12)
Poor feeding	7 (9)
Hypotonia	1 (1)
Hypoglycemia	1 (1)
Temperature instability	1 (1)
Blood culture	
Negative	64 (82)
Positive	12 (15)
E coli	5
Enterococcus	7
Treated for sepsis	59 (76)
Culture-positive sepsis	12 (15)
Days of antibiotics[a]	7 (5–7)
Lumbar puncture	32 (41)

[a] Median (25th–75th percentile).

chorioamnionitis-exposed infants ≥35 weeks' gestation with an approach eliminating immediate empirical antibiotic administration. Using our strategy, we avoided antibiotic exposure in a majority (67.5%) of asymptomatic chorioamnionitis-exposed newborns. No infant morbidities were identified due to a potential delay in antibiotic administration. There is a need to revisit currently recommended guidelines and consider abandoning the approach of treating well-appearing infants because of chorioamnionitis alone.[4,16,17]

A maternal clinical diagnosis of chorioamnionitis is often based on nonspecific signs, does not consistently convey the degree or severity of illness, and may not indicate true intrauterine infection. In our study, several mothers were diagnosed with chorioamnionitis based solely on a single fever and, in a few cases, even in the absence of an elevated temperature. With increased IAP use for maternal chorioamnionitis, recent data show the rate of culture-positive EOS has decreased from 80 to 200 per 1000 to 4 per 1000 newborns exposed to chorioamnionitis.[1] Given this significant reduction in EOS, presumptive antibiotic treatment of all infants is unwarranted. Using current CDC and AAP guidelines,[9,10] maternal diagnosis of chorioamnionitis commits infants to laboratory evaluation, antibiotic treatment, and hospitalization in higher acuity units. The optimal management strategy to safely replace previous recommendations continues to be intensely debated. A majority of clinicians already disagree with antibiotic treatment of asymptomatic infants[4] and are no longer adhering to previous guidelines.[15]

An initiative has been undertaken for alternative management strategies to prevent EOS in chorioamnionitis-exposed infants relying on maternal risk factors combined with an infant clinical examination.[19,20] In this model, maternal temperature is used as a quantitative risk factor adjusting for current variability in the diagnosis of chorioamnionitis. Infants in our study requiring admission for suspected sepsis showed significantly higher maternal maximum temperatures compared with infants remaining in the mother-infant unit. However, all other maternal risk factors were not significantly different.

Laboratory evaluation, including blood culture, CBC, and hsCRP for chorioamnionitis-exposed infants is part of our EOS monitoring strategy. Observation without a blood culture would have missed infants with a positive test that remained asymptomatic. Ten out of 12 bacteremic infants in our study were asymptomatic. This finding was confirmed in a study reporting asymptomatic cases of culture-confirmed EOS in chorioamnionitis-exposed neonates.[21] The utility of serial CBC and CRP in identifying infants who are at risk for EOS has been questioned and is not solely sufficient.[9,22,23] Laboratory data were not significantly different in infants with and without bacteremia in our study. These tests are acknowledged to have poor positive predictive value[24,25] and abnormal values can be observed in asymptomatic and potentially uninfected neonates. Some of our infants were asymptomatic, admitted to the NICU, and treated for sepsis exclusively based on abnormal laboratory values. Laboratory data can be an adjunct diagnostic tool, but it is vital that clinicians refrain from diagnosis and treatment based entirely on nonspecific laboratory data.[24] Additional studies are essential to develop improved diagnostic testing that will timely and accurately indicate EOS risk in asymptomatic chorioamnionitis-exposed infants.

In an era where antibiotic resistance is on the rise, health care providers are increasingly conscious of antibiotic stewardship.[11,26,27] When the overall risks of EOS are low,[1,2,5,6,8] exposure of large numbers of well-appearing infants to even short courses of antibiotics is no longer justified. Alterations in the infant gut microbiome have been shown after antibiotic administration[11] with potential for lasting health consequences on allergies,

early wheezing or asthma, and infections.[12,13] Once antibiotics are started in infants, they are often continued for prolonged courses even if the infant remains clinically well with a negative blood culture.[28] The rate of antibiotic usage was 18% at our institution for late preterm and term infants during this study period. In California NICUs, there is a 40-fold variation in antibiotic use, which does not correlate to the burden of infection.[29] Although the overall majority of our asymptomatic infants were not exposed to antibiotics, those started on antibiotics were often treated for a prolonged course. The threshold for initiating or continuing antibiotics in neonates for suspected infection needs to be carefully considered and additionally evaluated.[29]

Administration of antibiotics to chorioamnionitis-exposed newborns often requires NICU admission. Using our guidelines, we did not admit a majority of asymptomatic infants, and instead the newborns were monitored in the mother-infant unit. Avoiding separation between mother and newborn promoted bonding and prevented the detrimental consequences EOS evaluations have on successful breastfeeding.[30] The cost of a stay in the mother-infant unit for 2 days compared with a NICU stay, which averaged a week, is substantial. The charge for our NICU is $12 612 per day in contrast to $5300 per day in the mother-infant unit. The cost savings for the 162 infants who were cared for 2 days in the mother-infant unit compared with an EOS evaluation and antibiotic therapy in the NICU totals $2 369 088 or $359 861 per year.

In our institution, the placenta is routinely sent for pathology examination. Risk of NICU admission was twofold higher for infants with HCA compared with infants without, but culture-positive infection was not different between those infants with or without HCA. More often, HCA is associated with EOS[31–33] in preterm infants. In term infants, HCA has shown to be a result of a noninfectious inflammatory process.[34] In general, the diagnosis of HCA does not aid in the management of EOS in term infants.[31,32] Pathology results at our institution are not timely enough to be a factor in immediate clinical decision-making.

Our study has limitations. It was performed retrospectively with a small population at a single institution of a predominantly high-risk Hispanic population. It is possible for discrepancies in the identification of patient diagnosis and symptoms through paper charts, although chorioamnionitis was confirmed in both the infant and mother before study inclusion. Although all discharged newborns have scheduled follow-up at an outpatient clinic, they are not consistently followed at our hospital clinic. We did not have any infant return to our institution for readmission due to sepsis after discharge, but we have no knowledge of potential readmissions to other institutions.

CONCLUSIONS

Nonroutine use of empirical antibiotics in asymptomatic newborns ≥35 weeks' gestation with maternal chorioamninonitis avoided NICU admission in two-thirds of infants. This prevented unnecessary antibiotic exposure, increased hospitalization costs, and disruption in mother-infant bonding and breastfeeding. Laboratory evaluation and close clinical observation without immediate antibiotic administration may be incorporated into an alternative management strategy of asymptomatic chorioamnionitis-exposed neonates. Additional studies are needed to establish the safety of this approach.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
CBC: complete blood count
CDC: Centers for Disease Control and Prevention
CSF: cerebrospinal fluid
EOS: early-onset sepsis
GBS: group B *Streptococcus*
HCA: histologic chorioamnionitis
hsCRP: high-sensitivity C-reactive protein
IAP: intrapartum antibiotic prophylaxis
WBC: white blood cell

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