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ORIGINAL ARTICLE

Increased antibiotic exposure in early life is associated with adverse outcomes in very low birth weight infants

Wen-Yin Chen[a], Yu-Cheng Lo[b], Po-Han Huang[c], Yu-Xuan Chen[b], Pei-Chen Tsao[b,d,e,f], Yu-Sheng Lee[b,d,g], Mei-Jy Jeng[b,d,e], Miao-Chiu Hung[a,*]

[a]Division of Infectious Diseases, Department of Pediatrics, Taipei Veterans General Hospital and National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [b]Division of Neonatology and Critical Care, Department of Pediatrics, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [c]Division of Infectious Diseases, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [d]Department of Pediatrics, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [e]Institute of Emergency and Critical Care Medicine, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [f]Institute of Physiology, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [g]Institute of Public Health, School of Medicine, National Yang Ming Chiao Tung University Taipei, Taiwan, ROC

Abstract

Background: The use of antibiotics in the early lives of premature infants may alter the microbiota and influence their clinical outcomes. However, whether the administration of probiotics can influence these outcomes remains unknown. In our study, probiotics were routinely administered unless contraindicated. We explored whether increased antibiotic exposure with the routine use of probiotics was associated with necrotizing enterocolitis (NEC) or bronchopulmonary dysplasia (BPD).

Methods: A retrospective cohort study was conducted, enrolling very low birth weight (VLBW) infants admitted between January 1, 2016, and March 31, 2020, to a medical center. Days of antibiotic exposure in the first 14 days of life were recorded. The primary outcomes were NEC and BPD. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated using multivariable regression analyses to assess risk factors.

Results: Of 185 VLBW infants admitted to the medical center, 132 met the inclusion criteria. Each additional day of antibiotic treatment was associated with increased odds of NEC (aOR, 1.278; 95% CI, 1.025-1.593) and BPD (aOR, 1.630; 95% CI, 1.233-2.156). The association remained in the NEC analysis after adjustment for probiotic use.

Conclusion: Increased antibiotic exposure in the early lives of VLBW infants was associated with increased risks of NEC and BPD. The probiotics did not influence the outcomes. Our findings suggest that clinicians should be alerted to the adverse outcomes of antibiotic use in infants with VLBWs.

Keywords: Bronchopulmonary dysplasia; Necrotizing enterocolitis; Probiotics

1. INTRODUCTION

Very low birth weight (VLBW) infants (birth weight < 1500 g) often receive empirical antibiotics in their first few days of life because of the high fatality rates associated with early onset neonatal sepsis[1] and the limitations of diagnostic tools for accurate sepsis detection.[2,3] However, antibiotic treatment is often prolonged despite of negative culture results,[4] as the perceived risk of infection may be obscured by noninfectious conditions resembling sepsis. This practice has raised concerns regarding the adverse effects of prolonged antibiotic use.

Several observational studies have demonstrated that prolonged antibiotic exposure for premature infants early in life is associated with increased rates of necrotizing enterocolitis (NEC).[5–9] In addition, although little is known regarding the lung microbiota in preterm infants,[10] clinical studies have demonstrated a correlation between the duration of antibiotic exposure and bronchopulmonary dysplasia (BPD),[7,11] indicating that commensal bacteria in the lungs may play a role in immune homeostasis and, therefore, the pathogenesis of BPD.[12,13] In our study, we implemented care protocols for preterm infants that differed considerably from those employed in other studies. For example, the preferred first-line antibiotics were a combination of ampicillin and cefotaxime, which are more broad-spectrum than those in other studies.[8] Moreover, probiotics were routinely administered to clinically stable preterm infants as recommended by the American Gastroenterological Association[14]; by contrast, probiotics have not been universally adopted in other studies.[15] Because numerous systematic reviews have reported

*Address correspondence. Dr. Miao-Chiu Hung, Division of Infectious Diseases, Department of Pediatrics, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: mchung@vghtpe.gov.tw (M.-C. Hung).

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that probiotics significantly reduce the risk of NEC,[16,17] investigating whether the increased risk of NEC due to antibiotic exposure can be offset by the protective effects of probiotic use is essential.

In this study, we investigated the association between antibiotic use in VLBW infants in the first 14 days of life and prematurity-related adverse outcomes (ie, NEC and BPD) as well as whether the use of probiotics could influence the outcomes. We conducted a retrospective study using multivariable analyses to identify the risk factors for NEC and BPD.

2. METHODS

2.1. Study cohort

We conducted a retrospective study collecting data for VLBW infants who were admitted to Taipei Veterans General Hospital between January 1, 2016, and March 31, 2020. Infants (1) with major congenital anomalies (2) who died or developed NEC (modified Bell stage ≥ IIA) before 14 days of age, and (3) with culture-proven sepsis (defined as bacteremia or bacterial meningitis occurring in the first 14 days of life) were excluded. For BPD analysis, infants who died before 36 weeks postmenstrual age were excluded because they would not meet the criteria for BPD.[18] This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (IRB number 2021-01-027CC).

2.2. Protocols for premature infant care

In our study, clinicians followed protocols for premature infant care. The protocols that were relevant to our study were as follows. First, ampicillin and cefotaxime were used empirically for early onset sepsis, and teicoplanin and meropenem were reserved for ill-appearing infants. Second, early introduction of trophic feeding and a preference for human milk over formula were the principles of enteral feeding. Third, probiotics, either 250 mg of *Lactobacillus casei* daily or a 250-mg combination of *Lactobacillus acidophilus* and *Bifidobaterium bifidum* daily, were administered to all infants if they had started enteral feeding. The indication for and timing of surfactant administration were consistent with the 2014 recommendations of the American Academy of Pediatrics.[19]

2.3. Definitions

Antibiotic treatment was recorded for all infants from birth to 14 days of age. The length of antibiotic treatments was calculated as the number of calendar days that an infant received one or more kinds of antibiotics. Maternal pregnancy and delivery data and infant data from birth until discharge or death were collected. Chorioamnionitis was defined according to the criteria for confirmed intraamniotic infection endorsed by the American College of Obstetricians and Gynecologists.[20] Small for gestational age was defined as a birth weight lower than the 10th percentile according to the 2013 Fenton Preterm Growth Chart.[21] The Score for Neonatal Acute Physiology with Perinatal Extension-II (SNAPPE-II) was employed to capture illness severity of neonates.[22] Probiotic exposure was defined as feeding with probiotics for at least 3 consecutive days before 14 days of age. Human milk exposure was defined as feeding exclusively or partially with human milk for at least 3 consecutive days before 14 days of age. Days of oxygen supply was defined as the number of days that the neonates were supplied with a fraction of inspired oxygen (FiO_2) >40%.

The primary outcomes were NEC and BPD. NEC was classified according to the modified Bell criteria, and only NEC stage ≥IIA was included in analyses.[23] BPD was categorized according to the revised definition proposed by the National Institute of Child Health and Human Development in 2016,[18] and BPD of all severities was included in analyses.

2.4. Statistical analyses

To compare the characteristics of the neonates, the neonates were divided into 2 equal groups according to the median number of days of antibiotic exposure (ie, 0–8 vs 9–14 days). A group comparison of the categorical variables was conducted using the χ^2 or Fisher's exact test, as appropriate, with numbers and percentages provided for each measure. Mann–Whitney U tests were used

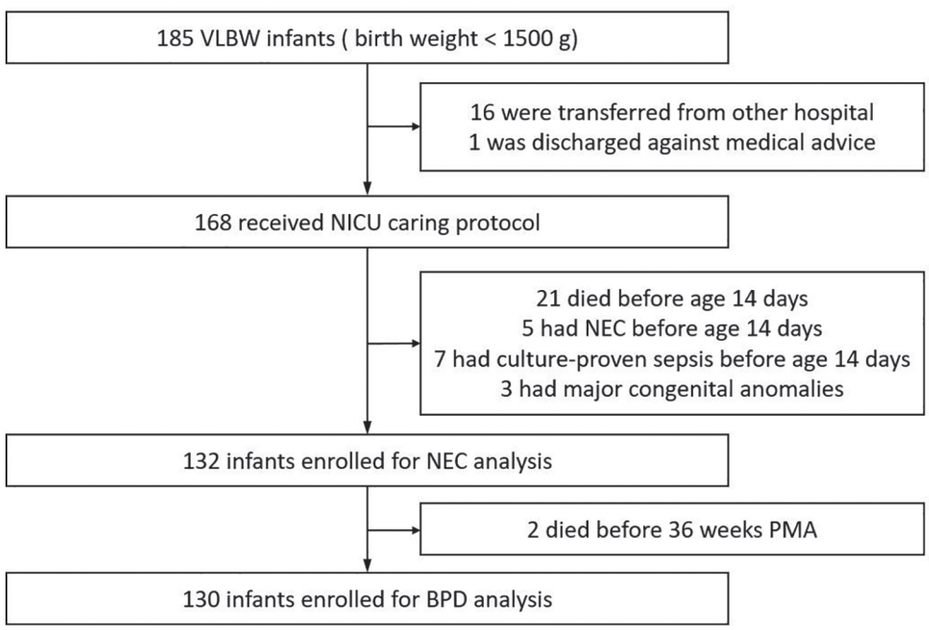

Fig. 1 Study population. BPD = bronchopulmonary dysplasia; NICU = neonatal intensive care unit; NEC = necrotizing enterocolitis; PMA = postmenstrual age; VLBW = very low birth weight.

for the comparisons of continuous variables, with medians and interquartile ranges (IQRs) provided for each measure.

Logistic regression models were used to assess risk factors, including the duration of antibiotic exposure and other variables shown previously to be associated with NEC or BPD.[16,17,24–28] These variables included chorioamnionitis, the SNAPPE-II, human milk feeding, probiotic use, days of mechanical ventilation, days of oxygen supplementation, days of postnatal steroid administration, and the presence of hemodynamically significant patent ductus arteriosus. We ran 2 logistic regression models: one treated the length of antibiotic exposure as a continuous variable, and the other treated it as a categorical variable (ie, 0–8 vs 9–14 days). Gestational age, birth weight, and Apgar score at the 5th minute were not included in the models to prevent collinearity due to their linear correlations with the SNAPPE-II. The logistic regression model fit was assessed using the Hosmer–Lemeshow statistic, with $P > 0.20$ providing adequate fit of the model to the data. Risk was reported as an adjusted odds ratio (aOR) along with a 95% confidence interval (CI).

3. RESULTS

Of the 185 VLBW infants admitted to the medical center during the study period, 132 met the inclusion criteria and were included in the analyses (Fig. 1). The demographic and clinical characteristics of the infants and their mothers are summarized in Table 1. The median number of days of antibiotic exposure during the first 14 days of life was 8. Regarding adverse outcomes, 12 infants (9%) developed NEC, 90 infants (69%) had BPD, and 4 infants (3%) died.

The enrolled subjects were grouped according to the length of early antibiotic exposure (0–8 vs 9–14 days) for comparative analysis (Table 1). Compared with the group with antibiotic exposure for 0 to 8 days, the group with antibiotic exposure for 9 to 14 days had smaller gestational ages, lower birth weights, lower Apgar scores at the 5th minute, higher SNAPPE-II, higher likelihood of requiring surfactant treatment, longer dependence on mechanical ventilation, and more oxygen and steroid administration. Infants with antibiotic exposure for 9 to 14 days also had significantly higher rates of adverse outcomes, including NEC, BPD, and death.

After adjustment for confounding variables, infants with longer antibiotic exposure (9–14 days) had higher odds of BPD than those with shorter antibiotic exposure (aOR, 10.104; 95% CI, 2.281–44.758; Table 2). When tested as a continuous variable, each additional day of antibiotic use was associated with higher odds of NEC (aOR, 1.278; 95% CI, 1.025–1.593) and BPD (aOR, 1.630; 95% CI, 1.233–2.156).

Table 1

Demographic and clinical characteristics of the enrolled infants and their mothers

		Antibiotic exposure		
	All	0–8 d	9–14 d	*p*[a]
Number of infants	132	70	62	
Antenatal information				
Maternal age, y, median (IQR)	35 (32–38)	36 (32–38)	35 (31–38)	0.259
Smoke, No. (%)	2 (2)	0 (0)	2 (3.2)	0.219
Chorioamnionitis, No. (%)	21 (19)	9 (13)	12 (19)	0.308
Preeclampsia, No. (%)	34 (26)	20 (29)	14 (23)	0.432
Antenatal steroid, No. (%)	80 (61)	41 (59)	39 (63)	0.611
Delivery information				
Rupture of membrane > 24 h, No. (%)	27 (20)	14 (20)	13 (21)	0.891
Cesarean section, No. (%)	116 (88)	62 (89)	54 (87)	0.796
Infant characteristic				
Gestational age, wks, median (IQR)	29 (27–32)	30 (29–33)	28 (26–29)	<0.001
Birth weight, g, median (IQR)	1157 (900–1342)	1304 (1186–1422)	988 (809–1126)	<0.001
Small for gestational age, No. (%)	30 (23)	22 (31)	8 (13)	0.011
Apgar score at the 5th minute, median (IQR)	8 (7–8)	8 (7–9)	7 (6–8)	<0.001
Male, No. (%)	67 (51)	35 (50)	32 (52)	0.853
Twin, No. (%)	31 (23)	16 (23)	15 (24)	0.857
Infant information to day 14				
SNAPPE-II, median (IQR)	10 (5–20)	5 (0–12)	15 (5–30)	0.001
Use of surfactant, No. (%)	53 (40)	18 (26)	35 (57)	<0.001
Human milk feeding, No. (%)	113 (86)	63 (90)	50 (81)	0.126
Use of probiotics, No. (%)	88 (67)	48 (69)	40 (65)	0.622
Presence ofhemodynamically significantPDA, No. (%)	50 (38)	15 (21)	35 (56)	<0.001
Days of mechanical ventilation, median (IQR)	2 (0–17)	0 (0–3)	14 (0–26)	<0.001
Days of oxygen supplementation >FiO_2 40%, median (IQR)	0 (0–0)	0 (0–0)	0 (0–1)	0.001
Days of steroid administration, median (IQR)	1 (0–2)	0 (0–1)	2 (0–3)	<0.001
Days of antibiotic exposure, median (IQR)	8 (7–12)	7 (5–7)	12 (10–14)	<0.001
Adverse outcomes				
NEC, No. (%)	12 (9)	3 (4)	9 (15)	0.041
BPD, No. (%)	90 (69)	33 (47)	57 (95)	<0.001
Death, No. (%)	4 (3)	0 (0)	4 (7)	0.046

BPD = bronchopulmonary dysplasia; FiO_2 = fraction of inspired oxygen; IQR = interquartile range; NEC = necrotizing enterocolitis; NSAID = nonsteroidal anti-inflammatory drug; PDA = patent ductus arteriosus; SNAPPE-II = Score for Neonatal Acute Physiology with Perinatal Extension-II.

[a]Comparison of characteristics and outcomes by the duration of antibiotic exposure.

Table 2

Multivariable logistic regression examining neonates' outcomes

	aOR	95% CI	*p*
NEC[a]			
Antibiotic exposure per day	1.278	1.025–1.593	0.03
Antibiotic exposure 9–14 d	3.436	0.818–14.431	0.092
BPD[b,c]			
Antibiotic exposure per day	1.630	1.233–2.156	0.001
Antibiotic exposure 9–14 d	10.104	2.281–44.758	0.002

Two different logistic regression models were calculated: one treated the length of antibiotic exposure as a continuous variable, while the other as a categorical variable (ie, 0–8 vs 9–14 days).

aOR = adjusted odds ratio; BPD = bronchopulmonary dysplasia; CI = confidence interval; NEC = necrotizing enterocolitis.

[a]Adjusted for SNAPPE-II, human milk feeding, and use of probiotics.

[b]Two neonates died before 36 weeks postmenstrual age, so they were excluded from the analysis as they could not meet the criteria for BPD.

[c]Adjusted for chorioamnionitis, SNAPPE-II, days of mechanical ventilation, days of oxygen supplementation, days of steroid administration, and presence of hemodynamically significant PDA.

4. DISCUSSION

In this study, we demonstrated that longer antibiotic exposure was associated with increased risks of developing NEC and BPD in VLBW infants. Notably, our study revealed that the association remained after adjusting for probiotic use in the NEC analysis, indicating that the probiotics did not offset the adverse effects of prolonged antibiotic exposure.

The increased risk of NEC may be explained by the reduced diversity of microbiota caused by perinatal antibiotics, which may lead to overgrowth of pathogenic microbes over commensal species.[29,30] This change became significant at 10 days of age and most profound at 30 days of age,[31] coinciding with the general timing of the presentation of NEC.[32] In addition, antibiotic therapy can alter and weaken the innate and adaptive immune system, resulting in increased cytokine-mediated inflammatory responses that can lead to gut injury.[33] However, the pathogenesis for an increased risk of BPD has not been directly verified. Only weak evidence suggests that airway microbial dysbiosis is associated with BPD progression and severity.[10]

Our findings are consistent with those of previous studies. Cotton et al used a multicenter database to demonstrate that prolonged initial antibiotic treatment for extremely low birth weight infants (birth weight < 1000 g) was associated with increased incidence of NEC or death.[6] Ting et al used antibiotic use rate, defined as the number of antibiotic exposure days divided by the total length of hospital stay, to demonstrate the associations between antibiotic exposure and adverse outcomes (i.e., periventricular leukomalacia, BPD, retinopathy and mortality).[34] Cantey et al used a single-center database to investigate the correlations between early antibiotic exposure and NEC, BPD and death.[8,11]

A strength of our study is the inclusion of probiotic use as a variable for the NEC analysis. Systematic reviews have reported that probiotics significantly reduced the risk of NEC.[16,17] However, whether probiotics have the benefit of preventing the development of NEC in preterm infants receiving antibiotics has not been widely studied. Our study revealed that probiotics did not reduce the adverse outcomes caused by increased antibiotic exposure. A possible explanation is that broad-spectrum antibiotics, which probiotics might be susceptible to, were used in our study. In addition, the length of the initial antibiotic treatment was longer in our study than in other studies, which might have undermined the effects of probiotics. Ting et al[7] reported that 42% of VLBW infants are administered antibiotics for >3 days, while all our enrolled infants received antibiotics for >3 days. Cantey et al reported a median number of days of antibiotic therapy was 5.5,[8] whereas the median was 8 in our study.

A second strength is that our study employed data spanning a 5-year period from a medical center, ensuring consistency in the principles of medical practice. Third, treating the length of antibiotic exposure as a continuous variable may provide valuable information for refining antibiotic therapy.

This study has several limitations. First, the infants at higher risk of adverse outcomes are likely the same infants who receive longer antibiotic treatment. However, we attempted to minimize this limitation by adjusting for SNAPPE-II. Second, the cohort size was relatively small. Future studies should involve a larger cohort and a prospective design.

In conclusion, our findings indicated that a longer duration of early antibiotic exposure contributed to increased risks of developing NEC and BPD in VLBW infants. The associations remained after adjustment for variables known to affect the incidence of outcomes. Notably, the potentially protective effect of probiotics was limited. Our findings suggest that rigorous antibiotic stewardship in VLBW infants to avoid adverse consequences is imperative.

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