

Role of Guidelines on Length of Therapy in Chorioamnionitis and Neonatal Sepsis



WHAT'S KNOWN ON THIS SUBJECT: Chorioamnionitis (CAM) is a major risk factor for early-onset neonatal sepsis. The Committee on the Fetus and Newborn recommends extending the duration of antimicrobial therapy in neonates exposed to CAM and intrapartum antibiotics if laboratory data are abnormal, even if culture results are sterile.



WHAT THIS STUDY ADDS: When managed by using a strategy similar to recent Committee on the Fetus and Newborn guidelines, a large number of term and late-preterm infants exposed to CAM who had sterile blood culture findings were treated with prolonged antibiotic therapy, subjected to additional invasive procedures, and had prolonged hospitalization.

abstract

BACKGROUND AND OBJECTIVE: Chorioamnionitis (CAM) is a major risk factor for neonatal sepsis. At our institution, neonates exposed to CAM and intrapartum antibiotics are treated with prolonged antimicrobial therapy if laboratory values are abnormal despite a sterile blood culture. Recently, the Committee on the Fetus and Newborn (COFN) recommended a similar strategy for treating neonates exposed to CAM. Our objective was to determine the frequency of abnormal laboratory parameters in term and late-preterm neonates exposed to CAM and evaluate the implication of recent COFN guidelines.

METHODS: This retrospective data analysis included late-preterm and term neonates exposed to CAM. Laboratory parameters, clinical symptoms and the number of infants treated with prolonged antibiotics were determined.

RESULTS: A total of 554 infants met the inclusion criteria. Eighty-three infants (14.9%) had an abnormal immature to total neutrophil ratio (>0.2) and 121 infants (22%) had an abnormal C-reactive protein level (>1 mg/dL) at 12 hours of age. A total of 153 infants (27.6%) had an abnormal immature to total neutrophil ratio and/or abnormal C-reactive protein level at 12 hours of age. Only 4 (0.7%) of 554 infants had a positive blood culture result. A total of 134 (24.2%) infants were treated with prolonged antibiotics (112 [20.2%] were treated solely based on abnormal laboratory data). Lumbar puncture was performed in 120 (21.6%) infants.

CONCLUSIONS: When managed by using a strategy similar to recent COFN guidelines, a large number of term and late-preterm infants exposed to CAM who had sterile blood culture findings were treated with prolonged antibiotic therapy due to abnormal laboratory findings. They were also subjected to additional invasive procedures and had a longer duration of hospitalization. *Pediatrics* 2014;133:992–998

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KEY WORDS

bacteremia, duration of antibiotics, infection, IT ratio, neonates

ABBREVIATIONS

CBC—complete blood cell count

CAM—chorioamnionitis

CDC—Centers for Disease Control and Prevention

COFN—Committee on the Fetus and Newborn

CRP—C-reactive protein

CSF—cerebrospinal fluid

IT—immature to total neutrophil

WBC—white blood cell count

Dr Kiser conceptualized the study, searched literature, collected and analyzed data, and drafted the initial manuscript; Dr Nawab extracted and analyzed the data, and critically reviewed and revised the manuscript; Dr McKenna collected and analyzed data, and reviewed and revised the manuscript; Dr Aghai conceptualized and designed the study, analyzed data, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

This research was presented in part at the annual meeting of the Pediatric Academic Societies; May 4–7, 2013; Washington, DC. www.pediatrics.org/cgi/doi/10.1542/peds.2013-2927

doi:10.1542/peds.2013-2927

Accepted for publication Mar 4, 2014

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found on page 1122, and online at www.pediatrics.org/cgi/doi/10.1542/peds.2014-0360.

Chorioamnionitis (CAM) is a major risk factor for early-onset neonatal sepsis, and it complicates 1% to 10% of all pregnancies.^{1,2} The incidence of early-onset neonatal sepsis is significantly increased in neonates exposed to CAM.^{3,4} The risk of early-onset neonatal sepsis is reduced with administration of antibiotics during labor and delivery to mothers who have CAM.^{5,6} However, the use of intrapartum antibiotics reduces the sensitivity of postnatal blood cultures in neonates.⁷ Management of neonates exposed to CAM and intrapartum antibiotics can be challenging for clinicians. If neonates are exposed to CAM, the Committee on the Fetus and Newborn (COFN) recommends evaluation of these neonates with a blood culture at birth and complete blood cell count (CBC) with differential count and/or C-reactive protein (CRP) at 6 to 12 hours of life.⁸ The recommendation also includes empiric treatment with broad-spectrum antibiotics even in asymptomatic infants. Antibiotics are discontinued after 48 hours if the blood culture result is negative, the infant remains asymptomatic, and laboratory study findings are normal. However, if laboratory test results are abnormal and the mother received intrapartum antibiotics, COFN recommends treating asymptomatic neonates with prolonged antibiotics despite a sterile blood culture finding.^{8,9}

Standard laboratory findings used to evaluate sepsis in neonates such as leukocytosis, leukopenia, absolute band counts, absolute neutrophil counts, immature to total neutrophil (IT) ratio, and elevated CRP level have limited positive predictive values.^{4,10,11} Despite the limited value of hematologic parameters to diagnose true sepsis, the most recent COFN statement recommends extending antimicrobial therapy in asymptomatic neonates exposed to CAM if laboratory parameters are abnormal, even with sterile

blood culture findings and particularly if intrapartum antibiotics were administered.^{8,9} At our institution, similar guidelines of treating such neonates with prolonged antibiotics were routinely practiced before the current COFN recommendations. The objective of the present review was to determine the frequency of abnormal laboratory parameters in term and late-preterm neonates exposed to CAM and to evaluate the implications of recent COFN guidelines on their management.

METHODS

This retrospective study was conducted in neonates (gestational age ≥ 35 weeks) born between November 2006 and September 2012 and admitted to a level III NICU. The institutional review committee at Thomas Jefferson University Hospital approved this study. The infants exposed to CAM during the study periods were identified from a neonatal database (Neodata, Isoprime Corporation, Lisle, IL). Relevant demographic, clinical, and laboratory data were collected from the database and medical records. The diagnosis of CAM was made by the obstetrician based on intrapartum fever (temperature $\geq 38^\circ\text{C}$) alone or in conjunction with maternal leukocytosis, uterine tenderness, foul-smelling amniotic fluid, and maternal and/or fetal tachycardia. At our institution, all neonates born to a mother with a clinical diagnosis of CAM are admitted to the NICU. Blood culture is obtained on admission, and empiric antibiotic therapy with ampicillin and gentamicin is initiated. CBC with differential and CRP are performed on admission and at 12 hours of age. The total white blood cell (WBC) count is measured by using a Sysmex XE-5000 (Sysmex Corporation, Kobe, Japan), and differential count is performed by trained technicians and confirmed by a hematologist. Antibiotics are discontinued if infants are asymptomatic, laboratory parameters are normal, and

blood culture results are negative for 48 hours. Lumbar puncture is performed in infants with clinical signs of sepsis, persistent abnormal laboratory parameters (IT ratio >0.2 and/or CRP >1 mg/dL at 12 hours of age), or a positive blood culture result. These infants are treated with prolonged antibiotics. The IT ratio is calculated as described by Manroe et al,¹² and a value ≥ 0.2 is considered elevated. Similarly, a CRP level >1 mg/dL was considered abnormal.

Statistical analyses were performed by using the SigmaStat 3.1 for Windows statistical package (Systat Software Inc, Point Richmond, CA). Comparisons between the 2 groups were performed by using Student's *t* test and the Mann-Whitney rank-sum test for continuous data and the χ^2 or Fisher's exact test for categorical data. Statistical significance was set a $P < .05$.

RESULTS

A total of 12 121 infants were born during the study period, and 554 (4.6%) were exposed to CAM. Demographic and clinical characteristics are presented in Table 1. Four infants (0.7%) had a positive blood culture result. An additional 22 infants (4%) were treated for sepsis based on clinical signs and symptoms (respiratory distress requiring prolonged respiratory support, hypothermia, and hypoglycemia).

TABLE 1 Demographic and Clinical Characteristics of the Study Subjects ($N = 554$)

Gestational age, mean \pm SD, wk	39.4 \pm 1.4
Male gender	299 (54)
African-American race	260 (47)
GBS colonization	126 (23)
ROM >18 h	184 (33)
Apgar at 5 min (median, range)	9 (1–10)
Culture-negative sepsis	22 (4.0)
Lumbar puncture	120 (22)
Positive blood culture result	4 (0.7)

Unless otherwise indicated, data are presented as *n* (%). GBS, group B streptococcus; ROM, rupture of membranes.

Laboratory parameters at birth and at 12 hours of age are depicted in Fig 1. At 12 hours of age, 153 infants (27.6%) had an abnormal IT ratio and/or abnormal CRP level, but only 55 infants (9.9%) had an abnormal IT ratio and an elevated CRP level.

In total, 134 (24.2%) infants were treated with prolonged antibiotics (≥ 7 days) and 420 (75.8%) with a shorter course (48–72 hours). A total of 112 infants (20.2%) were treated with prolonged antibiotics based solely on abnormal laboratory data. More infants were symptomatic and had abnormal laboratory parameters in the group treated with prolonged antibiotics (Table 2).

Lumbar puncture was performed in 120 infants (22%) due to signs and symptoms of infection, positive blood culture results, or abnormal laboratory parameters. Cerebrospinal fluid (CSF) culture results were negative in all 120 infants. Only 1 infant was treated with 14 days of antibiotics for presumed meningitis secondary to an abnormal corrected WBC count on a traumatic lumbar puncture. This infant was asymptomatic,

the blood culture result was negative, and lumbar puncture was performed because of a high IT ratio (0.3) at 12 hours of age.

Only 4 (0.7%) of 554 infants had a positive blood culture result (Table 3). One infant had unexplained respiratory distress requiring mechanical ventilation for 2 days. The other 3 infants were depressed at birth; 2 required positive pressure ventilation and 1 required continuous positive airway pressure in the delivery room, but symptoms resolved by NICU admission. All 4 infants had an IT ratio >0.3 at birth; 3 of 4 infants had an IT ratio >0.2 at 12 hours. The CRP was normal at birth but increased at 12 hours of life in all 4 infants. CSF culture results were negative, and WBC, protein, and glucose levels were normal in all 4 infants. In the 22 symptomatic neonates treated for culture-negative sepsis, the IT ratio was normal in 10 (46%) and CRP was normal in 7 (32%) at 12 hours of life. Four neonates (18%) with culture-negative sepsis had no abnormalities of the IT ratio or CRP at 12 hours of life.

DISCUSSION

Recently, COFN recommended extending the course of antibiotics in asymptomatic, CAM-exposed neonates with abnormal screening laboratory data if intrapartum antibiotics were administered, even with sterile blood culture findings.⁸ Because the use of intrapartum antibiotics may alter the reliability of blood cultures in neonates, the COFN recommends using laboratory data (CBC \pm CRP) to guide the duration of antibiotic therapy.⁷ At our institution, even before the COFN recommendation, asymptomatic neonates exposed to CAM and intrapartum antibiotics were treated with prolonged antibiotics if the IT ratio and/or CRP were abnormal. We found that 27.6% of infants exposed to CAM had an abnormal IT ratio and/or CRP at 12 hours of age. By following current COFN guidelines, $\sim 28\%$ of neonates exposed to CAM would be treated with prolonged antibiotics.

The COFN recommends CBC with differential count and/or CRP at 6 to 12 hours of age in neonates exposed to CAM, noting the mediocre positive

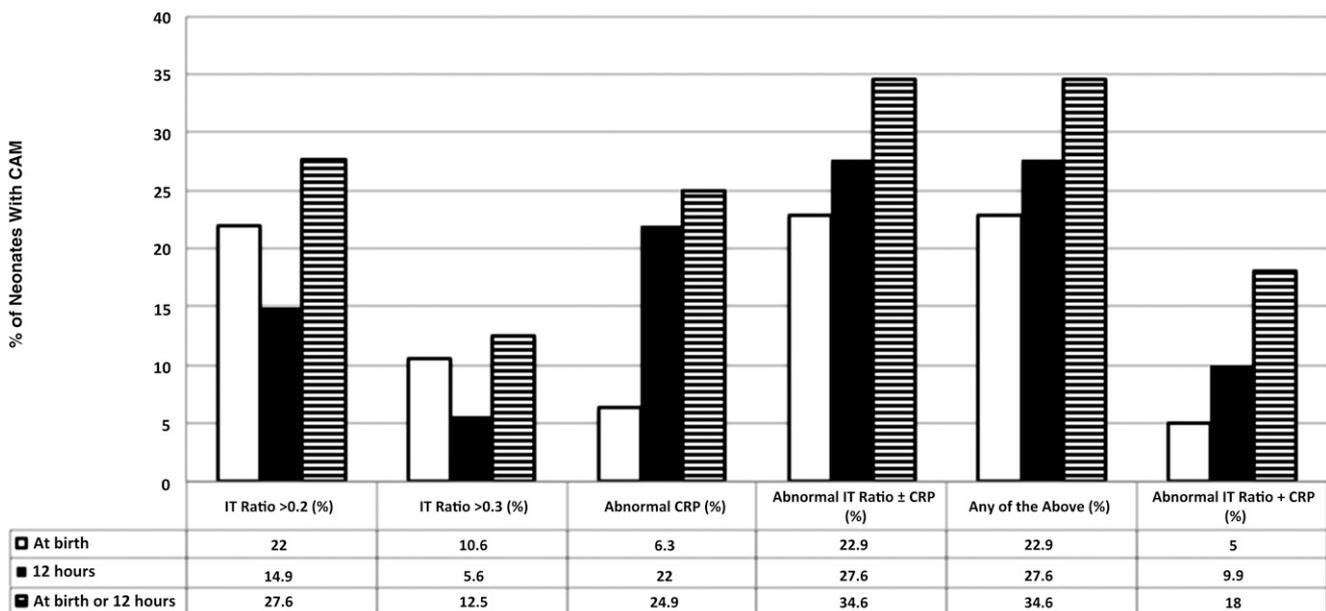


FIGURE 1
Laboratory data (IT ratio and CRP) at birth and 12 hours of life.

TABLE 2 Infants Treated With Short Course Versus Longer Course of Antibiotics

Variable	Short Course (n = 420)	Longer Course (n = 134)	P
Gestational age, mean \pm SD, wk	39.4 \pm 1.3	39.2 \pm 1.6	.2
Male gender	232 (55)	67 (50)	.3
African-American race	193 (46)	67 (50)	.5
GBS colonization	107 (25)	19 (14)	.01
ROM >18 h	136 (32)	48 (36)	.5
Apgar at 5 min (median, range)	9 (1–10)	9 (1–9)	<.001
Signs and symptoms suggestive of sepsis	0	22 (16)	<.001
Abnormal IT ratio at 12 h	13 (3.1)	70 (52.2)	<.001
Abnormal CRP at 12 h	26 (6.2)	95 (70.9)	<.001
Abnormal CRP \pm IT ratio at 12 h	35 (8.3)	118 (88.1)	<.001
Abnormal CRP + IT ratio at 12 h	3 (0.7)	52 (38.8)	<.001
Lumbar puncture	17 (4)	103 (77)	<.001
Days of hospitalization, mean \pm SD	3.5 \pm 2.5	9.1 \pm 8.1	<.001

Unless otherwise indicated, data are presented as n (%). GBS, group B streptococcus; ROM, rupture of membranes.

predictive value of these tests.⁸ For interpretation of CBC, the COFN guidelines rely on data from a study by Manroe et al,¹² which is >3 decades old and has a small sample size of convenience with only a few infants with culture-proven sepsis. In a study by Jackson et al,¹³ 99% of infants exposed to CAM had at least 1 abnormal finding on the CBC during the first 24 hours of life. In a cohort of 3154 neonates, Murphy et al¹⁴ found that ~50% of infants had an abnormal IT ratio during the first 24 hours of life. Both the IT ratio and CRP have a high negative predictive value for neonatal

infections.^{4,10,11,15,16} Therefore, if either the IT ratio or CRP is normal at 6 to 12 hours of life, the likelihood of having an infection is very low. In our cohort, 14.9% of infants had an abnormal IT ratio and 22% of infants had an abnormal CRP finding at 12 hours of age. Moreover, 27.6% of infants had an abnormal laboratory finding (abnormal IT ratio and/or abnormal CRP) at 12 hours of life, which according to current COFN guidelines, would require prolonged antibiotics. Recently, Mikhael et al¹⁷ described the use of a neutrophil value score, which evaluates 9 neutrophil indices corrected for postnatal age.

They found the reliability to be >80% when >6 or 7 indices were normal, which could have reduced those treated for suspected sepsis by 22% or 43%, respectively.

The management of infants born to mothers with CAM and treated with intrapartum antibiotics can be challenging. For neonates exposed to CAM, the Centers for Disease Control and Prevention (CDC) recommends an evaluation with blood culture at birth, CBC (including differential and platelets) at 6 to 12 hours of life, and treatment with broad-spectrum antibiotics.² However, the CDC does not comment on duration of antibiotic therapy. The COFN has similar recommendations for managing neonates exposed to CAM with the option of performing a CRP at age 6 to 12 hours.⁸ In addition, the COFN made recommendations regarding prolonging antibiotic therapy in this population. Per COFN guidelines, antibiotic therapy should be extended in neonates exposed to CAM if the mother received intrapartum antibiotics, even if the infant appears well with a sterile blood culture result but has abnormal laboratory data. No recommendation is

TABLE 3 Infants With Positive Blood Culture Results

Variable	Infant 1	Infant 2	Infant 3	Infant 4
Organism	<i>Escherichia coli</i>	GBS	α -Hemolytic <i>Streptococcus</i>	<i>Streptococcus intermedius</i>
Gestational age, wk	39	38	39	40
Birth weight	2800	3190	3929	3905
GBS colonization	No	No	No	No
ROM, h	23	17	27	45
Criteria met for CAM	Fever 102.7°F, foul smelling amniotic fluid	Fever 103.4°F, fetal tachycardia	Fever 102.3°F, fetal tachycardia	Fever 101.4°F
Antepartum antibiotics	Ampicillin/sulbactam 1 h PTD	Ampicillin/sulbactam 1 h PTD	Ampicillin/sulbactam 40 min PTD	Ampicillin, gentamicin 3 h PTD
Apgar (1, 5 min)	5, 8	1, 6	1, 7	8, 9
Symptoms	CPAP in DR for poor respiratory effort; well appearing at 6–8 h	Depressed in DR; required intubation and PPV. Well appearing at 6–8 h	Depressed at birth; required PPV via mask. Well appearing at 6–8 h	Respiratory distress required mechanical ventilation for 2 d
IT ratio				
Birth	0.38	0.36	0.34	0.35
12 h	0.13	0.36	0.36	0.34
CRP				
Birth	0.24	<0.1	<0.2	<0.2
12 h	7.6	2.0	5.0	1.2
CSF culture	Negative	Negative	Negative	Negative
Duration of antibiotics, d	10	7	7	7

CPAP, continuous positive airway pressure; DR, delivery room; GBS, group B streptococcus; PPV, positive pressure ventilation; PTD, preterm delivery; ROM, rupture of membranes.

made regarding the exact duration of antimicrobial therapy. At our institution, these infants are treated with broad-spectrum antibiotics for 7 days. Following guidelines similar to recent COFN recommendations, 24.2% of late-preterm and term infants exposed to CAM were treated with extended courses of antibiotics (≥ 7 days), and 20% of infants were treated with prolonged antibiotics solely on the basis of abnormal laboratory data. In addition, they were subjected to invasive procedures (lumbar puncture, peripheral and/or central intravenous lines, and umbilical venous catheterization) and had a longer duration of hospitalization. Some experts argue that if a mother is treated with systemic antibiotics and the infant is asymptomatic and has a negative culture result, the infant is “cured.” No agreement exists on what constitutes a “cure” because of the lack of data to support this opinion. A massive sample size would be needed to prove that these infants do not require further treatment. Jackson et al¹³ reported follow-up data on 98 asymptomatic infants with an abnormal IT ratio at 12 or 24 hours of life. These infants were discharged from the hospital with negative blood culture results after receiving antibiotics for 48 hours. Telephone follow-up by parent report was performed 10 and 21 days after discharge. None of these infants had presumed or proven sepsis at follow-up. The authors concluded that extended antibiotic therapy should be reserved for neonates with clinical signs of infection and/or who have a positive blood culture result. In their study, only 38 (4.4%) of 856 infants met the criteria for extended antibiotic therapy (4–7 days). If we used similar criteria for extending antibiotics in our cohort, only 26 (4%) of 554 infants would have been treated with a longer duration of antibiotics. This method would not only reduce duration of hospitalization, health care costs, and chance of complications related to lumbar puncture

and intravenous access but would prevent unnecessary separation of infants from their mothers. Moreover, extended use of antibiotics may also have adverse effects. Gentamicin, commonly used to treat early-onset sepsis in neonates, has potential renal and ototoxicity.¹⁸ Prolonged use of antibiotics in neonates can affect the bacterial balance of the intestinal microbiome, increasing the risk of subsequent infection with resistant bacteria, invasive candidiasis, and affecting early immune programming.^{19,20} In addition, treatment with antibiotics in the neonatal period is an independent risk factor for wheezing requiring inhaled corticosteroids.²¹ In preterm infants, prolonged antibiotics is associated with increased mortality and necrotizing enterocolitis.^{22,23}

After publication of the COFN statement on the management of neonates with suspected or proven early-onset bacterial sepsis,⁸ several experts raised concerns regarding extending the antimicrobial course in asymptomatic neonates exposed to CAM and intrapartum antibiotics with abnormal laboratory data and sterile blood culture results.^{24,25} Responding to these concerns, the COFN stated that they would not treat well-appearing, asymptomatic term infants (exposed to CAM and intrapartum antibiotics) who had a negative blood culture result for longer than 48 to 72 hours even when laboratory data are abnormal, indicating that revised algorithms were being submitted to *Pediatrics* as an erratum to the clinical report.²⁶ However, in the most recent commentary clarifying their 2012 policy statement, the COFN did not comment or change the algorithm (Fig 1 and Fig 2 in the 2012 policy statement) recommending extension of antibiotic course in such cases.⁹ Replying to experts' concern, the COFN cited the study by Jackson et al, in which only 13% of asymptomatic infants had an elevated IT ratio at 12 hours,

implying only a small number of infants would require additional treatment.^{13,26} However, they continue to include the option of CRP analysis at 6 to 12 hours of life. Although our findings were similar regarding an abnormal IT ratio (14.9%) at 12 hours in neonates exposed to CAM, the addition of an abnormal CRP (22%) or abnormal CRP and/or IT ratio (27.6%) markedly increases the number of infants requiring prolonged antibiotics. According to current COFN recommendations, ~28% of neonates exposed to CAM and intrapartum antibiotics despite sterile blood culture findings would require prolonged broad-spectrum antibiotics.⁸ By using elevated CRP combined with a high IT ratio, the number of infants treated with an extended course of antibiotics would be reduced. Perhaps reevaluating how we define an abnormal laboratory finding by using a scoring system such as the neutrophil value score may be warranted to decrease unnecessary prolonged antibiotic use.

Only 0.7% (4 of 554) of the study infants had a positive blood culture result. This low incidence of positive results is likely due to use of intrapartum antibiotics and is consistent with the literature.¹³ Clinical signs of sepsis have been found to be a more sensitive indicator of early-onset neonatal sepsis than hematologic parameters.⁴ In our cohort of 4 infants with a positive blood culture result, 3 infants were depressed at birth (2 required intubation and positive pressure ventilation, and 1 required continuous positive airway pressure) in the delivery room. However, all 3 infants were well appearing by 6 to 8 hours of life. Only 1 infant had respiratory distress requiring mechanical ventilation for 2 days. At 12 hours of age, 1 of 4 infants with a positive blood culture had an IT ratio < 0.2 , but all 4 infants had an abnormal CRP. Using these data, the COFN guidelines (performing CBC and/or CRP)

would identify all 4 infants, but the CDC guidelines (without CRP) would potentially miss 1 in 4 infants with positive blood culture results. However, a significant number of symptomatic infants with culture-negative sepsis had a normal IT ratio (46%) or CRP (32%) at 12 hours of life. Overall, 18% of infants with culture-negative sepsis had a normal IT ratio as well as normal CRP at 12 hours of age. In the study by Jackson et al,¹³ 3 of 4 infants with positive blood culture results had no signs and symptoms of sepsis, and all 4 infants with positive blood culture results had an IT ratio <0.2 at age 12 hours.

Meningitis is common in neonates with early-onset sepsis.^{27,28} Blood culture results can be negative in as many as 38% of infants with meningitis, and clinical signs suggestive of meningitis may be lacking in neonates.^{29,30} Both COFN and CDC guidelines are ambiguous regarding lumbar puncture in asymptomatic late-preterm and term infants exposed to CAM and intrapartum antibiotics with abnormal laboratory and negative blood culture findings.^{2,8} The COFN recommends extending the antibiotic course without making a recommendation on lumbar puncture. According to the COFN, "lumbar puncture should be performed for infants with signs of sepsis who can safely undergo procedure, for infants with positive blood culture, for

infants likely to be bacteremic (on the basis of laboratory data), and infants who do not respond to antimicrobial therapy in expected manner."⁸ Asymptomatic neonates exposed to CAM and intrapartum antibiotics with abnormal laboratory values may be bacteremic, but blood cultures can be sterile due to the use of antibiotics during labor and delivery. The COFN recommends extending the antibiotic course in these infants because they are likely to be bacteremic, as indicated by abnormal laboratory data. At our institution, a lumbar puncture is performed in all infants receiving an extended course of antibiotics to determine length of treatment. A CSF culture may not be reliable due to use of intrapartum and postnatal antibiotics, but the course of antibiotics can be extended to 14 to 21 days in the presence of pleocytosis or biochemical abnormalities (low glucose, high protein). In our cohort, lumbar puncture was performed in 22% of infants; none had a positive CSF culture result. In 1 infant, the course of antimicrobial therapy was extended to 14 days due to CSF pleocytosis.

Our study has important limitations. This study was a retrospective trial, from a single center including only late-preterm and term infants exposed to CAM and evaluated for early-onset sepsis. Results from this study may not be applicable to premature

neonates with early-onset sepsis and infants with late-onset sepsis. The strength of the study is the large of number of neonates exposed to CAM and managed by using guidelines similar to the recent COFN recommendations.

CONCLUSIONS

When managed by using guidelines similar to the recent COFN statement, a large number of term and late-preterm infants exposed to CAM who had sterile blood culture findings were treated with prolonged antibiotics due to abnormal laboratory findings. They were also subjected to additional invasive procedures and had a longer hospital stay. The health care costs and risks associated with an extended course of antibiotics, prolonged hospitalization, lumbar puncture, intravenous access, and separation of infant from mother may be too high to justify such treatment. The COFN should consider changing their recommendation on extending the course of antimicrobial therapy in asymptomatic late-preterm and term neonates exposed to CAM and intrapartum antibiotics with abnormal laboratory data and negative blood culture results. A more specific test or tool, such as the neutrophil value score, is needed to guide therapy in asymptomatic neonates exposed to CAM and sterile blood culture findings.

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Pediatrics 2014;133;992

DOI: 10.1542/peds.2013-2927 originally published online May 5, 2014;

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Courtney Kiser, Ursula Nawab, Kristin McKenna and Zubair H. Aghai
Pediatrics 2014;133;992

DOI: 10.1542/peds.2013-2927 originally published online May 5, 2014;

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