Duration of Initial Empirical Antibiotic Therapy and Outcomes in Very Low Birth Weight Infants

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abstract

BACKGROUND: Overuse of antibiotics can facilitate antibiotic resistance and is associated with adverse neonatal outcomes. We studied the association between duration of antibiotic therapy and short-term outcomes of very low birth weight (VLBW) (<1500 g) infants without culture-proven sepsis.

METHODS: We included VLBW infants admitted to NICUs in the Canadian Neonatal Network between 2010–2016 who were exposed to antibiotics but did not have culture-proven sepsis in the first week. Antibiotic exposure was calculated as the number of days an infant received antibiotics in the first week of life. Composite primary outcome was defined as mortality or any major morbidity (severe neurologic injury, retinopathy of prematurity, necrotizing enterocolitis, chronic lung disease, or hospital-acquired infection).

RESULTS: Of the 14 207 included infants, 21% (n = 2950), 38% (n = 5401), and 41% (n = 5856) received 0, 1 to 3, and 4 to 7 days of antibiotics, respectively. Antibiotic exposure for 4 to 7 days was associated with higher odds of the composite outcome (adjusted odds ratio 1.24; 95% confidence interval [CI] 1.09–1.41). Each additional day of antibiotic use was associated with 4.7% (95% CI 2.6%–6.8%) increased odds of composite outcome and 7.3% (95% CI 3.3%–11.4%) increased odds in VLBW infants at low risk of early-onset sepsis (born via cesarean delivery, without labor and without chorioamnionitis).

CONCLUSIONS: Prolonged empirical antibiotic exposure within the first week after birth in VLBW infants is associated with increased odds of the composite outcome. This practice is a potential target for antimicrobial stewardship.

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Drs Ting and Shah conceptualized and designed the study, analyzed and interpreted the data, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Roberts, Sherlock, Ojah, Cieslak, Dunn, and Barrington and Mr Yoon contributed to the analysis and interpretation of the data and critically reviewed the manuscript for intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2018-2286

Accepted for publication Dec 11, 2018

WHAT'S KNOWN ON THIS SUBJECT: Previous studies reported that either mortality or individual morbidity was associated with prolonged antibiotic exposure in preterm infants. However, studies on composite adverse outcomes or initial prolonged antibiotic use in reflection of turnaround time of blood culture results are lacking.

WHAT THIS STUDY ADDS: This study revealed increased adverse composite outcomes associated with >3 calendar days and each additional day of antibiotic exposure within the first week of life among infants with very low birth weight without culture-proven sepsis.

To cite: Ting JY, Roberts A, Sherlock R, et al. Duration of Initial Empirical Antibiotic Therapy and Outcomes in Very Low Birth Weight Infants. *Pediatrics*. 2019;143(3): e20182286

Early-onset sepsis (EOS) is a serious problem among infants with very low birth weight (VLBW). The reported incidence of EOS among VLBW infants has ranged from 11 to 20 cases per 1000 births over the past 20 years.[1] In daily clinical practice, the majority of VLBW or preterm infants are treated with empirical antibiotics after birth. In the United States, it has been estimated that 60 to 1400 neonates receive diagnostic evaluations and antibiotics per each infected neonate.[2] Common practice is to initiate antibiotics after birth and discontinue them in 36 to 48 hours if the microbiologic cultures do not reveal any pathogen growth. However, Cotten et al[3] reported that more than half of infants with extremely low birth weight (ELBW) in their cohort were continued on antibiotics for at least 5 days despite having sterile blood cultures.

Antibiotics can be lifesaving for the few infants who are truly infected, but overuse can facilitate antibiotic resistance and is associated with increased neonatal morbidities, mortality, or significant neurodevelopmental impairment.[4,5] Advances in blood culture techniques, including the use of optimized enriched broths, have resulted in the ability to detect bacteremia at $<$10 colony-forming units per mL.[6] Culture media with antimicrobial neutralization properties enhance the reliability of blood cultures when the mother has received intrapartum treatment. When the blood culture test is performed properly, it allows clinicians to stop antibiotic treatment with confidence.

Epidemiologic studies have shown that prolonged initial empirical antibiotic treatment is associated with adverse outcomes, including the development of hospital-acquired infections (HAIs), necrotizing enterocolitis (NEC), or death.[3,7] However, most of these studies used 5 days of therapy as a cutoff, consistent with the EOS definition in the *Eunice Kennedy Shriver* National Institutes of Child Health and Human Development Neonatal Research Network (NICHD NRN) registry (positive blood culture result within the first 3 postnatal days and treatment of $\geq$5 days), despite a typical time-to-positivity for aerobic blood cultures of within 48 hours.[3,7–9] Our objective was to compare the short-term outcomes of VLBW infants who received different durations of antibiotic exposure (none versus 1–3 days and 4–7 days) without culture-proven sepsis in the first 7 days after birth.

METHODS

This was a retrospective cohort study in which we used data from the Canadian Neonatal Network (CNN) database, which has been shown to have high consistency and reliability.[10] Data were abstracted from infant medical records according to standardized definitions and transmitted to the CNN coordinating center at Mount Sinai Hospital in Toronto, Ontario, Canada. We included data from infants with VLBW ($<$1500 g) admitted to participating NICUs between January 1, 2010, and December 31, 2016. The data were obtained from 29 tertiary NICUs, which encompasses ~90% of eligible neonates born in Canada during the study period. Infants who had a major congenital anomaly, were outborn, developed culture-proven sepsis (positive blood or cerebrospinal fluid culture results) or any intestinal perforation or NEC within the first 7 days of life, died, were discharged to level II hospitals within the first 7 days, or were moribund on admission were excluded.

Initial antibiotic treatment was defined as antibiotic treatment within the first week after birth. The duration of initial antibiotic therapy was defined as the total number of calendar days of antibiotic administration. Infants were classified into 3 groups (antibiotic exposure: none, 1–3 days, and 4–7 days). Because we did not collect information on antibiotic duration in hours, we used a cutoff of 3 calendar days to define short and prolonged initial empirical antibiotic therapy. Additionally, we investigated the effect of each additional day of antibiotic use and its impact on outcome using antibiotic days as a continuous measure. Antibiotics included agents prescribed to actively inhibit or kill infecting pathogens according to the CNN drug classification list in the CNN Abstractor's Manual.[11] Prophylactic administration of trimethoprim or amoxicillin for the prevention of urinary tract infections in patients with a suspected renal anomaly was not included.

Study variables were defined according to the CNN Abstractor's Manual.[11] Gestational age (GA) was defined as the best obstetric estimate based on early prenatal ultrasound, obstetric examination, and obstetric history unless the postnatal pediatric estimate of gestation differed from the obstetric estimate by $>$2 weeks. In this case, the pediatric estimate of GA was used instead. An infant was considered small for GA if the birth weight was $<$10th percentile for GA. The Score for Neonatal Acute Physiology II (SNAP-II) is a validated measure of newborn severity of illness that captures physiologic derangements within the first 12 hours of admission to the NICU.[12] Extensive cardiopulmonary resuscitation (CPR) was defined as chest compressions for $>$30 seconds, the use of epinephrine during initial resuscitation immediately after birth, or both. EOS was indicated by positive bacterial, viral, or fungal culture results in blood or cerebrospinal fluid from birth to age 2 days.

The composite primary outcome was defined as mortality or major

morbidity. Major morbidity was defined as the presence of any of the following findings during the hospital stay: severe intraventricular hemorrhage (IVH) (grade 3 or 4),[13] periventricular leukomalacia (PVL),[14] stage 3 through 5 retinopathy of prematurity (ROP) in either eye,[15] greater than or equal to stage 2 NEC,[16] chronic lung disease (CLD) (classified operationally as the receipt of oxygen at 36 weeks' postmenstrual age or at discharge, whichever came first),[17] or HAI (positive blood or cerebrospinal fluid culture results after 7 days of age). The individual components of the composite primary outcome and patent ductus arteriosus (PDA) were regarded as secondary outcomes. Severe neurologic injury referred to either severe IVH or PVL. Because the majority of IVH cases occur within 48 to 72 hours after birth and more than half occur during the first 24 hours (ie, before completion of an antibiotic course for presumed EOS), we analyzed a composite outcome excluding severe IVH ("composite outcome II") as well.

We also analyzed the primary and secondary outcomes among infants considered to be at low risk of developing EOS (born via cesarean delivery, without labor and without chorioamnionitis)[1,18] and among a subcohort of infants with ELBW (<1000 g).

The distribution of baseline characteristics among infants receiving 0, 1 to 3, or 4 to 7 days of initial empirical antibiotics was assessed by using χ^2 and/or Fisher exact tests and analysis of variance and/or Student's *t* tests for categorical and continuous variables, respectively. Odds ratios and 95% confidence intervals (CIs) were initially estimated by using univariate logistic regression analyses to quantify the association between the composite outcome and duration of antibiotic treatment. Multivariable logistic regression was performed after adjusting for potential confounders and other covariates on the basis of findings in the univariate analysis. Similar analyses were conducted by using the per-day increase in antibiotic use and its association with primary and secondary outcomes. All statistical analyses were conducted by using a software program (SAS version 9.3; SAS Institute, Inc, Cary, NC), with statistical significance evaluated by using 2-sided *P* values at the 5% testing level.

Data collection and transmission from each site to the CNN coordinating center was approved by an individual ethics board or quality-improvement committee. This study was approved by the Children's and Women's Research Ethics Board at The University of British Columbia and the CNN Executive Committee.

RESULTS

There were 20 741 VLBW infants identified between 2010 and 2016. After excluding infants with a major congenital anomaly (*n* = 658), who were outborn (*n* = 3113), and who were missing data (*n* = 410), the overall EOS rate in the VLBW group was 230 per 16 560 infants (1.39%). VLBW infants shown to be at lower risk of EOS in previous reports[1,18] (born through cesarean delivery, no labor, and with no chorioamnionitis) were found to have a substantial lower rate of EOS (0.49% vs 1.79% [$P < .01$] or an adjusted odds ratio [aOR] of 0.51 [95% CI 0.32–0.81]) compared with other VLBW infants without these characters (adjusted for GA, SNAP-II score, extensive CPR, prolonged rupture of membranes ≥24 hours, and multiple births). Using the same criteria, we found that very low–risk ELBW infants also had a lower rate of EOS (0.79% vs 2.57% [$P < .01$] or an aOR of 0.52 [95% CI 0.28–0.93]) than other ELBW infants.

In the analysis of early antibiotic use, we further excluded death or discharge to a level II hospital within the first 7 days of birth (*n* = 1303), spontaneous intestinal perforation or NEC within the first 7 days, or an unknown number of days of diagnoses (*n* = 472) and culture-proven sepsis in the first 7 days (*n* = 578). The remaining 14 207 infants were included in this study, of whom 2950 (21%), 5401 (38%), and 5856 (41%) received 0, 1 to 3, or 4 to 7 days of antibiotics, respectively (Table 1). Among CNN-participating NICUs, the proportion of VLBW infants who received 4 to 7 days of antibiotics ranged from 22% to 73%, with an average of 41% (Fig 1).

Neonates with lower birth weight; of earlier GA; of male sex; with a lower Apgar score at 5 minutes; with a higher SNAP-II score; with extensive resuscitation; who received surfactant; of vaginal delivery; with prolonged rupture of membranes (PROM) ≥24 hours; with suspected or confirmed chorioamnionitis; with pneumothorax; or with a need for

TABLE 1 Initial Empirical Antibiotic Use in Canada

	No. Infants	Antibiotic Exposure, *n* (%)			Antibiotic Use Within the First wk After Birth,[a] Median d (IQR)
		None	1–3 d	4–7 d	
All infants with BW <1500 g	14 207	2950 (21)	5401 (38)	5856 (41)	4 (3–6)
All infants with BW <1000 g	5572	698 (13)	1775 (32)	3099 (56)	5 (3–7)

BW, birth wt; IQR, interquartile range.

[a] Only includes infants treated with antibiotics.

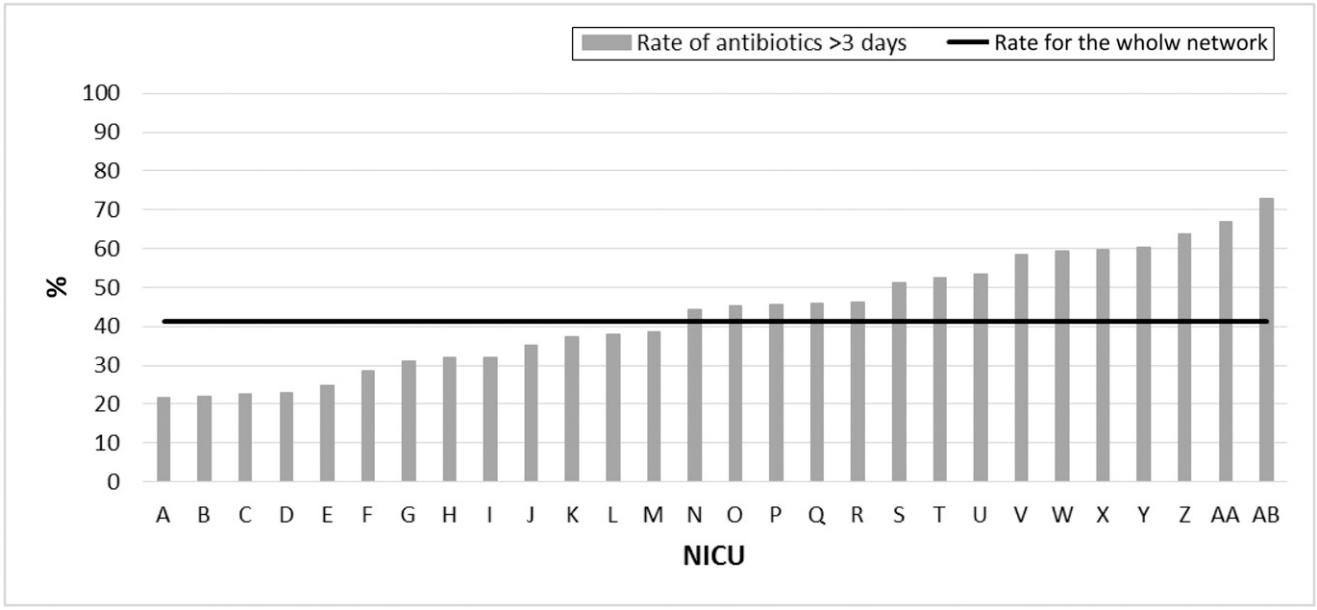

FIGURE 1
Variation in the proportion of neonates who received antibiotics >3 days by NICU. The denominator is all VLBW infants (N = 20 741).

mechanical ventilation, inotropes, or inhaled nitric oxide (iNO) in the first 3 days were more likely to have received longer durations of antibiotics (Table 2).

After adjusting for the confounding variables, prolonged antibiotic exposure for 4 to 7 days in the first week after birth was associated with higher adjusted odds of composite outcomes than receiving no antibiotics (aOR 1.24; 95% CI 1.09–1.41) or 1 to 3 days of antibiotics (aOR 1.38; 95% CI 1.25–1.51; Table 3). Similar results were identified when we reanalyzed the composite outcomes, excluding infants with grade 3 or 4 IVH (composite outcome II). Four to 7 days of antibiotic treatment was also associated with increased adjusted odds of CLD, PDA requiring

TABLE 2 Perinatal Characteristics Among Infants Receiving Initial Empirical Antibiotics of Various Durations

Characteristics	Antibiotic Exposure			P^a	P^b
	None (N = 2950)	1–3 d (N = 5401)	4–7 d (N = 5856)		
Multiple pregnancy, *n* (%)	915 (31)	1798 (33)	1596 (28)	<.01	<.01
Cesarean delivery, *n* (%)	2560 (87)	3376 (63)	3569 (61)	<.01	.09
PROM ≥24 h, *n* (%)	101 (4)	1144 (22)	1729 (30)	<.01	<.01
Suspected or confirmed chorioamnionitis, *n* (%)	101 (4)	823 (20)	1471 (31)	<.01	<.01
Completed antenatal steroids, *n* (%)	2240 (78)	4033 (75)	4381 (76)	<.01	.55
Male sex, *n* (%)	1375 (47)	2828 (52)	3079 (53)	<.01	.84
Birth wt, mean (SD)	1169 (236)	1111 (250)	987 (269)	<.01	<.01
GA, mean (SD)	30.3 (2.3)	28.3 (2.3)	27.2 (2.4)	<.01	<.01
SGA, *n* (%)	1275 (43)	797 (15)	852 (15)	<.01	.76
Apgar score <7 at 5 min, *n* (%)	409 (14)	1330 (25)	2182 (37)	<.01	<.01
Extensive CPR,[c] *n* (%)	19 (1)	131 (2)	275 (5)	<.01	<.01
SNAP-II score >20, *n* (%)	132 (4)	742 (14)	1660 (28)	<.01	<.01
Receipt of any doses of surfactant, *n* (%)	706 (24)	2587 (48)	4015 (69)	<.01	<.01
Mechanical ventilation for all first 3 d after birth, *n* (%)	152 (5)	886 (16)	2342 (40)	<.01	<.01
Inotropes in any of first 3 d after birth, *n* (%)	38 (1)	244 (5)	813 (14)	<.01	<.01
iNO in any of first 3 d after birth, *n* (%)	4 (0)	78 (1)	269 (5)	<.01	<.01
Pneumothorax treated with chest tube, *n* (%)	17 (1)	91 (2)	244 (4)	<.01	<.01

SGA, small for gestational age.
[a] Comparisons of 3 groups (none versus 1–3 d and 4–7 d).
[b] Comparisons of 2 groups (1–3 d vs 4–7 d).
[c] Chest compression or epinephrine.

TABLE 3 Distribution of Mortality and Morbidities and the Composite Outcome Among VLBW Infants

Outcome	Antibiotic Exposure			aOR[a] (95% CI) 1–3 d Versus None[b]	aOR[a] (95% CI) 4–7 d Versus None[b]	aOR[a] (95% CI) 4–7 d Versus 1–3 d[c]
	None (*N* = 2950), *n* (%)	1–3 d (*N* = 5401), *n* (%)	4–7 d (*N* = 5856), *n* (%)			
Composite outcome[d]	646 (22)	1987 (37)	3403 (58)	0.90 (0.79–1.02)	1.24 (1.09–1.41)	1.38 (1.25–1.51)
Composite outcome II[e]	631 (21)	1935 (36)	3334 (57)	0.89 (0.78–1.00)	1.21 (1.06–1.37)	1.36 (1.24–1.50)
Mortality after 7 d of age	30 (1)	144 (3)	354 (6)	1.11 (0.72–1.69)	1.20 (0.78–1.83)	1.08 (0.87–1.34)
Severe neurologic injury[f]	55 (2)	255 (5)	564 (10)	1.48 (1.08–2.03)	1.87 (1.37–2.57)	1.27 (1.07–1.50)
PDA requiring treatment	263 (9)	1101 (20)	2004 (34)	1.16 (0.98–1.38)	1.29 (1.09–1.53)	1.11 (0.99–1.23)
Greater than or equal to stage 2 NEC	81 (3)	177 (3)	273 (5)	0.74 (0.55–0.99)	0.75 (0.56–1.02)	1.02 (0.83–1.25)
HAI	258 (9)	666 (12)	1149 (20)	0.83 (0.70–0.99)	0.93 (0.78–1.10)	1.11 (0.99–1.25)
CLD	391 (16)	1358 (27)	2497 (46)	0.89 (0.77–1.03)	1.22 (1.06–1.41)	1.37 (1.25–1.51)
Greater than or equal to stage 3 ROP or ROP treated	42 (3)	203 (7)	580 (14)	0.76 (0.52–1.11)	0.98 (0.68–1.42)	1.29 (1.07–1.56)
PVL	31 (1)	111 (2)	219 (4)	1.26 (0.82–1.94)	1.49 (0.97–2.30)	1.18 (0.92–1.52)

[a] Adjusted for GA, SNAP-II score >20, extensive CPR, PROM ≥24 h, multiple births, surfactant use, mechanical ventilation for all first 3 d, inotropes in any of first 3 d, iNO in any of first 3 d, and pneumothorax treated with chest tube in a logistic regression model (significant variables identified by using univariate tests between 0, 1–3, and 4–7 d). Chorioamnionitis was not included in the model because of too many missing values.

[b] Reference is 0 d.

[c] Reference is 1–3 d.

[d] Composite outcome is any severe IVH (grade 3 or 4), NEC (greater than or equal to stage 2), CLD, severe ROP (greater than or equal to stage 3), HAI, or death.

[e] Composite outcome II is any PVL, NEC (greater than or equal to stage 2), CLD, severe ROP (greater than or equal to stage 3), HAI, or death.

[f] Severe neurologic injury is IVH grade 3 or 4 or PVL.

treatment, and ROP than shorter antibiotic durations.

Subgroup analyses of VLBW infants at low risk of EOS (born via cesarean delivery, without labor and without chorioamnionitis) revealed that 31% (1168 in 3797) of subjects received prolonged antibiotics for 4 to 7 days (Table 4). Prolonged antibiotic exposure for 4 to 7 days in this subpopulation was also associated with increased adjusted odds of composite outcome and CLD compared with having no exposure to any antibiotics. Subgroup analyses of ELBW infants also yielded similar results (Table 5).

Finally, each additional day of antibiotic use, when tested as a continuous variable, was associated with 4.7% higher odds (95% CI 2.6%–6.8%) of composite outcome in

TABLE 4 Distribution of Mortality and Morbidities and the Composite Outcome Among VLBW Infants in the Low-Risk Category

Outcome	Antibiotic Exposure			aOR[a] (95% CI) 1–3 d Versus None[b]	aOR[a] (95% CI) 4–7 d Versus None[b]	aOR[a] (95% CI) 4–7 d Versus 1–3 d[c]
	None (*N* = 1512), *n* (%)	1–3 d (*N* = 1117), *n* (%)	4–7 d (*N* = 1168), *n* (%)			
Composite outcome[d]	364 (24)	419 (38)	687 (59)	1.03 (0.84–1.26)	1.51 (1.22–1.87)	1.47 (1.19–1.80)
Composite outcome II[e]	356 (24)	409 (37)	679 (58)	1.02 (0.83–1.25)	1.51 (1.22–1.86)	1.48 (1.20–1.81)
Mortality after 7 d of life	18 (1)	38 (3)	54 (5)	1.59 (0.86–2.91)	1.18 (0.64–2.18)	0.74 (0.47–1.17)
Severe neurologic injury[f]	28 (2)	49 (5)	73 (6)	1.67 (1.01–2.77)	1.60 (0.96–2.68)	0.96 (0.64–1.43)
PDA requiring treatment	140 (9)	226 (20)	407 (35)	1.12 (0.85–1.47)	1.29 (0.98–1.68)	1.15 (0.91–1.45)
Greater than or equal to stage 2 NEC	43 (3)	36 (3)	48 (4)	0.79 (0.49–1.27)	0.69 (0.42–1.12)	0.87 (0.55–1.39)
HAI	125 (8)	127 (11)	229 (20)	0.98 (0.74–1.30)	1.42 (0.94–1.64)	1.27 (0.99–1.64)
CLD	251 (19)	304 (30)	544 (50)	0.97 (0.77–1.22)	1.39 (1.11–1.75)	1.44 (1.16–1.78)
Greater than or equal to stage 3 ROP or ROP treated	21 (3)	29 (5)	90 (11)	0.77 (0.41–1.47)	1.24 (0.71–2.19)	1.61 (0.98–2.64)
PVL	17 (1)	23 (2)	32 (3)	1.33 (0.68–2.61)	1.19 (0.59–2.40)	0.90 (0.51–1.59)

Those in the low-risk category included infants delivered via cesarean, with no labor onset and no chorioamnionitis.

[a] Adjusted for GA, SNAP-II score >20, extensive CRP, PROM ≥24 h, multiple births, surfactant use, mechanical ventilation for all first 3 d, inotropes in any of first 3 d, iNO in any of first 3 d, and pneumothorax treated with chest tube in a logistic regression model (significant variables identified by using univariate tests between 0, 1–3, and 4–7 d). Chorioamnionitis was not included in the model because of too many missing values.

[b] Reference is 0 d.

[c] Reference is 1–3 d.

[d] Composite outcome is any severe IVH (grade 3 or 4), NEC (greater than or equal to stage 2), CLD, severe ROP (greater than or equal to stage 3), HAI, or death.

[e] Composite outcome 2 is any PVL, NEC (greater than or equal to stage 2), CLD, severe ROP (greater than or equal to stage 3), HAI, or death.

[f] Severe neurologic injury is IVH grade 3 or 4 or PVL.

TABLE 5 Distribution of Mortality and Morbidities and the Composite Outcome Among ELBW Infants

Outcome	Antibiotic Exposure			aOR[a] (95% CI) 1–3 d Versus None[b]	aOR[a] (95% CI) 4–7 d Versus None[b]	aOR[a] (95% CI) 4–7 d Versus 1–3 d[c]
	None (N = 698), n (%)	1–3 d (N = 1775), n (%)	4–7 d (N = 3099), n (%)			
Composite outcome[d]	314 (45)	1100 (62)	2429 (78)	0.98 (0.80–1.20)	1.51 (1.23–1.86)	1.55 (1.34–1.79)
Composite outcome II[e]	311 (45)	1084 (61)	2397 (77)	0.96 (0.78–1.18)	1.45 (1.18–1.79)	1.52 (1.32–1.75)
Mortality after 7 d of life	20 (3)	118 (7)	302 (10)	1.32 (0.78–2.23)	1.29 (0.77–2.17)	0.98 (0.77–1.24)
Severe neurologic injury[f]	20 (3)	133 (8)	400 (13)	1.52 (0.92–2.53)	1.89 (1.15–3.11)	1.24 (1.00–1.55)
PDA requiring treatment	146 (21)	698 (39)	1553 (50)	1.15 (0.91–1.46)	1.30 (1.03–1.64)	1.23 (0.98–1.29)
Greater than or equal to stage 2 NEC	37 (5)	95 (5)	195 (6)	0.78 (0.51–1.19)	0.79 (0.52–1.21)	1.02 (0.78–1.33)
HAI	114 (16)	402 (23)	849 (27)	0.92 (0.72–1.19)	0.93 (0.72–1.20)	1.01 (0.87–1.17)
CLD	234 (36)	799 (48)	1862 (66)	0.85 (0.69–1.05)	1.31 (1.06–1.62)	1.55 (1.35–1.77)
Greater than or equal to stage 3 ROP or ROP treated	34 (7)	186 (14)	537 (21)	0.81 (0.53–1.23)	0.98 (0.65–1.48)	1.22 (0.99–1.49)
PVL	11 (2)	54 (3)	148 (5)	1.29 (0.64–2.62)	1.41 (0.70–2.82)	1.09 (0.78–1.52)

[a] Adjusted for GA, SNAP-II score >20, extensive CRP, PROM ≥24 h, multiple births, surfactant use, mechanical ventilation for all first 3 d, inotropes in any of first 3 d, iNO in any of first 3 d, and pneumothorax treated with chest tube in a logistic regression model (significant variables identified by using univariate tests between 0, 1–3, and 4–7 d). Chorioamnionitis was not included in the model because of too many missing values.

[b] Reference is 0 d.

[c] Reference is 1–3 d.

[d] Composite outcome is any severe IVH (grade 3 or 4), NEC (greater than or equal to stage 2), CLD, severe ROP (greater than or equal to stage 3), HAI, or death.

[e] Composite outcome II is any PVL, NEC (greater than or equal to stage 2), CLD, severe ROP (greater than or equal to stage 3), HAI, or death.

[f] Severe neurologic injury is IVH grade 3 or 4 or PVL.

VLBW infants, 7.3% higher odds (95% CI 3.3%–11.4%) in low-risk VLBW infants, and 7.0% higher odds (95% CI: 3.8–10.4) in ELBW infants.

DISCUSSION

In this large, population-based retrospective study, we identified that 42% of VLBW neonates were exposed to >3 days of empirical antibiotics without evidence of culture-proven sepsis, with marked variations in treatments between NICUs in Canada. Even among VLBW infants at low risk of EOS, 31% were exposed to 4 to 7 days of empirical antibiotics. A prolonged initial antibiotic exposure of >3 days within the first week after birth was associated with increased odds of mortality or significant morbidities, including CLD, PDA, ROP, and severe neurologic injury, after adjustment for baseline differences in population characteristics.

Researchers in previous studies have reported similar findings to ours, although the cutoff for the classification of prolonged duration has not been consistent. For example, in a study of 19 neonatal centers in the NICHD NRN, 53% of ELBW infants received prolonged antibiotics, defined as ≥5 days.[3] In a retrospective study by Cordero and Ayers,[19] the average duration of treatment among 695 infants (<1000 g) with negative blood culture results was 5 ± 3 days. Approximately half of these infants received a ≥7-day course of antibiotics with no antepartum historical risk factors or neonatal clinical signs to explain such a prolonged administration.[19] Novitsky et al[20] reported that only 18% (159 of 960) of VLBW infants received >48 hours of antibiotics during the first week of life, which was substantially lower than what we reported in this study.

Our findings of grave unintended consequences caused by antibiotic overuse were similar to those reported in the literature. Antibiotic duration >48 hours in the first week after birth was associated with subsequent CLD (31% vs 14%; $P <$ .01) and the presence of resistant bacteria in routine endotracheal aspirate cultures (7% vs 2%; $P <$ .01) in 906 VLBW infants.[20] Cantey et al[21] reported that each additional day of antibiotic therapy in the first 2 weeks after birth was associated with both increased risk and severity of bronchopulmonary dysplasia in 1324 VLBW infants. Prolonged initial empirical antibiotic treatment ≥5 days with sterile blood cultures was associated with increased odds of NEC and/or death in ELBW infants (n = 5963).[3] Although it can be debatable whether to start empirical antibiotics in an individual infant with critical conditions right after birth, any prolonged antimicrobial course >3 days without a positive microbiology finding should be the exception rather than the rule. Moreover, our analyses highlight the association of increased adverse composite outcomes with each additional day of antibiotic exposure and suggest that the duration of antibiotic use matters more than defining a specific cutoff for antibiotic treatment.

In Table 3, we found VLBW infants receiving 1 to 3 days of antibiotics had significantly lower ratios of infants with greater than or equal to stage 2 NEC (aOR 0.74; 95% CI 0.55–0.99) or HAI (aOR 0.83; 95% CI

0.70–0.99) than infants who did not receive antibiotics. However, the same ratios were not significantly different for VLBW infants at low risk of EOS or ELBW infants (Tables 4 and 5). With the CIs at the upper margins (ie, 0.99), we believe the significance in the VLBW group is likely because of sample size rather than protective effects.

At the individual level, antibiotic use either perinatally or postnatally has been linked to disruptions in the microbiome.[22,23] The alteration in intestinal microbiota has been postulated to play a critical role in the development of significant neonatal morbidities, including PVL, ROP, CLD, and NEC, through the regulation of systemic inflammation.[4,24] Prolonged broad-spectrum antibiotic exposure, especially third-generation cephalosporin agents, is known to be associated with increased risks of colonization with multiresistant organisms, which can become the source of subsequent bloodstream infections.[25] Aminoglycoside-induced vasorelaxation of PDA may potentially offset the benefits of prophylactic indomethacin for the prevention of IVH.[26,27] To the best of our knowledge, our study is the largest to date to investigate the impact of early antibiotic exposure on various neonatal outcomes by using the pragmatic definition of 3 days of antibiotics as a cutoff, which reflects the usual turnaround time of blood culture results.

The adverse health effects of antibiotic use may extend well beyond early infancy. Our group previously reported associations between high antibiotic use rates and increases in neonatal morbidities as well as death or significant neurodevelopmental impairment among infants without culture-proven sepsis or NEC.[4,5] Antibiotic treatment in the first week after birth may also increase the subsequent risk of wheezing and infantile colic.[28] Repeated exposure to broad-spectrum antibiotics in early life has also been reported to be linked to childhood obesity.[29] Unfortunately, we do not have medium- or long-term health outcome data on infants with varying antibiotic exposures in early life.

Concerns about occult intrauterine infection precipitating preterm labor, preterm rupture of membranes, and chorioamnionitis often prompt the initiation of empirical antibiotics for possible EOS.[7] Clinicians often face the dilemma of striking a balance between overuse and underuse of antibiotics. Birth characteristics of preterm infants can be used to identify premature infants at low risk of EOS, and those without major risk factors should not have unnecessarily prolonged antibiotics if blood culture results come back negative.[1]

A finding of major concern was that 31% of VLBW infants at low risk of EOS received >3 days of antibiotics within their first week after birth. Virtually all cultures growing clinically significant Gram-positive and Gram-negative organisms had positive results within 48 hours of incubation in studies of both term infants and VLBW infants.[1,8] Inoculation of 1 mL of blood into a single blood culture bottle should provide excellent sensitivity even at low levels of infectious organisms (1–4 colony-forming units per mL), although submission of inadequate blood volume was not infrequent, resulting in the reliability of negative blood culture results being questioned.[30] In the Surveillance and Correction of Unnecessary Antibiotic Therapy study, infants with sterile blood cultures who received 36 to 48 hours of empirical therapy virtually never required retreatment.[31] Our finding of increased composite outcomes and CLD among VLBW infants in the low risk of EOS category (born through cesarean delivery, with no labor and no chorioamnionitis) was strikingly similar to the finding reported by the NICHD NRN for low-risk ELBW infants (delivered via cesarean, with membrane rupture at delivery and absence of clinical chorioamnionitis).[18] The similar magnitude of potential harm in 2 large studies from different national databases suggests that prolonged antibiotic treatment of infants with low EOS risk deserves particular attention in NICU antimicrobial stewardship programs.

A major strength of our study is that it represents a national, population-based sample and the inclusion of a population without clear indications for prolonged empirical antibiotics. However, this study also has some limitations. First, we did not collect data on the exact nature of antibiotics used, which is likely to have a profound impact on gut microbiota composition. Thus, we cannot comment on which antibiotics might be more harmful than others. However, the usual initial antibiotic of choice in most units in Canada include ampicillin and an aminoglycoside. Second, prolonged use of empirical antibiotics may merely reflect the degree of severity of illness in early life. However, after adjusting for confounders, including the severity-of-illness score, we still identified higher rates of composite outcomes among the infants who received prolonged empirical antibiotics. Any antibiotic exposure was associated with severe neurologic injury in VLBW infants (Tables 3 and 4). We acknowledge that the issue of residual confounding and confounding by indication remains and can only be addressed in a randomized clinical trial, which is unlikely to be feasible in this population. Third, the diagnosis of chorioamnionitis could be somewhat subjective and not always consistent.

In the multivariate logistic regression model, we were not able to include chorioamnionitis as a confounding variable because of a significant proportion of missing values. This limitation may be overcome in subsequent studies because guidance on how to define suspected or confirmed intraamniotic infection has been published by the Committee on Obstetric Practice of the American College of Obstetricians and Gynecologists recently.[32]

CONCLUSIONS

We demonstrated potential harm from prolonged empirical antibiotic use within the first week after birth in VLBW infants. This practice can be a potential target for antimicrobial stewardship in neonatal units to optimize antibiotic use, especially among infants at low risk of EOS.

ACKNOWLEDGMENTS

We gratefully acknowledge all site investigators and abstractors of the CNN. We also thank Sarah Hutchinson, PhD, from the Maternal-Infant Care Research Centre at Mount Sinai Hospital (Toronto, Ontario) for her editorial assistance in the preparation of this article and other Maternal-Infant Care staff for their organizational support of the CNN and this project. The Maternal-Infant Care Research Centre is supported by a team grant from the Canadian Institutes of Health Research (CTP 87518), the Ontario Ministry of Health and Long-Term Care, and in-kind support from Mount Sinai Hospital. CNN site investigators included the following: Prakesh S. Shah, MD, MSc (director, CNN and site investigator), Mount Sinai Hospital, Toronto, Ontario; Jaideep Kanungo, MD, Victoria General Hospital, Victoria, British Columbia; Joseph Ting, MD, British Columbia. Women's Hospital and Health Centre, Vancouver, British Columbia; Zenon Cieslak, MD, Royal Columbian Hospital, New Westminster, British Columbia; Rebecca Sherlock, MD, Surrey Memorial Hospital, Surrey, British Columbia; Wendy Yee, MD, Foothills Medical Centre, Calgary, Alberta; Jennifer Toye, MD, Royal Alexandra Hospital, Edmonton, Alberta; Carlos Fajardo, MD, Alberta Children's Hospital, Calgary, Alberta; Zarin Kalapesi, MD, Regina General Hospital, Regina, Saskatchewan; Koravangattu Sankaran, MD, MBBS, Royal University Hospital, Saskatoon, Saskatchewan; Sibasis Daspal, MD, Royal University Hospital, Saskatoon, Saskatchewan; Mary Seshia, MBChB, Winnipeg Health Sciences Centre, Winnipeg, Manitoba; Ruben Alvaro, MD, St Boniface General Hospital, Winnipeg, Manitoba; Amit Mukerji, MD, Hamilton Health Sciences Centre, Hamilton, Ontario; Orlando Da Silva, MD, MSc, London Health Sciences Centre, London, Ontario; Chuks Nwaesei, MD, Windsor Regional Hospital, Windsor, Ontario; Kyong-Soon Lee, MD, MSc, Hospital for Sick Children, Toronto, Ontario; Michael Dunn, MD, Sunnybrook Health Sciences Centre, Toronto, Ontario; Brigitte Lemyre, MD, Children's Hospital of Eastern Ontario and Ottawa General Hospital, Ottawa, Ontario; Kimberly Dow, MD, Kingston General Hospital, Kingston, Ontario; Ermelinda Pelausa, MD, Jewish General Hospital, Montréal, Québec; Keith Barrington, MBChB, and Anie Lapoint, MD, Hôpital Sainte-Justine, Montréal, Québec; Christine Drolet, MD, Hôpital Sainte-Justine, Montréal, Québec; Bruno Piedboeuf, MD, Centre Hospitalier Universitaire de Québec, Sainte-Foy, Québec; Martine Claveau, MSc, LLM, NNP, Montreal Children's Hospital at McGill University Health Centre, Montréal, Québec; Marc Beltempo, MD, Montreal Children's Hospital at McGill University Health Centre, Montréal, Québec; Valerie Bertelle, MD, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Québec; Edith Masse, MD, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Québec; Roderick Canning, MD, Moncton Hospital, Moncton, New Brunswick; Hala Makary, MD, Dr Everett Chalmers Hospital, Fredericton, New Brunswick; Cecil Ojah, MBBS, Saint John Regional Hospital, Saint John, New Brunswick; Luis Monterrosa, MD, Saint John Regional Hospital, Saint John, New Brunswick; Julie Emberley, MD, Janeway Children's Health and Rehabilitation Centre, St John's, Newfoundland; Jehier Afifi, MB BCh, MSc, IWK Health Centre, Halifax, Nova Scotia; Andrzej Kajetanowicz, MD, Cape Breton Regional Hospital, Sydney, Nova Scotia; and Shoo K. Lee, MBBS, PhD (chairman, CNN), Mount Sinai Hospital, Toronto, Ontario.

ABBREVIATIONS

aOR: adjusted odds ratio
CI: confidence interval
CLD: chronic lung disease
CNN: Canadian Neonatal Network
CPR: cardiopulmonary resuscitation
ELBW: extremely low birth weight
EOS: early-onset sepsis
GA: gestational age
HAI: hospital-acquired infection
iNO: inhaled nitric oxide
IVH: intraventricular hemorrhage
NEC: necrotizing enterocolitis
NICHD NRN: *Eunice Kennedy Shriver* National Institutes of Child Health and Human Development Neonatal Research Network
PDA: patent ductus arteriosus
PROM: prolonged rupture of membranes
PVL: periventricular leukomalacia
ROP: retinopathy of prematurity
SNAP-II: Score for Neonatal Acute Physiology II
VLBW: very low birth weight

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

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

FUNDING: The Canadian Neonatal Network received organizational support from the Maternal-Infant Care Research Centre at Mount Sinai Hospital in Toronto, Ontario, Canada. The Maternal-Infant Care Research Centre is supported by a team from the Canadian Institutes of Health Research (CTP 87518), the Ontario Ministry of Health and Long-Term Care, and in-kind support from Mount Sinai Hospital. Dr Ting receives salary support from the Investigator Grant Award Program of the British Columbia Children's Hospital Research Institute. Dr Shah holds an Applied Research Chair in Reproductive and Child Health Services and Policy Research awarded by the Canadian Institutes of Health Research (APR 126340). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the article; or decision to submit the article for publication. Dr Shah had full access to all data in the study and final responsibility for the decision to submit the article for publication.

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 online at www.pediatrics.org/cgi/doi/10.1542/peds.2018-3902.

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