ARTICLE

Short-course empiric antibiotic therapy for possible early-onset sepsis in the NICU

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OBJECTIVE: On 2/2019, the Neonatal Antimicrobial Stewardship Program at Nationwide Children's Hospital recommended reducing empirical antibiotic therapy for early-onset sepsis (EOS) from 48 to 24 hours with a TIME-OUT. We describe our experience with this guideline and assess its safety.
METHODS: Retrospective review of newborns evaluated for possible EOS at 6 NICUs from 12/2018-7/2019. Safety endpoints were re-initiation of antibiotics within 7 days after discontinuation of the initial course, positive bacterial blood or cerebrospinal fluid culture in the 7 days after antibiotic discontinuation, and overall and sepsis-related mortality.
RESULT: Among 414 newborns evaluated for EOS, 196 (47%) received a 24 hour rule-out sepsis antibiotic course while 218 (53%) were managed with a 48 hour course. The 24-hour rule-out group were less likely to have antibiotics re-initiated and did not differ in the other predefined safety endpoints.
CONCLUSION: Antibiotic therapy for suspected EOS may be discontinued safely within 24 hours.

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INTRODUCTION

Antibiotics are the most prescribed medications in the neonatal intensive care unit (NICU) [1]. Prolonged antibiotic exposure in preterm infants has been associated with bronchopulmonary dysplasia, necrotizing enterocolitis, late-onset sepsis, invasive candidiasis, retinopathy of prematurity, neurodevelopmental impairment, and death, as well as emergence of multi-drug resistant organisms [2–10]. Importantly, each additional day of antibiotic therapy increases the risk of adverse outcomes in infants ≤32 weeks' gestation or birth weight ≤1500 after controlling for initial severity of illness [9, 11, 12]. In full term infants, prolonged therapy has been associated with delayed initiation of breastfeeding, obesity, recurrent wheezing, gastrointestinal disorders, as well as autism [13–17]. Among all infants, concern exists for potential toxicity such as hearing loss and renal dysfunction [18].

In February 2019, the Neonatal Antimicrobial Stewardship Program (NEO-ASP) team at Nationwide Children's Hospital (NCH) recommended reducing empiric antibiotic therapy for possible early-onset sepsis from 48 to 24 hours in 9 NICUs and 8 Newborn Nurseries in Columbus, OH. Previous studies had shown that each additional day of antibiotic therapy provided to preterm, very-low-birth-weight (≤1500 g) infants in the first seven to fourteen days of age was associated with major morbidities or mortality [3, 12]. In addition, a retrospective review of blood cultures obtained from infants in the NICU at NCH had found that the median time to positivity was 13 hours with a range of 9 to 21 hours. Accordingly, newborns evaluated for early-onset sepsis receive 2 doses of ampicillin every 12 hours and a single dose of gentamicin with a TIME-OUT set at 24 hours. These recommendations were implemented into the electronic health record as part of the NICU early-onset order set with an electronic hard stop at 24 hours. Education was provided to all health care professionals with prospective auditing and feedback performed. The objective of this study is to describe the safety of providing empiric antibiotic therapy for 24 hours compared to 48 hours among high risk newborns in the NICU. Our hypothesis was that such a practice was safe.

METHODS

This retrospective study included all newborns evaluated for possible early-onset sepsis at <72 hours of age at six NCH NICUs (1, Level 4 outborn NICU; 4, level 3 inborn NICUs; and 1, level 2 inborn NICU) [19] from December 1, 2018 to July 31, 2019. The Neo-ASP recommendation was communicated to all of the neonatologists in February 2019. Newborns with suspected early-onset sepsis at <72 hours of age received 24 or 48 hours of empirical antibiotic therapy with intravenous ampicillin (100 mg/kg/dose every 12 hours) and intravenous or intramuscular gentamicin (5 mg/kg/dose every 24 hours if gestational age ≥33 weeks, every 48 hours if gestational

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age <28 weeks, and 4 mg/kg/dose every 24 hours if gestational age 28 to 32 weeks). For infants <28 weeks in whom gentamicin dosing was every 48 hours, discontinuation of ampicillin at either 24 or 48 hours determined the duration of empirical therapy. The admission order set in the electronic health record was changed to have the antibiotic order time out at 24 hours. If the health care provider decided to extend antibiotic therapy beyond 24 hours, either the previous order was updated or a new order was created with a new stop date at 48 hours. As per hospital policy, the microbiology laboratory at each of the NICU hospitals notifies the positive blood culture result to the clinical team.

Infants who had antibiotics extended beyond 48 hours for treatment of positive bacterial cultures or culture-negative conditions such as pneumonia were excluded from analysis. Outborn infants who received antibiotics before arrival to any of the NCH NICUs also were excluded. The study was approved by the Institutional Review Board of Nationwide Children's Hospital with waiver of informed consent.

Evaluation for suspected early onset sepsis and components of the evaluation were at the discretion of the attending neonatologist, including the use of the Kaiser Permanente Sepsis Risk Calculator [20, 21]. In general, a minimum of 1 ml of blood was obtained from a single site, e.g. peripheral vein or artery or from umbilical vessels at the time of catheter placement. Early onset sepsis was defined as a positive blood culture for a recognized neonatal pathogen with organisms such as coagulase-negative staphylococci, *Micrococcus*, *Bacillus species*, *Corynebacterium*, *Propionibacterium*, and viridans group streptococci considered contaminants unless ≥2 cultures were positive for the organism. The microbiology laboratory at each hospital utilized automated continuous monitoring blood culture systems [22].

Consecutive newborns who received 24 versus 48 hours of antibiotic therapy were compared. Pertinent clinical, laboratory, and microbiologic data were obtained from the electronic health records. Chorioamnionitis was present if documented on the maternal or neonatal medical record. Severity of illness was calculated using the Clinical Risk Index for Babies (CRIB)-II score, a validated risk-adjustment instrument for prediction of mortality among very-low-birth-weight infants [23]. CRIB-II scores range from 0-27 with higher scores predictive of greater mortality risk.

Query of the electronic health record (EPIC) was conducted to obtain doses of all antibiotics administered to infants throughout the hospitalization. The length of therapy (LOT) of antibiotics used in the first 72 hours of age and during the entire hospitalization was determined. Specifically, the metric LOT refers to the number of calendar days that the infant received at least one antibiotic. In infants less than 28 weeks' gestation, one gentamicin dose was considered as 2 days for length of therapy as the interval of gentamicin administration was every 48 hours. However, if the intent and practice was to provide the infant with only dose of gentamicin, then the infant was classified into the 24 hour group for analysis. Safety endpoints were re-initiation of antibiotics within 7 days after discontinuation of the initial course, positive bacterial culture of blood or cerebrospinal fluid in the 7 days after antibiotic discontinuation, and overall and sepsis-related mortality while in the NICU.

Statistical analysis

Mean with standard deviation (SD) were used to summarize continuous variables and absolute count with percent used for categorical data. Data from the 24 hour antibiotic group were compared to that from the 48 hour antibiotic group. Independent t test was used for continuous variables, while Fisher exact (for categorical values of ≤5) and Chi square tests were used to compare categorical variables. Data management and descriptive statistics were conducted using Microsoft Excel. Analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY).

RESULTS

During the eight month study period, 414 newborns were evaluated for early-onset sepsis in the six NCH NICUs. Of the 414, 196 (47%) infants received a 24 hour rule-out sepsis antibiotic course while 218 (53%) were managed with the traditional 48 hour antibiotic course. Newborns who received 24 hours versus 48 hours of antibiotics had a lower mean gestational age but did not differ in birth weight, sex, race, mode of delivery, Apgar scores at 1 and 5 minutes, and CRIB-II scores (Table 1). Infants in the 48 hour rule out group were more likely to have a surgical

Table 1. Maternal and infant characteristics of the newborns who received a 24 vs. 48 hour course of empirical antibiotics for early-onset sepsis in the neonatal intensive care unit.

	Antibiotic Course		*P*-value
	24 h	48 h	
No. of infants	196	218	–
Gestational age (week; mean ± SD)	33.7 ± 4.5	34.8 ± 5	0.02
Gestational age (%):			<0.01
≤28 weeks	28 (14)	29 (13)	
29–33 weeks	57 (29)	42 (19)	
34–36 weeks	53 (27)	49 (22)	
≥37 weeks	58 (30)	98 (45)	
Birth weight (gram; mean ± SD)	2327 ± 956	2512 ± 971	0.05
Birth weight (%):			0.1
≤1000 g	23 (12)	19 (9)	
1001–1500 g	18 (9)	20 (9)	
1501–2500 g	68 (35)	57 (26)	
>2500 g	87 (44)	122 (56)	
Male sex (%)	115 (59)	125 (57)	0.08
Race (%):			0.23
White	112 (57)	142 (65)	
Black	44 (22)	36 (17)	
Asian	6 (3)	5 (2)	
Other	24 (12)	30 (14)	
Not known	10 (5)	5 (2)	
Ethnicity (%):			0.25
Hispanic	13 (7)	9 (4)	
Non-Hispanic	56 (29)	76 (35)	
Unknown	127 (65)	133 (61)	
Maternal GBS colonization (%):			0.52
Positive	44 (23)	40 (18)	
Negative	86 (44)	99 (46)	
Not known	63 (33)	78 (36)	
Intrapartum antibiotics (%)			0.02
Yes	107 (55)	92 (42)	
No	71 (36)	108 (50)	
Unknown	18 (9)	18 (8)	
Chorioamnionitis (%)	15 (8)	15 (7)	0.87
Vaginal delivery (%)	101 (52)	103 (47)	0.38
ROM ≥ 18 hours	52 (37%)	35 (21%)	<0.01
Apgar scores: 1, 5 minutes	6, 8	6, 7	0.17; 0.24
CRIB-II score	5.1 ± 4.2 ($n = 70$)	5.2 ± 4 ($n = 60$)	0.93
Surgical diagnosis (%)	8 (4)	26 (12)	<0.01
Anorectal atresia	2	3	
Congenital heart disease	0	6	
Diaphragmatic hernia	2	1	
Esophageal atresia	0	3	
Gastroschisis	1	4	
Hirschsprung disease	1	1	
Myelomeningocele	0	1	
Omphalocele	2	2	
Small bowel atresia	0	5	

SD standard deviation, *GBS* group B streptococcal, *ROM* rupture of membranes, *CRIB* Clinical Risk Index for Babies.

diagnosis (Table 1). In addition, 29 infants had antibiotic therapy continued past 48 hours for the following indications: 10, "culture-negative sepsis;" 7, pneumonia; 3, early onset sepsis; 3, spontaneous intestinal perforation, 3 prophylaxis; 1, congenital syphilis; 1 other; and 1, not known. These 29 infants were not included in the analysis.

The two groups also did not differ in maternal group B streptococcal colonization and chorioamnionitis. Mothers of infants who received a 24 hour course of antibiotic therapy were more likely to have received intrapartum antibiotics and have rupture of fetal membranes greater than 18 hours.

Infants in the 24 hour rule-out group had significantly lower length of antibiotic therapy both during the initial course initiated at <72 hours of age as well as for the entire hospitalization (Table 2). One infant who initially was ordered to receive a 24 hour course of antibiotic therapy had a blood culture positive for *Klebsiella pneumoniae* at 11.5 hours and subsequent analysis of cerebrospinal fluid showed pleocytosis, while 2 infants initially ordered 48 hours of antibiotics had *Escherichia coli* detected in blood cultures at 12.5 hours and 14 hours (Table 2). None of the infants had a positive cerebrospinal fluid culture and none missed any antibiotic doses before the blood culture result was known. One infant had a blood culture positive for viridans group streptococci that was assessed by the attending neonatologist as a contaminant.

Infants in the 24-hour rule-out group were significantly less likely to have antibiotic therapy re-initiated within 7 days after discontinuation of the initial course (Table 2). Otherwise, the two groups did not differ in positive bacterial culture of blood or cerebrospinal fluid in the 7 days after antibiotic discontinuation, and overall and sepsis-related mortality while in the NICU (Table 2). Of the 4 deaths in the initial 24 hour antibiotic group, 3 infants subsequently died from a sepsis-related condition. One 25 weeks' gestational age infant developed septic shock due to gentamicin-resistant *E. coli* at 6 days of age. A second 25 weeks' gestational age infant had posthemorrhagic hydrocephalus with placement of a ventricular drain device; at 4 weeks of age, infant had an acute decompensation and was allowed a natural death. Cerebrospinal fluid culture from the ventricular device subsequently yielded *Cutibacterium acnes* postmortem. A third 25 weeks' gestational age infant died secondary to necrotizing enterocolitis totalis with a concomitant urinary tract infection due to *K. oxytoca* at 5 weeks of age. Of the 7 deaths in the 48 hour group, none were related to an infectious condition.

Table 2. Safety outcomes of newborns who received a 24 vs. 48 hour course of empirical antibiotics for early-onset sepsis in the neonatal intensive care unit.

	Antibiotic Course		*P*-value
	24 Hours	48 Hours	
No. of infants	196	218	–
Length of therapy (LOT; days; median, IQR):			
Initial empirical course	1 (1, 2)	3 (2, 3)	< 0.01
Entire hospitalization	2 (1, 2)	3 (2, 4)	< 0.01
Length of hospitalization (days; median, IQR)	19 (7, 44)	22 (9, 52)	<0.01
Positive blood culture (%)	1 (1)[a]	2 (1)[b]	1
Re-initiation of antibiotics within 7 days (%):	9 (5)	23 (11)	0.02
Cellulitis	1	0	
Culture-negative sepsis	0	2	
Late-onset sepsis	2	3	
Pneumonia	1	4	
Prophylaxis	1	1	
Rule-out sepsis	2	10	
Spontaneous intestinal perforation	0	1	
Surgical site infection	1	0	
Urinary tract infection	0	1	
Mortality (%)	4 (3)	7 (4)	0.46
Sepsis-related (%)	3 (2)	0 (0)	0.1

IQR Interquartile range.
[a]*Klebsiella pneumoniae* (time to positivity, 11.5 hours).
[b]*Escherichia coli* (time to positivity, 12.5 and 14 hours).

DISCUSSION

Prolonged antibiotic therapy in neonates has been associated with adverse consequences, presumably from disruption of the infant's bacterial microbiome [24]. Diminishing the duration of antibiotic exposure in these infants has been a goal of neonatal antimicrobial stewardship programs [25], although the exact duration of antibiotic therapy that may result in adverse outcomes is unknown. Assuming that any antibiotic exposure may predispose to dysbiosis and contribute to antimicrobial resistance, we instituted a guidance of providing only 24 hours of empirical antibiotic therapy for possible early-onset sepsis in the NCH NICUs and delivery hospital newborn nurseries in Columbus, OH. We report our experience with this guidance in 6 NCH NICUs and in our experience, have shown it to be a safe practice.

The guidance was based on our previous experience that the time to positivity of bacterial blood cultures was within 24 hours after its collection. More recently, using Monte Carlo simulations, Le et al. [26] showed that in very-low-birth-weight infants, ampicillin and to a lesser extent gentamicin exposure remained therapeutic beyond the last dose and throughout a typical blood culture incubation period. Specifically, post-discontinuation antibiotic exposure, or the time from the last dose to time when the antibiotic concentration decreased below the mean inhibitory concentration, for ampicillin ranged from 34 to 50 hours for *E. coli* and 82 to 104 hours for group B *Streptococcus*. Single-dose 5 mg/kg gentamicin provided mean inhibitory concentration >2 for 26 hours. Prolonged antibiotic exposure may have occurred among the newborns who received a 24 hour course of antibiotic therapy as their mothers were more likely to have received intrapartum antibiotics.

Compared to infants who received a 48 hour rule-out sepsis course of antibiotics, newborns who received a 24 hour antibiotic course were not more likely to have antibiotic therapy re-initiated within 7 days of their discontinuation nor have positive bacterial cultures of blood or cerebrospinal fluid during that time. On the contrary, antibiotics were more often restarted within 7 days after discontinuation in the 48 hour group (Table 2). In addition, in-hospital mortality, whether overall or sepsis-related, did not differ between the two groups (Table 2).

More infants in the 48 hour antibiotic rule out group had a surgical diagnosis (Table 1). Although the reason remains unclear, we suspect that this may be due to late adoption of the guideline by the surgical team. Efforts have since been directed during daily surgical patient rounds of informing them of the change in practice.

Limitations of the study include its retrospective nature as well as possible changes in intrapartum obstetric practices during the study period that may have affected the safety of the guidance. In addition, all of the six NICUs that participated in the study belonged to one NCH neonatal network and therefore the safety of the shortened course of antibiotic therapy should be studied in different demographic and geographic regions. The input from the NEO-ASP during the study period informed practice and was a

driving force responsible for its implementation and adherence [27]. The finding of only three positive bacterial blood cultures during the study period limits the safety of the intervention. However, the majority of antibiotic use in the NICU is in situations where the cultures are sterile and therein lies the relevance to every day NICU practice [11]. Recently, Arias-Felipe et al. [28] have shown that in 98% of blood cultures from infants in the NICU, the time to positivity was <24 hours. In addition, morbidity from a shortened course of empirical antibiotic therapy such as bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, and neurodevelopmental outcomes was not investigated. Nevertheless, both overall in-hospital and infection-related mortality did not differ before and after implementation of the guideline.

CONCLUSION

In conclusion, in our NICU network utilizing currently recommended EOS guidance and located at hospitals whose microbiology laboratories utilize automated continuous monitoring blood culture systems, antibiotic therapy for suspected EOS can be discontinued safely within 24 hours if blood cultures are sterile and there is no sign of site-specific infection. Additional studies are needed across other demographic and geographic centers. Ongoing education, prospective auditing and feedback, and collaboration among inborn and referral centers helped inform antimicrobial prescribing in the NICU and allowed the successful incorporation of a "24-hour rule-out" with "Time-Out" into our NEO-ASP bundle.

DATA AVAILABILITY

The de-identified dataset generated from the study is available from the corresponding author on reasonable request and following approval by the Institutional Review Board of Nationwide Children's Hospital.

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AUTHOR CONTRIBUTIONS

PJS conceptualized and designed the study, coordinated and supervised data collection, and drafted and revised the manuscript. PP conceptualized and designed the study, designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. CdeAR collected and helped to analyze the data, reviewed and revised the manuscript, and approved the final manuscript as submitted. EZ-F collected and helped to analyze the data, reviewed and revised the manuscript, and approved the final manuscript as submitted. MCRE collected and helped to analyze the data, reviewed and revised the manuscript, and approved the final manuscript as submitted. NOW conceptualized and designed the study, reviewed and revised the manuscript. RRM conceptualized and designed the study, reviewed and revised the manuscript. RM conceptualized and designed the study, reviewed and revised the manuscript. ART conceptualized and designed the study, reviewed, and revised the manuscript. JKM conceptualized

and designed the study, collected data, reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

COMPETING INTERESTS

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ADDITIONAL INFORMATION

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NATIONWIDE CHILDREN'S HOSPITAL NEONATAL ANTIMICROBIAL STEWARDSHIP PROGRAM (NEO-ASP)

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A full list of members and their affiliations appears in the Supplementary Information.