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Review Article

Association Between Broad-Spectrum Antibiotic Use at Different Stage and Neonatal Enteral Nutrition and Prognosis in Very Low-Birth-Weight Infants with Culture-Negative Sepsis

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Abstract

Objective: Our study is to evaluate the association between broad-spectrum antibiotic and enteral nutrition and outcomes among Very Low-Birth-Weight (VLBW) infants without culture-proven sepsis and exploring the timing of antibiotics use which has the minimum effect on enteral nutrition.

Methods: A retrospective cohort study was conducted in a tertiary Neonatal Intensive Care Unit (NICU) in China between November 2011 and November 2017. Infants are divided into four groups, including one no broad-spectrum antibiotic group and three broad-spectrum antibiotic groups. The three broad-spectrum antibiotic groups were divided according to the initiating time of broad-spectrum antibiotic use: <3d group, 3~13d group, and ≥14d group.

Results: Among the 571 infants, four hundred and ninety-one (85.99%) of the infants were treated with broad-spectrum antibiotics. The distribution in four groups is 14.01%, 64.97%, 12.96% and 8.06%, respectively. The median days reaching the target amount of milk (120mL/kg) in the four groups were 21.66d, 30.52d, 29.52d, and 29.06d, respectively, with statistical significance analyzed by the log-rank test (P=0.023). Bronchopulmonary Dysplasia (BPD) incidence in the <3d group was significantly higher than those in the no broad-spectrum antibiotics groups (P <0.008). Broad-spectrum antibiotics were given after the age of nine days, which had the highest possibility to reach Milk120 within short time (RR=1.41, 95% CI: 0.98-2.04).

Conclusions: Broad-spectrum antibiotic for VLBW infants with culture-negative sepsis, influences enteral nutrition process and increases the incidences of BPD. The broad-spectrum antibiotic use after the age of nine days is more beneficial for enteral nutrition than that at an earlier age.

Keywords: Broad-spectrum antibiotics; Enteral nutrition; Prognosis; VLBW infants; Culture-negative sepsis

Introduction

Antibiotics are administered shortly after birth to nearly all preterm infants with Very Low Birth Weight (VLBW) (birth weight <1500g) because of the risk of sepsis [1]. Many neonates accepted antibiotic treatment when the sepsis is suspicious. Physicians are often reluctant to discontinue antibsiotics once initiated for many reasons, including the relatively high risk of infection among preterm infants and the relatively high rate of mortality attributable to infection. Early antibiotic use in premature infants negatively influences the colonization of the intestinal tract with normal flora, causing near-term or long-term health issues.

Until now, most investigations have been focusing on the effects of early empirical antibiotic use on the prognosis of neonates. However, empirical antibiotic use is common in clinic without positive culture results, not only within the first three days after birth. It is known that antibiotic use influences negatively the establishment of intestinal flora in infants. But the effects of antibiotic use, especially broad-spectrum antibiotics, on enteral nutrition and prognosis of premature infants at different stages are not known.

Aminoglycosides, such as gentamicin, are forbidden in neonates in China because of their side effects. The empirical antibiotics use in NICU in China has wider variety. Our aim was to analyze the conditions of broad-spectrum antibiotic use in Very-Low-Birth-Weight (VLBW) infants with culture-negative sepsis in a tertiary NICU in China, in order to promote more rational antibiotics prescription. Analysis was also performed on the influence of broad-spectrum antibiotic use at different stages after birth on target enteral nutrition and prognosis. The research on the more beneficial timing for broad-spectrum antibiotic use for suspicious infection could help to discover the key timing when the intestinal microbiota has established in premature infants after birth.

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Methods

Study design and patients

We conducted a retrospective cohort study in the largest tertiary NICU in Southern China. The hospital's Research Ethics Committee approved the study protocol. Premature infants with a Very Low Birth Weight (VLBW; Birth Weight [BW] <1500g) and negative culture results were included. Anti-infection agents were antibiotics that were prescribed to actively treat infection according to the Practice of Neonatology of China (4th Edition) [2]. Patients with chromosomal abnormalities, metabolic diseases, gastrointestinal diseases, or positive blood culture before antibiotic use were not eligible. Eventually, 571 VLBW admitted to the NICU between November 2011 and November 2017 were included in the research.

Nutrition supply strategy

Enteral Nutrition (EN) was initiated within 24h after birth. Breast milk, donated milk, or formula milk were started depending on the infants' enteral feeding intolerance and advanced by 10~20mL/kg•d. Parenteral Nutrition (PN) initiated within 24 h after birth. Both amino acid and lipids started at 1g/kg•d and advanced by 0.5~1g/kg•d to a maximum of 3.0~3.5g/kg•d. PN was discontinued when the infant tolerates 120mL/kg•denterally. PN and EN supports were performed according to the guidelines of the Chinese Society for Parenteral and Enteral Nutrition for neonates and preterm infants [3], which was drafted by referring to the nutrition guidelines in the United States and Europe [4-6].

Measures and management

The data of neonates enrolled was obtained from the Medical Centre's database. Information was collected on the age of the first antibiotic use, antibiotic type, and total duration of treatment. Then, the neonates were divided into the following four groups: (1) No broad-spectrum antibiotic group: no broad-spectrum antibiotic treatment or only single penicillin treatment was applied. (2) <3d group: antibiotic administration was initiated between day 0 and less than day 3 after birth. (3) 3~13d group: antibiotic administration was initiated between day 3 and less than day 14 after birth. (4) ≥14d group: antibiotic administration was initiated at day 14 or later.

Outcomes

The primary outcome were recorded when infants tolerated 120mL/kg.d (Milk120) before 90 days after birth. Secondary safety outcomes rather than infection-related morbidities were death, Bronchopulmonary Dysplasia (BPD), and Retinopathy of Premature (ROP) before discharged from the hospital. These outcomes were chosen to be included in this study because of their association with systemic inflammatory response and their chronological sequence of usually occurring after the median age of infection in preterm neonates. The time to final weaning from mechanical ventilator support (live) and the time to (live) discharge from the hospital were also assessed.

Statistical analysis

Data are expressed as frequencies (percentages) or means (Standard Deviation, SD). We first compared the timing of antibiotic treatment in VLBW infants using four categories. Univariate comparisons were performed using the Chi-square test (or two-tailed Fisher's exact test if appropriately), and analysis of variance. Bonferroni's correction for post-hoc pairwise comparisons was employed to variables with significance in the univariate comparisons. The Kaplan-Meier plot was utilized to determine the time-to-event effect with log-rank testing for Milk 120. The Multivariate cox proportional-hazards analysis was used for the time-to-event outcomes, including Milk 120 and the secondary efficacy outcomes. As we were not certain when they will occur, multivariate logistic regression models were used to ascertain the effect of timing of antibiotic treatments on the secondary safety outcomes. In the broad-spectrum antibiotic treatments of infants, we used restricted cubic splines with knots placed at 1, 3 and 14 days of age for Milk 120. In order to adjust the effect of illness severity and other factors on the stage of the broad-spectrum antibiotics treatment, all the outcomes were adjusted for the statuses of premature babies at admission: gestational age; birth weight group; gender; Apgar scores group at 1 and 5 minutes after birth; maternal age; and preterm rupture of membranes. Additionally, the factors related to the management of the premature babies or the conditions of their mothers were also evaluated: age at admission and age at initiation of enteral feeding; type of milk at first intake; mode of respiratory support at admission; and antenatal corticosteroid use. Statistical analyses were performed using SAS software (version 9.4; SAS Institute, Inc., Cary, NC, USA). Two-tailed *P*-values <0.05 were considered statistically significant, and the *P*-value for pairwise comparisons had to be below 0.05/6=0.008.

Results

Patients

Among the 571 patients included in the study, 491(85.99%) were treated with broad-spectrum antibiotics, including 64.97% accepted antibiotic treatment between day 0 and less than day 3 after birth, 12.96% between day 3 and less than day 14 after birth, and 8.06% at day 14 or later. Broad-spectrum antibiotic treatment was not applied in only 14.01% of the patients. Birth weight, age at admission, and mode of respiratory support differed among the four groups. More specifically, all premature infants with BW <1000 g were prescribed to broad-spectrum antibiotic treatment. The <3d group were younger than the 3~13d group at admission (*P*=0.005). The infants with mechanical ventilator support or non-invasive auxiliary ventilation at study entry were more likely to be earlier treated with broad-spectrum antibiotics. There were no difference in the other characteristics among the four groups (Table 1).

Antibiotics

The top three broad-spectrum antibiotics used were third-generation cephalosporins (448/491), meropenem (239/491), and broad-spectrum penicillin (155/491). The proportion of carbapenem in single use and combination was 48.7%. For the types of broad-spectrum antibiotics, 3~13d group had a significant higher proportion of cephalosporin use (139/371). The proportion of broad-spectrum penicillin use combined with cephalosporin was 2.6% (15/571). A negative correlation was found between the age of broad-spectrum antibiotics initiated and its duration (r=-0.16, *P* <0.001).

Primary outcome

The no broad-spectrum antibiotic group spent shorter time to the goal of Milk 120 than any of the broad-spectrum antibiotic groups

Table 1: Clinical characteristics.

	Broad-spectrum antibiotics groups					
Indicators, n (column%)	**Total broad-spectrum antibiotics, n=491 (85.99)**	**<3d, n=371 (64.97)**	**3~13d, n=74 (12.96)**	**≥14d, n=46 (8.06)**	**No, n= 80 (14.01)**	***P* value**
Infant						
Gestational age, wk						0.171
<28	59 (12.02)	44 (11.86)	12 (16.22)	3 (6.52)	5 (6.25)	
28 to ≤34	432 (87.98)	327 (88.14)	62 (83.78)	43 (93.48)	75 (93.75)	
Birth weight, kg						0.003
<1.00	64 (13.03)	52 (14.02)	9 (12.16)	3 (6.52)	0 (0)*†	
≥1.00	427 (86.97)	319 (85.98)	65 (87.84)	43 (93.48)	80 (100)	
Gender						0.788
Male	280 (57.03)	208 (56.06)	46 (62.16)	26 (56.52)	44 (55.00)	
Female	211 (42.97)	163 (43.94)	28 (37.84)	20 (43.48)	36 (45.00)	
Apgar score 1minute after birth						0.145
≤7 points	111 (22.61)	90 (24.26)	16 (21.62)	5 (10.87)	14 (17.50)	
>7 points	380 (77.39)	281 (75.74)	58 (78.38)	41 (89.13)	66 (82.50)	
5minute after birth						0.862#
≤7 points	32 (6.52)	24 (6.47)	6 (8.11)	2 (4.35)	6 (7.50)	
>7 points	459 (93.48)	347 (93.53)	68 (91.89)	44 (95.65)	74 (92.50)	
Age at admission, d						0.009
≤1.00	443 (90.22)	341 (91.91)	59 (79.73)*	43 (93.48)	69 (86.25)	
>1.00	48 (9.78)	30 (8.09)	15 (20.27)	3 (6.52)	11 (13.75)	
Age at initiation of enteral feeding, d						0.634
≤1	244 (49.69)	185 (49.87)	36 (48.65)	23 (50.00)	46 (57.50)	
>1	247 (50.31)	186 (50.13)	38 (51.35)	23 (50.00)	34 (42.50)	
Type of milk at first intake						0.646#
Breast milk	17 (3.46)	13 (3.50)	1 (1.35)	3 (6.52)	3 (3.75)	
Formula milk	275 (56.01)	208 (56.06)	44 (59.46)	23 (50.00)	50 (62.50)	
Mixed feeding	199 (40.53)	150 (40.43)	29 (39.19)	20 (43.48)	27 (33.75)	
Mode of respiratory support at study entry						<0.001
Mechanical ventilator support	242 (49.29)	187 (50.41)	33 (44.59)	22 (47.83)*	19 (23.75)*†	
Non-invasive auxiliary ventilation	178 (36.25)	143 (38.54)	25 (33.78)	10 (21.74)	25 (31.25)	
Oxygen supply	57 (11.61)	33 (8.89)	13 (17.57)	11 (23.91)	17 (21.25)	
None	14 (2.85)	8 (2.16)	3 (4.05)	3 (6.52)	19 (23.75)	
Maternal						
Age, y						0.26
<35	383 (78.00)	292 (78.71)	60 (81.08)	31 (67.39)	65 (81.25)	
≥35	108 (22.00)	79 (21.29)	14 (18.92)	15 (32.61)	15 (18.75)	
PROM						0.259#
No	369 (75.15)	276 (74.39)	58 (78.38)	35 (76.09)	51 (63.75)	
0–6	99 (20.16)	77 (20.75)	13 (17.57)	9 (19.57)	27 (33.75)	
≥7	23 (4.68)	18 (4.85)	3 (4.05)	2 (4.35)	2 (2.50)	
Antenatal corticosteroid use						0.899
No	238 (48.47)	183 (49.33)	33 (44.59)	22 (47.83)	38 (47.50)	
Yes	253 (51.53)	188 (50.67)	41 (55.41)	24 (52.17)	42 (52.50)	

#Fisher's exact test. When '<3d' was reference group:*P <0.008; When '3~13d' was the reference group:†P< 0.008; No statistical difference was found between 3~13d and ≥14d group, and no statistical difference was found between ≥14d and no broad-spectrum antibiotic group.

(P=0.023). The later antibiotic use resulted in the faster reaching of the target amount of milk. The median day of reaching target amount of milk in no broad-spectrum antibiotic, <3d, 3~13d, and ≥14d group were 21.66d, 29.06d, 29.52d, and 30.52d, respectively. In terms of time to reach Milk120, there was also significant difference in four groups by adjusted multivariable analysis (P=0.003) (Figure 1). However, in terms of proportion to reach Milk 120 at the age of 90d, no statistically significant difference was found in the four groups (P=0.338), (Table 2). Patients who were initiated with broad-spectrum antibiotics after 9 days of age had the highest probability of reaching at Milk 120 in the short term, which had significant differences (RR=1.41, 95% CI: 0.98-2.04). However, the beneficial trend continued to the age of 14 days, after which it declined (Table 2), (Figure 2). In addition, the likelihood of reaching at Milk 120 has significant relation with

Table 2: Outcomes.

	Broad-spectrum antibiotics groups					
Indicators	**Totalbroad-spectrum antibiotics**	**<3d**	**3~13d**	**³14d**	**No**	***P** value**
Primary Outcome						
Milk120, No. (%)	456 (92.87)	346 (93.26)	67 (90.54)	43 (93.48)	78 (97.5)	0.338
Secondary Outcomes						
Death, No. **(%)**	12 (2.44)	8 (2.16)	3 (4.05)	1 (2.17)	0 (0)	0.298#
BPD, No. (%)	120 (24.44)	94 (25.34)	18 (24.32)	8 (17.39)	8 (10.00)*	0.021
ROP, No. (%)	72 (14.66)	58 (15.63)	7 (9.46)	7 (15.22)	6 (7.50)	0.172
Time to final weaning from mechanical ventilator support (live)-days, mean±SD	6.07±11.90	6.27±12.48	6.64±10.58	3.46±8.51	1.06±3.08*† Ψ	<0.001
Time to (live) discharge from the hospital-days, mean±SD	51.94±20.56	52.27±21.66	50.09±17.44	52.30±15.65	37.38±12.17*† Ψ	<0.001

#Fisher's exact test. *P <0.008, reference: <3d group; †P <0.008, reference: 3~13d group; ΨP <0.008, reference: ≥14d group. No statistical difference was found among the <3d, 3~13d and ≥14d groups.

Table 3: Multivariate cox proportional-hazard analysis for VLBW reaching at Milk120/kg#.

Indicators	***β***	**SE**	**Hazard Ratio (95% CI)**	χ^2	***P*-value**
Groups, ref: <3d					
3~13d	0.17	0.14	1.18 (0.90,1.55)	1.43	0.231
≥14d	-0.14	0.17	0.87 (0.62,1.21)	0.72	0.396
No antibiotics	0.63	0.15	1.87 (1.41,2.49)	18.52	<0.001
Gestational age, ref: <28 wk	0.72	0.15	2.05 (1.52,2.78)	21.78	<0.001
Birth weight, ref: <1.00 kg	1.01	0.16	2.73 (1.99,3.76)	38.1	<0.001
Gender, ref: female	0.17	0.09	1.18 (0.99,1.41)	3.33	0.068
Apgar score at 1 minute after birth, ref: ≤7 points	-0.01	0.14	0.99 (0.76,1.29)	0	0.952
Apgar score at 5 minute after birth, ref: ≤7 points	0	0.21	1.00 (0.66,1.53)	0	0.991
Age at admission,ref: >1.00 d	-0.11	0.16	0.9 (0.66,1.22)	0.5	0.481
Age at initiation of enteral feeding, ref: <1.00 d	0.3	0.1	0.74 (0.61,0.90)	9.4	0.002
Type of milk at first intake, ref: Mixed feeding					
Breast milk	-0.21	0.26	0.81 (0.49,1.34)	0.66	0.415
Formula milk	-0.38	0.09	0.68 (0.57,0.82)	16.11	<0.001
Mode of respiratory support at study entry, ref: ventilator assists					
Non-invasive auxiliary ventilation	0.39	0.11	1.47 (1.18,1.83)	12.03	0.001
Oxygen supply	0.28	0.15	1.32 (0.99,1.77)	3.53	0.06
None	0.82	0.23	2.27 (1.44,3.56)	12.66	<0.001
Maternal age, ref: ≥35 y	-0.08	0.11	0.93 (0.75,1.15)	0.46	0.496
PPROM, ref: >7 d					
No	-0.14	0.23	0.87 (0.55,1.37)	0.35	0.553
0~6	-0.18	0.24	0.84 (0.52,1.35)	0.53	0.467
Antenatal corticosteroid use, ref: yes	-0.01	0.1	0.99 (0.82,1.20)	0	0.946

the gestational age and birth weight (RR=2.05, 95% CI: 1.52–2.78; RR=2.73, 95% CI: 1.99–3.76). The later the initiation of enteral feeding, the less likelihood to reaching at Milk 120 (RR=0.74, 95% CI: 0.61–0.90). Compared with the mixed feeding, the single breast milk treatment displayed no significant difference while the single formula milk had less likelihood of reaching at Milk 120 (RR=0.81, 95% CI: 0.49–1.34; RR=0.68, 95% CI: 0.57–0.82). The VLBW assisted by non-invasive ventilation or with no respiratory support on admission were more likely to reach Milk 120 than those who were under invasive mechanical ventilator support (RR=1.47, 95% CI: 1.18–1.83; RR=2.27, 95% CI: 1.44–3.56). However, the likelihood to reach the target Milk 120 of children who had oxygen was not different from those with mechanical ventilator support (Table 3).

Secondary outcome

Time to final weaning from mechanical ventilator support (live) of all the three broad-spectrum antibiotics groups were longer than that of the no-broad-spectrum-antibiotic group. The 3~13d group had the longest time. The prevalence of BPD in the <3d group was significantly higher than that in the no-broad-spectrum-antibiotic

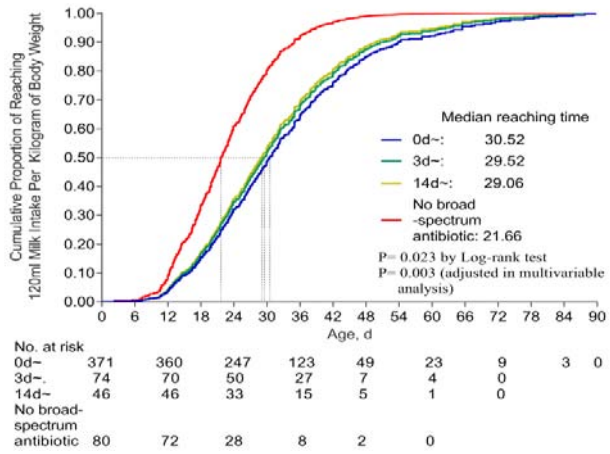

Figure 1: Kaplan-Meier Plot for the Time to Reaching at Milk120.

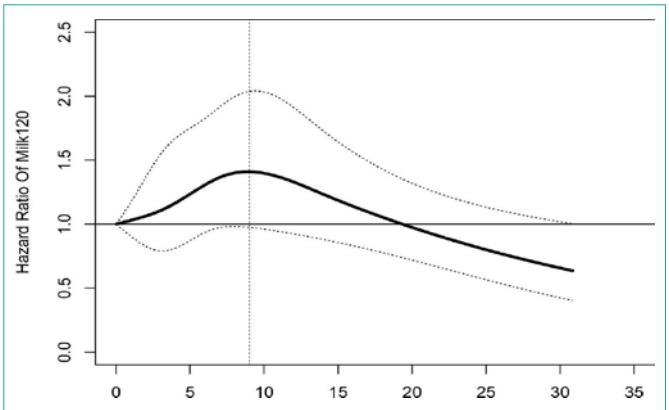

Figure 2: Age of First Broad-spectrum Antibiotics Use.

group. No significant difference was detected in the distribution of mortality and ROP. All three broad-spectrum antibiotics groups had significant longer hospitalization stays than the no-broad-spectrum-antibiotic group, while there was no significant difference among the three broad-spectrum antibiotics groups (Table 2). The results of the multivariate analysis were presented in (Table 4).

Discussion

A study including 29 Neonatal Intensive Care Units (NICU) reported that more than 47% of the admitted neonates received at least one type of antibiotic treatment in their early birth [7]. The rates of positive bacterial culture results in premature infants are not high. Up to 80% of the neonates reportedly received empirical antibiotic treatment with no high-risk infection and etiology evidence [8-10]. Because evidence showed that for administration of antibiotics in sepsis, every hour of delay is associated with a mean decrease in survival of 7.6% [11]. In premature infants, the death risk is higher. Some premature infants with infection manifestations receive antibiotics, but the possible non-infectious diseases with same manifestations are not excluded [12,13]. The results of the study indicated that 85.99% of the VLBW received empirical broad-spectrum antibiotic treatment, and 64.97% of them received it within three days after birth. Gentamicin is not suggested to treat neonates in China. The portion of cephalosporin in the medications used in premature infants was the highest, and that of carbapenems was 41.9%. It showed that the rate of broad-spectrum antibiotic use in premature infants in NICU in China was still very high.

This is a single-center retrospective cohort study, which analyzes VLBW infants relevant data admitted in a tertiary NICU in China during November 2011 to November 2017. Our data show that the later antibiotic use resulted in the faster reaching of the target amount of milk. It has been reported that early (<3 days) empirical antibiotic use could influence enteral feeding progress of premature infants [14]. Other studies confirmed that antibiotics significantly reduced the colonization with *Bifidobacterium* and *Lactobacillus* in the intestinal tract of neonates, severely damaging the intestinal barrier and absorption function [15,16]. The possible reason is that antibiotics influence the establishment of the intestinal microflora in premature infants, and the earlier use of broad-spectrum antibiotics will have higher effects on the intestinal microflora as well as the establishment of enteral nutrition. The early use of antibiotics after birth negatively influences the establishment of intestinal microflora in neonates, but there is still no report revealing the most suitable time for their application with the lowest adverse influence on intestinal microflora. In this study, we found that antibiotics treatment after nine days from birth had beneficial influence on the enteral nutrition establishment compared the earlier use, suggesting the first week after birth might be an important timing for establishment of intestinal microflora. Avoiding the empirical antibiotics use at this stage may have protective effects on the establishment of intestinal microflora in premature infants and reduce bad prognosis. We suggest that clinicians should try to avoid using broad-spectrum antibiotics before this key time if the infection is just suspicious. Keeping monitoring the babies' symptoms will be better than giving antibiotics immediately. However, such a beneficial effect might be diminished after 14 days after birth, suggesting that delayed antibiotic use could increase the risk of bad prognosis, which requires more studies to be confirmed.

Recently, studies showed that the use of antibiotics extended the time of parenteral nutrition and increased the risks of neonatal

Table 4: Adjusted hazard ratio or odds ratio (95% CI) for secondary outcomes[a].

	Broad-spectrum antibiotics groups			
Secondary Outcomes	**<3d**	**3~13d**	**≥14d**	**No**
Death[b], No. (%)	1[reference]	2.02 (0.42,9.68)	1.67 (0.18,15.47)	-[c]
BPD[b], No. (%)	1[reference]	1.12 (0.58,2.15)	0.62 (0.26,1.52)	0.57 (0.24,1.35)
ROP[b], No. (%)	1[reference]	0.56 (0.23,1.37)	1.21 (0.48,3.04)	0.78 (0.31,2.02)
Time to final weaning from mechanical ventilator support (live)-days	1[reference]	0.91 (0.64,1.31)	1.80 (1.14,2.84)	1.87 (1.15,3.04)
Time to (live) discharge from the hospital-days	1[reference]	1.04 (0.80,1.35)	0.82 (0.59,1.13)	1.97 (1.48,2.61)

[a]Death, BPD, and ROP are assessed by multivariate logistic regression and the other indicators are assessed by multivariate cox proportional-hazard analyses. All analyses were adjusted for premature babies' admission condition and factors related management of the premature babies or their mother which had been described in the statistical method. [b]These values are adjusted odds ratios and the other are adjusted hazard ratios. [c]Thereare no death in the no broad-spectrum antibiotic group.

Necrotizing Enterocolitis (NEC), Bronchopulmonary Dysplasia (BPD), and preterm infant Retinopathy (ROP) [17,18].

Another study revealed that extending the early empirical antibiotic course of treatment increased the risks of neonatal necrotizing enterocolitis and death in extremely premature infants [19]. In this study, we found no statistical difference in BPD incidence after broad-spectrum antibiotic use at different stages. However, BPD incidences in <3d group was significantly higher than those in the no broad-spectrum antibiotic group. These results indicate that the antibiotic use at different stages after birth increases the probability of bad prognosis, and the risk was the greatest in the <3d group. The durations of mechanical ventilation in the broad-spectrum antibiotic groups were longer than those in the no broad-spectrum antibiotic group, and the duration in the 3~13d group was the longest. The incidences of bad prognosis in the no broad-spectrum antibiotic group were significantly decreased, and the length of hospitalization was significantly shortened compared with the other groups.

The excessive use of broad-spectrum antibiotics, especially the 3rd generation of cephalosporin, was established to elevate the death risk in neonates [20]. The abusive use of antibiotics not only harms the organisms of neonates in which they are applied, but also exerts a negative influence on other neonates by the horizontal transmission in NICU [21]. Multiple studies have indicated that the extensive application of antibiotics in NICU is not necessary [12]. The investigations on the adverse effects of empirical antibiotics on premature infants are exceedingly important for improving NICU standard medication and prognosis of premature infants.

Conclusion

Empirical broad-spectrum antibiotic use for VLBW, even carbapenem is ordinary in NICU of China. It influences enteral nutrition, and did not reduce deaths or other adverse outcomes such as BPD. We suggest that clinicians should try to avoid using broad-spectrum antibiotics before the first 9 days after birth if the infection is just suspicious. Avoiding the empirical antibiotics use at this stage may have protective effects on the establishment of intestinal microflora in premature infants and reduce bad prognosis.

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