


# A Multi-Center Survey of Necrotizing Enterocolitis Prevention Strategies in Very Low Birth Weight Infants

Xiaoshan Hu , Miao Qian, Wenjuan Chen, Shushu Li, Xiaohui Chen, Shuping Han

Department of Pediatrics, Nanjing Women and Children's Healthcare Hospital, Nanjing City, Jiangsu Province, People's Republic of China

Correspondence: Shuping Han, Department of Pediatrics, Nanjing Women and Children's Healthcare Hospital, Nanjing City, Jiangsu Province, People's Republic of China, Tel +86 025-52226578, Email shupinghan@njmu.edu.cn

**Objective:** To compare the prevention practices of necrotizing enterocolitis (NEC) across 17 neonatal intensive care units (NICUs) in China.

**Methods:** A web-based survey was sent to 17 level 3 NICUs in China on September 21, 2023, to evaluate the prevention strategies for NEC.

**Results:** All 17 Neonatal Intensive Care Units (NICUs) responded to the survey. There was significant variation in the initial empirical use of antibiotics for early-onset sepsis, late-onset sepsis, and NEC among different NICUs. Out of the 17 NICUs, only 5 (29.4%) used donor human milk. Additionally, 15 (88.2%) NICUs performed routine echocardiography (Echo) in preterm infants after birth to evaluate cardiac function and/or Patent Ductus Arteriosus (PDA) status. Out of those 15 NICUs, 11 (73.3%) performed Echo within 24 to 72 hours after birth. Furthermore, 8 NICUs (47.1%) did not alter enteral nutrition management during drug treatment for PDA, while 12 NICUs (70.6%) stopped 1 or 2 feeds during red blood cell transfusion.

**Conclusion:** The findings of this survey conducted through questionnaires revealed both differences and similarities in the strategies employed to prevent NEC in 17 NICUs in China.

**Keywords:** very low birth weight infants, necrotizing enterocolitis, survey, prevention strategies

## Introduction

Necrotizing enterocolitis (NEC) is a severe gastrointestinal disease with serious complications in neonates, especially in preterm infants.<sup>1</sup> The incidence of NEC varies in different NICUs due to different management strategies. In China, the incidence of NEC varies between 3% and 12% depending on gestational age (GA) and birth weight (BW),<sup>2,3</sup> similar to the current worldwide incidence rate.<sup>4</sup>

So far, NEC is considered a multi-factorial disease that results in profound inflammation and intestinal injury.<sup>5</sup> Some studies suggest that the causal mechanisms for the development of NEC include impaired mucosal intestinal barrier, immature vascular regulation, and an abnormal microbiome.<sup>6</sup> In response to these factors, some NICUs have taken quality improvement (QI) measures to reduce the incidence of NEC, including the early use of human milk feedings, reasonable use of antibiotics, ensuring optimal intestinal perfusion, et al, and all of them have reduced the incidence of NEC to varying degrees.<sup>7-9</sup>

Early human milk feeding, including mother's own milk (MOM) and donor human milk (DHM) feeding, was proven to reduce the occurrence of NEC,<sup>10</sup> but some studies believed this effect was tentative.<sup>11</sup> Long-term (4-7 days) use or use of multiple antibiotics could increase the risk of NEC and death.<sup>12</sup> Intestinal perfusion changes when hemodynamic significant patent ductus arteriosus (hsPDA) exists or is treated by anti-inflammatory drugs, such as ibuprofen and indomethacin.<sup>13</sup> Red blood cell (RBC) transfusing can also cause ischemia/hypoxia reperfusion changes in the intestine.<sup>14</sup>

In this context, we conducted a multi-center survey questionnaire to investigate the uptake of preventative approaches for NEC at various units. This will provide a basis for QI projects to reduce NEC in the later stage.

## Methods

### Survey Method

On September 21, 2023, a web-based, cross-sectional survey was sent to the director or representative of 17 level 3 NICUs participating in the Suxinyun Neonatal Perinatal Network (SPNP) in China. SPNP, which was established 7 years ago, is a perinatal collaboration network consisting of 17 level 3 NICUs in China (see [supplemental material 1](#)). This network collects perinatal and neonatal data of infants with BW less than 1500 g (very low birth weight, VLBW) or GA less than 32 weeks. The study was approved by the ethics committee of Nanjing Women and Children's Hospital and all procedures were performed according to the tenets of the Declaration of Helsinki, this survey does not involve patient information, therefore, it is exempt from informed consent.

The survey contained questions about the current status of NEC prevention strategies. This questionnaire, which consisted of single-choice, multiple-choice, and open-ended questions, gathered information about the demographic features of the unit, human milk feeding characteristics, use of antibiotics, PDA management, initiation and advancement of enteral feeding, and indications for and the use of human milk fortifier (HMF), among other data (see [supplemental material 2](#)).

The unit director or representative was responsible for completing the survey and was instructed to provide answers based on common unit-level practice rather than their personal opinions/practice alone. They needed to fill in the basic information for the NICUs, and no personal information was attached to the data. Reminders were sent twice (at a month interval) to units that did not respond.

### Data Collection and Statistical Analysis

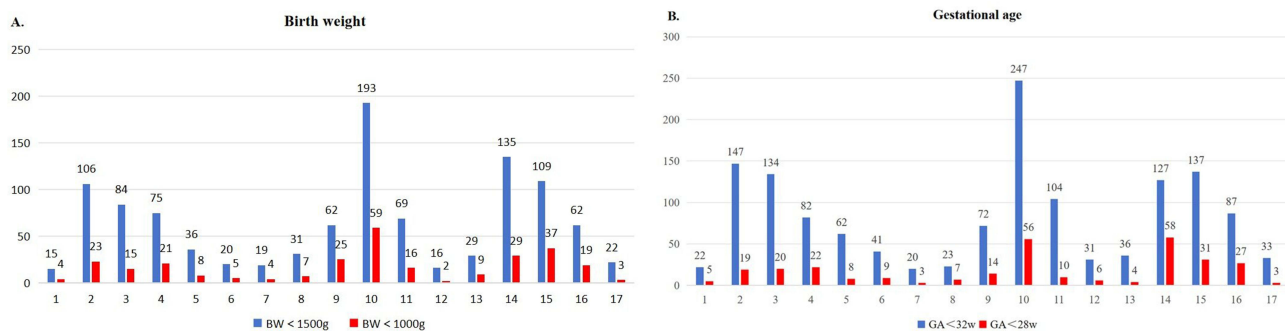
The data collection was concluded on December 10, 2023, after the last NICU responded. The results were analyzed using Microsoft Excel after being collected online. All questions had to be completed before submission, duplicate responses were verified and eliminated. The descriptive results expressed as numbers and percentages (%).

## Results

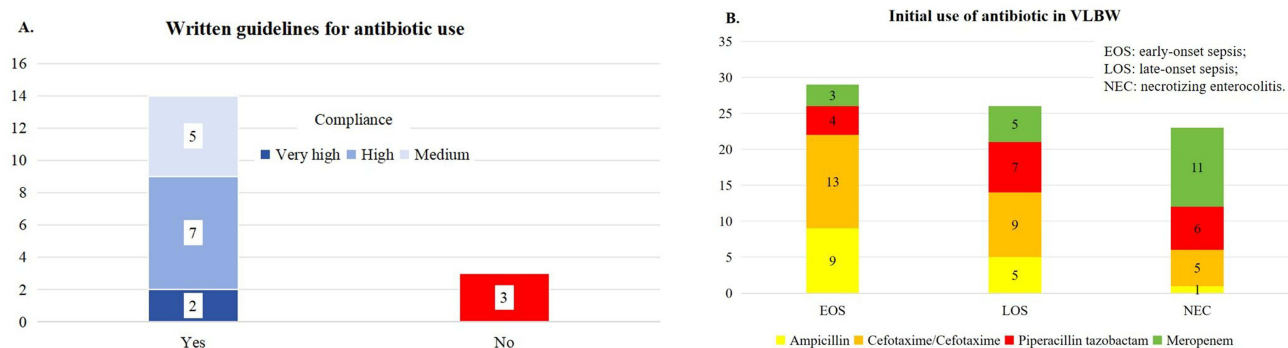
Among these 17 NICUs, 9 (52.9%) belonged to general hospitals and 8 (47.1%) belonged to maternity hospitals. [Figure 1](#) shows the number of infants born with BW less than 1500 g or 1000 g ([Figure 1A](#)) and GA less than 32 weeks or 28 weeks in each unit ([Figure 1B](#)).

### Use of Antibiotics

Out of 17 NICUs, 14 (82.4%) had documented guidelines regarding the use of antibiotics. However, the extent to which these guidelines were followed varied significantly among the NICUs ([Figure 2A](#)). There was a great deal of variation in the empirical use of antibiotics for early-onset sepsis, late-onset sepsis, and NEC in different NICUs ([Figure 2B](#)).



**Figure 1** Number of infants born with BW less than 1500g or 1000g(A) and GA less than 32 weeks or 28 weeks(B).  
**Abbreviations:** BW, birth weight; GA, gestational age.



**Figure 2** Number of NICUs with written guidelines for antibiotic use and their compliance(A). Initial use of antibiotic in VLBW with EOS, LOS, and NEC(B). **Abbreviations:** EOS, early-onset sepsis; LOS, late-onset sepsis; NEC, necrotizing enterocolitis.

### PDA Management

Only 2 out of the 17 NICUs will not undergo routine echocardiography (Echo) in VLBW infants after birth to evaluate cardiac function and/or PDA status. Among the other 15 NICUs, 11 would perform Echo within 24 to 72 hours after birth, 2 after 72 hours after birth, 1 within 24 hours and 1 would decide based on clinical symptoms. In 4 (23.5%) NICUs, PDA was usually treated based on the Echo results, even if the infant did not have clinical symptoms. Only one NICU did not administer anti-inflammatory drugs for PDA treatment. Among the 16 that did, 14 would conduct an Echo after one course of treatment (Table 1).

### Enteral Feeding

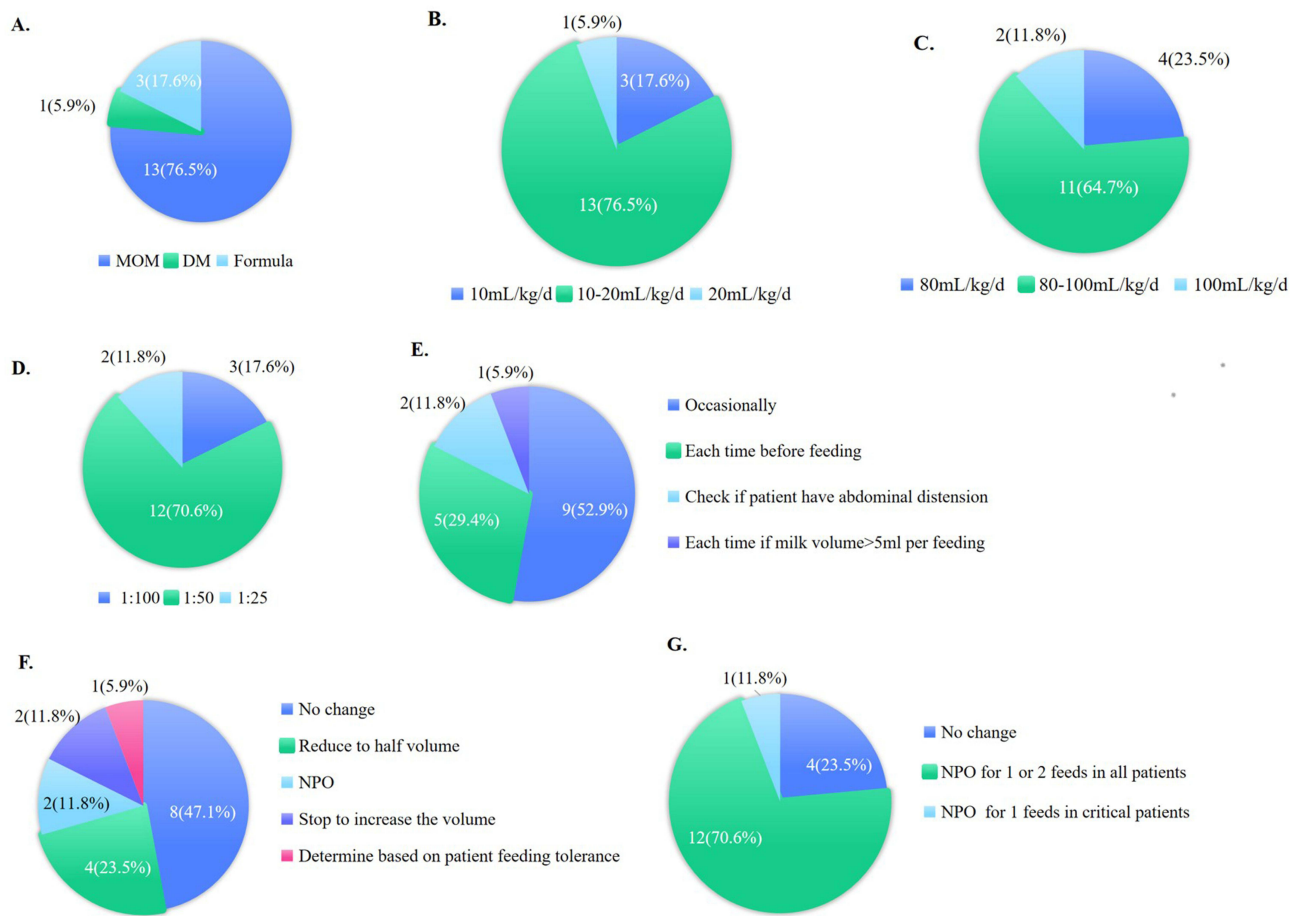
5 (29.4%) out of the 17 NICUs used DHM. 3 (17.6%) NICUs did not have any standardized enteral feeding protocol, 13 (76.5%) NICUs chose fresh MOM to initiate enteral feeding after birth (Figure 3A). 13 (76.5%) NICUs increased feeding volumes with 10–20mL/kg.d (Figure 3B). Human milk fortifier (HMF) was added when enteral feeding reaches to 80–100mL/kg.d in 11 (64.7%) NICUs with initial ratio of 1:50 (HMF to human milk) (70.6%) (Figure 3C and D).

9 (52.9%) NICUs occasionally checked the gastric residual content before enteral feeding (Figure 3E). At 8 NICUs (47.1%), the course of enteral nutrition management was not changed during treatment for PDA. At 12 NICUs (70.6%), enteral feeding was stopped for 1 or 2 feeds during RBC to prevent NEC (Figure 3F and G).

**Table 1** PDA Management

		Routine Echo	PDA was Usually Treated Based on the Echo Results	Anti-inflammatory Drugs for PDA Closure	
<b>No</b>		2	13	1	
<b>Yes</b>		15	4	16	
<b>Time</b>	Routine Echo perform	11 within 24h to 72h after birth		Echo perform after treatment	14 after one course of treatment
		2 after 72h after birth			1 after each dosage of treatment
		1 within 24h after birth 1			I do not conduct Echo but depending on the judgement of clinician
		1 based on clinical symptoms			

**Abbreviations:** Echo, echocardiography; PDA, patent ductus arteriosus.



**Figure 3** EF strategies. (A) Milk resources for initial EF; (B) Increasing Rate of milk volume for EF; (C) Volume of EF before the use of human milk fortifier; (D) Initial Ratio of human milk fortifier added in human milk; (E) Time point for assessment of gastric residual content; (F) Changes in EF strategies during drug treatment for PDA; (G) EF changes during red blood cell transfusion.

**Abbreviations:** MOM, mother's own milk; DM, donor milk; EF, enteral feeding; PDA, patent ductus arteriosus.

## Discussion

It is widely recognized that severe NEC can exacerbate the suffering of children and put additional strain on healthcare systems and families. Although the incidence of NEC has decreased considerably over time with the advancement of medical technology, it remains relatively high in some regions of China. As a result, many NICUs are looking for effective measures to mitigate the incidence of NEC, and so are we. Therefore, we constructed this questionnaire to provide a foundation for the best measures for future quality improvement, and this multi-center questionnaire survey revealed the variation and similarity in prevention strategies for NEC among 17 NICUs in China.

The effect of empirical antibiotic use on the risk of NEC is still a debatable topic. Some studies suggest that prolonged initial empirical antibiotic therapy in VLBW infants with sterile culture results can increase the risk of NEC or death.<sup>15,16</sup> The reason behind this is that early antibiotic use might lead to abnormal gut colonization in neonates.<sup>17,18</sup> However, some studies indicate that the delay in bacterial colonization can help preterm gut defenses mature and reduce the risk of NEC.<sup>19,20</sup> Nonetheless, this theory is based on animal models of older premature infants, and it is not yet clear whether it applies to smaller premature infants.

According to the survey results, most of the 17 NICUs preferred to use a combination of broad-spectrum antibiotics (BSAs) as the initial empirical treatment for EOS, LOS, or NEC. Unreasonable combination of antibiotics and over-exposure to BSAs may increase the risk of NEC in preterm infants.<sup>21</sup> Exposure to antibiotics in the first 7 days of life for  $\leq 3$  days is a protective factor for NEC (Greater than or equal to stage 2) in VLBW infants.<sup>12</sup> However,  $\geq 5$  days of exposure to antibiotics was associated with an increased risk of NEC among neonates without proven sepsis.<sup>15,22</sup> These

results suggest that timely discontinuation (less than 3 days) of initial empirical antibiotics in VLBW infants with negative bacteria cultures may be an effective intervention of QI to reduce the incidence of NEC.

The issue of “to treat or not to treat a PDA” is controversial. PDA is an independent risk factor for NEC in preterm infants.<sup>23</sup> However, the treatment of PDA, especially using indomethacin, also could increase the risk of NEC.<sup>24</sup> Compared to indomethacin, ibuprofen was more effective and could reduce the NEC for the treatment of PDA.<sup>24</sup>

According to the survey results, only one out of the 17 NICUs did not administer anti-inflammatory drugs for PDA treatment. This unit preferred conservative treatment to close PDA. The prophylactic treatment of PDA before it is symptomatic, once popular, has now become controversial as it unnecessarily exposes a large proportion of preterm babies to the side effects of treatment who would have closed the PDA spontaneously.<sup>25</sup>

Enteral feeding plays a chief role in the prevention and treatment of NEC. There is established evidence that providing MOM and standardization of feeding regimens leads to a decreased risk for NEC.<sup>26</sup> Standard fortification of pasteurized DM did not increase the incidence of NEC among preterm neonates.<sup>27</sup> Compared with 15 to 20 mL/kg, daily feed intake increments of 30 to 35 mL/kg did not increase the risk of NEC, mortality, or interruption of feeds but could reduce the time to achieve full enteral feeding and the duration of TPN.<sup>28</sup> According to the survey results, most units opted to increase feeding at a rate of 10 to 20mL/kg daily. The primary reason medical staff were hesitant to increase feeding too quickly may be due to concerns about the increased incidence of NEC. Therefore, changing the awareness of these people will be an important QI intervention.

Most of units chose to NPO during RBC transfusion. Withholding feeds during packed red blood cell transfusion significantly reduced the incidence of transfusion-associated NEC in preterm infants,<sup>29</sup> and most NICUs had come to a consensus on this matter based on the results of the survey. On the other hand, continuous enteral feeding during pharmacologic closure of PDA would not change the blood flow velocity of superior mesenteric artery and increase NEC.<sup>30</sup>

## Conclusion

The findings of this survey conducted through questionnaires revealed both differences and similarities in the strategies employed to prevent NEC in 17 NICUs in China. Despite numerous interventions being implemented, there is still controversy surrounding their effectiveness. Therefore, further work is required to successfully carry out the QI project to reduce NEC in these NICUs.

## Data Sharing Statement

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under licenses. The corresponding author will accept requests to access the data and provide details regarding the restrictions and conditions under which such access may be provided.

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## Disclosure

The authors declare no conflicts of interest.

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