



# Necrotizing enterocolitis in a Chinese perspective: a narrative review

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**Background and Objective:** Necrotizing enterocolitis (NEC) is one of the most life-threatening diseases in neonates. As a populous country, the incidence of NEC has increased in China, and some original viewpoints have been proposed recently. We aim to generalize the latest research on NEC in China and report some different opinions from a Chinese perspective in this review.

**Methods:** We searched PubMed using the term “necrotizing enterocolitis” and “China” for articles published from July 2002 to June 2022. Those studies performed in the Chinese population and reported in English were included.

**Key Content and Findings:** In China, the morbidity and mortality of NEC is comparable to that in other countries, and they can range based on the level of medical institutions and the regional economic development in China. Quantities of NEC cases are reported in term infants for whom breastmilk is introduced later. Risk factors such as transfusion, intrahepatic cholestasis and meconium aspiration syndrome have been proposed. For the diagnosis, the value of pneumatosis intestinalis and portal vein gas should be re-evaluated, and ultrasound examination as well as new manifestations on abdominal X-rays are being given more attention. New explorations of biomarkers, microbiota and metabolites based on the Chinese population are needed. Controversies regarding treatment, including the duration of fasting and decompression, the choices of antibiotics, especially the usage of anti-anaerobic treatment, and the safety and efficacy of probiotics still exist in China, and the exploration of ideal surgery indications will be a new direction in the future.

**Conclusions:** Although great success has been achieved in NEC exploration based on the Chinese population, there is still a long and difficult road ahead for the clinical application of these new findings, and further research is needed.

**Keywords:** Necrotizing enterocolitis; etiology; diagnosis; treatment; China

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## Introduction

### Background

Necrotizing enterocolitis (NEC) is a lethal gastrointestinal

disease, in which the patients present with abdominal distension, vomiting or bloody stool; it has high morbidity and mortality, especially in preterm infants (1,2); and complications such as severe neurological retardation,

**Table 1** The search strategy summary

Items	Specification
Date of search	1 <sup>st</sup> Jul, 2022
Database searched	PubMed
Search terms used	“necrotizing enterocolitis”, “China”
Timeframe	1 <sup>st</sup> Jul, 2002–30 <sup>th</sup> Jun, 2022
Inclusion and exclusion criteria	Inclusion criteria: performed in the Chinese population and reported in English Exclusion criteria: case reports, literature reviews, animal and vitro researches, system reviews and meta-analyses not based on Chinese population
Selection process	Similar conclusion from multicenter studies were preferred to that from single-center studies. Selection of references was agreed on by both authors

enterostenosis and short bowel syndrome after surgery can subsequently affect the quality of life of infants (3,4). Prematurity, hypoxia and infection are commonly considered to be important risk factors for NEC (2,5,6).

### ***Rationale and knowledge gap***

However, wide variations in the incidence and outcomes of NEC in race and ethnicity have been reported, and these variations may result from social and biological determinants (7). Hispanic ethnicity and Asian or Pacific Islander race were associated with a higher incidence of NEC (8). As a populous country in Asia and due to the increasing preterm birth rate (9), the incidence of NEC has also increased in China (10,11). Meanwhile, many Chinese scholars have focused on this serious disease, and some original viewpoints have been proposed in recent years.

### ***Objective***

Here, the latest researches of NEC from Chinese population are reviewed, and some interesting opinions are given from a Chinese perspective. We present this article in accordance with the Narrative Review reporting checklist (available at <https://pm.amegroups.com/article/view/10.21037/pm-22-39/rc>).

### **Methods**

We searched for papers published from July 2002 to June 2022 on the PubMed ([www.pubmed.org](http://www.pubmed.org)) databases using the title and abstract keywords “necrotizing enterocolitis” and “China”. Those studies performed in the Chinese population

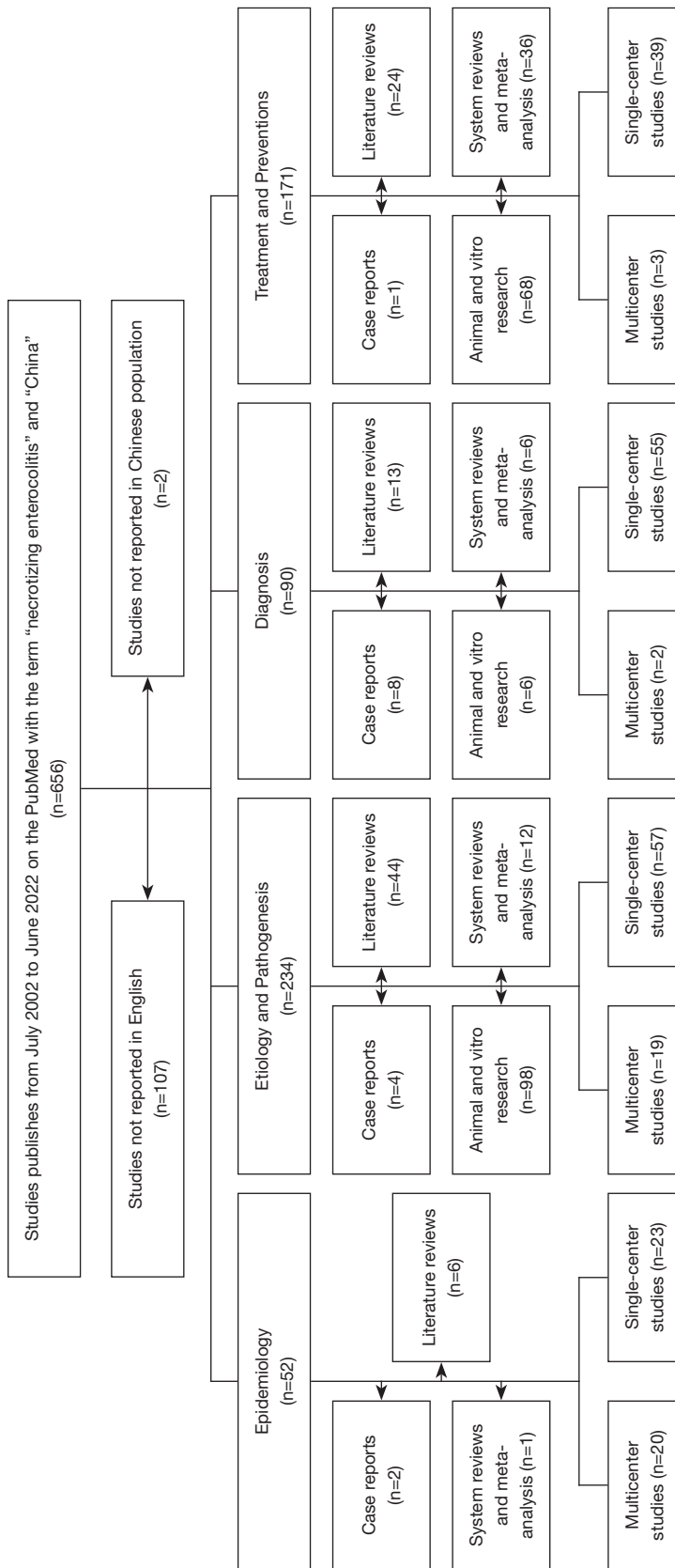
and reported in English were included in our review. Case reports, literature reviews, animals and vitro researches were excluded for the low evidence-based level and system reviews and meta-analyses not based on Chinese population were also excluded. Similar conclusion from multicenter studies were preferred to that from single-center studies. The selection of references was agreed upon by both authors (*Table 1, Figure 1*).

### **Narrative**

#### ***Epidemiology***

#### **The morbidity and mortality in China are comparable to that in other countries**

In the United States, the incidence of NEC is reported to be 5–12% in preterm infants and is as high as 13% in those born with very low birth weight (1,2), and in Europe, it ranges from 3–8.7% in preterm infants (12,13). The mortality reported of NEC in the United States and Europe ranges from 20% to 30%, and especially in those requiring surgery, it is even high (12,14). Multicenter studies in China showed a comparable result with these countries. The incidence of NEC ranges from 2.5% to 6%, varying by region and economy (15–18) and in very preterm and low-birth-weight infants, it ranges from 4.9–10.1% (19,20). The mortality of NEC in China is 9.4–17.6% (15,21–23) and in those requiring surgeries, it can be up to 29.4–41.7% (24–26). Although the morbidity and mortality in China are comparable to that in other countries, it is worth mentioning that it is extremely unbalanced and ranges from the level of medical institutions and regional economic development. In a neonatal intensive care unit from a tertiary medical institution in southwest China, the mortality of NEC after



**Figure 1** Included and excluded processes of the researches in our study. Single lines are used for inclusion and arrows are used for exclusion.

laparotomy reported was 31.4% (24) while in a single-center study from a tertiary medical institution in eastern China with a specialized pediatric surgery department showed that 68.5% of NEC neonates underwent surgeries, and the postoperative mortality rate was only 12.8% (27). This may result from the poor overall medical care due to the fewer physicians serving more infants in some parts of China and some hospitals of level I or II in China did not have sufficient facilities to deal with the critically ill infants.

### *Etiology and pathogenesis*

#### **A number of NEC cases are reported in term infants**

Preterm birth is considered to be the most important risk factor for NEC in patients with an immature gut with imperfect intestinal mucosal barrier structure defense mechanisms (28,29), and it has been widely reported that NEC mostly occurs in preterm infants worldwide (28-30). However, many NEC cases have also been reported in term infants one week after birth in China (31,32). This can be explained by the following causes. First, there is a large population of term infants in Chinese hospitals for the high mortality of preterm infants resulting from the poorer overall medical care and high rate of discharge against medical service. A large cohort study of preterm infants in 25 tertiary neonatal intensive care units in China showed that 12% of neonates with gestational age <31 weeks and 23% of very low birth weight infants did not receive complete medical care due to financial hardship (33). Second, most term infants are fed with formula milk due to the lack of breastmilk from their mothers one week after the infant was born and the fact that few milk banks can be found in China (34-37). It has been widely reported that formula feeding is one of the risk factors for NEC because high osmotic pressure triggers intestinal mucosal hypoxia and intestinal damage (38,39). In addition, the dysbiosis caused by contamination during the production of formula milk can also be a potential etiology of NEC. *Cronobacter*, a foodborne pathogen associated with severe infections and high mortality in neonates (40,41), and the *Bacillus cereus* group, a human pathogenic bacterium (42,43), have been found in infant formula milk in China.

#### **Transfusion, intrahepatic cholestasis and meconium aspiration syndrome may be new risk factors for NEC**

Any factor directly causing hypoxia or ischemia can be a risk factor for NEC due to the redistribution of blood and the release of oxygen radicals and inflammatory factors (44,45). Placental abruption, neonatal asphyxia, congenital heart

disease (such as patent ductus arteriosus) and anemia has been reported as risk factors for NEC related to hypoxia and ischemia (44-47). Interestingly, blood cell transfusion has also been reported to be a potential risk factor for NEC in Chinese population (47-49). The sudden increase of viscosity in the circulating blood after transfusion can alter blood flow to the bowel and increase the intestinal injury (50,51) and the increase affinity of red blood cells for oxygen will shift the recipient's oxygen dissociation curve and predispose recipients to ischemia (52,53). In addition, intrahepatic cholestasis and meconium aspiration syndrome were first reported to be risk factors for NEC due to their role in hypoxia and ischemia (54). Excessive bile acid in the blood of mothers with intrahepatic cholestasis can cause swelling of the trophoblast in the placenta and edema of the villous matrix, thereby reducing blood flow and fetal oxygenation (55). In infants with meconium aspiration syndrome, as well as ischemia caused by meconium aspiration, numerous cytokines in the lung induce inflammation and alter the protective barrier in the gastrointestinal tract through vascular circulation, while meconium-contaminated amniotic fluid can also lead to an excessive immune response in the gut (56).

Regarding the etiology and pathogenesis of NEC, similar conclusions were also obtained in some studies based on the Chinese population. Abnormal intestinal microbiota colonization, especially increased pathogenic bacteria caused by delayed enteral feeding (57) and early exposure to broad-spectrum antibiotics (58), can increase the incidence of NEC and are associated with an increased inflammatory response and abnormal bacterial glycosylation patterns (29,59). Breast milk fortifiers (60) and parenteral nutrition (61,62) can increase osmotic pressure, slow gastric emptying, cause gastric retention, affect intestinal barrier function, and lead to intestinal damage. In addition, various invasive procedures, such as catheterization, can block the microcirculation of intestinal vessels and lead to intestinal injury (63).

### *Diagnosis*

#### **NEC should be redefined based on different diagnostic criteria**

Nowadays, the definitions of NEC are mainly based on clinical manifestations and imaging presentation and there is not a generally agreed gold-standard. Bell staging criteria (64) and modified Bell staging criteria (65) are the most accepted criteria worldwide. However, the staging and clinical criteria across definitions are highly variable for the

subjective evidence. For example, non-specific findings like feeding intolerance and abdominal distention can also be found in separate diseases such as sepsis and infants with spontaneous intestinal perforation can also be found with pneumoperitoneum (66). Also, new definitions of NEC including Vermont Oxford Network definition, Centers for Disease Control and Prevention definition, Gestational Age-Specific Case Definition of NEC, 2 of 3 rule, Stanford NEC score and International Neonatal Consortium NEC workgroup definition have been also proposed in recent years (67-71). Thus, how to redefine the diseases that are currently being called “NEC” is an important problem and challenge.

One strategy of redefining is simply using the terms “medical NEC” for those infants with better condition of clinical symptoms and imaging signs and “surgical NEC” for those with intestinal necrosis in surgery or autopsy (72). Another strategy is to assess the performance of current NEC definitions. Large cohort studies with infants “NEC” are needed for the comparison of current 8 definitions to assess the ability to predict short and long-term outcomes and once a case definition and relevant outcomes have been agreed upon, NEC redefinitions could be achieved (71). And the third strategy is to evaluate the components of each NEC definition of current 8 definitions. Assessing of the incidence of single indicator (such as abdominal distension, vomiting, bloody stool, diarrhea, abdominal wall redness) will help eliminate the interference of rare clinical symptoms and signs (71). And multicenter prospective studies with the participation of family members who provide information about the daily changes and final outcomes are needed for a consensus definition (69,73). Meanwhile, we should re-recognize the existing diagnostic criteria more objectively.

#### **The value of pneumatosis intestinalis and portal vein gas in the diagnosis of NEC should be reacquired**

Pneumatosis intestinalis (PI) and portal vein gas (PVG) are the characteristic presentation of NEC on imaging. However, making a diagnosis based on these two signs should be re-evaluated these days because the sensitivity and specificity have been challenged. First, in preterm infants with lower gestational age, NEC might be easily misdiagnosed with feeding intolerance for the atypical clinical manifestation and at that time, intestinal obstruction and intestinal perforation on imaging are common (74,75). More importantly, PI and PVG are not a patent for intestinal diseases. Many non-intestinal diseases such as asthma, pulmonary fibrosis, emphysema, bronchitis and other pulmonary diseases and systemic

autoimmune diseases such as scleroderma, dermatomyositis may present with these signs. Some pharmaceutical factors and even iatrogenic operations also lead to PI and PVG. Moreover, even in neonates, PI and PVG can also be found in other diseases such as ischemic intestinal necrosis, congenital intestinal malrotation, intestinal obstruction, diverticulitis, and Hirschsprung disease (76). Food-protein induced enterocolitis, a non-IgE-mediated gastrointestinal inflammatory disease has similar clinical presentations to NEC (77) and RNA viruses, such as *Astroviridae*, *Caliciviridae*, and *Picornaviridae* have also been detected in the human intestine (53). They can also have a radiologic finding of PI and PVG and make it easily misdiagnosed as NEC (78-81). Therefore, PI and PVG cannot be absolute evidence for NEC, and those patients without these two signs will have a missed diagnosis. It is necessary to explore more manifestations for an accurate diagnosis.

#### **More attention is paid to ultrasound examinations in China**

Compared with X-ray, ultrasound has advantages that include being noninvasive and having a high rate of positive detection and dynamic monitoring. Minor changes in the intestine from the disease, such as decreased blood perfusion in the intestinal wall, edema and slowed peristalsis, can be detected with ultrasound and can also show the amount and nature of the ascites (82,83). Specific imaging of PI and PVG in NEC infants can be found as hyperechoic bubbles on abdominal ultrasound examinations (84). In addition, ultrasonic findings of bowel wall thickening (greater than 2.5 mm), decreased bowel motility, and Doppler production of high peak systolic velocity and differential velocity can help in the diagnosis of NEC (85,86). Free peritoneal gas, portal gas, bowel dilatation, bowel wall thickening and ascites can predict the timing of surgery (82,87-89). Thus, ultrasound may be more clinically practical for the diagnosis and progression of NEC. The diagnosis of NEC based on abdominal ultrasound has been listed as a new diagnostic criterion by the Vermont Oxford Network (90) and has received more attention in China.

#### **New imaging presentations on supine abdominal X-rays are helpful in the diagnosis of perforation and surgery decision-making**

For infants with advanced NEC, perforation is the most serious complication, and pneumoperitoneum along with increased free air on imaging examination is the absolute indication for surgery (83). Early identification of perforation

and accurate surgical decisions may reduce mortality and sequelae. Subdiaphragmatic air is the most obvious imaging feature on erect abdominal X-rays to identify pneumoperitoneum. However, for sick neonates with suspected NEC, it is impractical to transport them to the radiology department for an erect X-ray examination (91). Therefore, supine abdominal X-rays with cross-table or lateral decubitus images are a good option. Our previous study that focused on the features of perforation on supine abdominal X-rays showed that a lucency over the liver shadow, the presence of the liver falciform ligament sign, the football sign, the Rigler sign and the triangle sign have a sensitivity of 86.73% and a specificity of 100% for the confirmation of perforation in neonates with NEC (92). Thus, these new imaging presentations are helpful in surgery decision-making and may be clinically acceptable in the future.

### **Biomarker exploration based on the Chinese population is needed for clinical application**

Biomarker exploration, including nonspecific biomarkers related to infection and intestinal injury-specific biomarkers in NEC, has been a trend in recent years. Nonspecific biomarkers, such as calprotectin, human  $\beta$ -defensin and resistin-like molecule  $\beta$ , are released into the intestinal lumen by neutrophils or monocytes and can cause gastrointestinal mucosal injury. They have been reported to be increased in inflammation and have high potential for the early diagnosis of NEC in the Chinese population (93-95). Intestinal injury-specific biomarkers are those that are found in the gastrointestinal mucosa and intestinal wall when the gut is damaged and can be detected in the blood, urine or feces. High-mobility group box 1, fatty acid binding protein intestinal trefoil factor-3, and claudin-3 are related to intestinal injury and have been reported to be valuable in the early diagnosis and prediction of the prognosis of NEC (96-101). Although these biomarkers can be helpful in the prediction or diagnosis of NEC, most of them can be increased in other infectious diseases, such as neonatal sepsis and purulent meningitis, or any diseases that cause intestinal injury, which makes them less sensitive to some extent. Currently, most of these can only be used as the basis for scientific research. Therefore, high-quality, multicenter, and large-scale clinical studies are needed for clinical practice, especially in the Chinese population.

### **The microbiota and metabolites have been a new focus in the prediction of NEC**

Recently, gut microbiota as well as its metabolites in the

early prediction of NEC have become a new focus. Previous studies have found that NEC infants have microbiota with lower diversity (102), and the microbiota composition of NEC infants is significantly different from that of healthy infants. The microbiota of these infants features an increase in *Proteobacteria* and a decrease in *Firmicutes* and *Bacteroidetes* before the onset of NEC (103,104). Meanwhile, the metabolites of the microbiota of NEC infants also show significant differences, especially those related to the activities of enzymes, lipid metabolism and amino acid metabolism. *Klebsiella*, *Clostridium*, *Clostridium perfringens* and metabolites such as alanine and histidine in urine, acylcarnitine and acylcarnitine (105-109). Our latest study found that *Streptococcus salivarius* and *Rothia mucilaginosa* were increased and *Bifidobacterium animalis subsp. lactis* was decreased seven days before NEC, and the main metabolites and short-chain fatty acids also changed. Decreases in acetic, propionic and butyric acids may help in the early prediction of NEC (110). In addition, autoinducer-2, which is an important signaling molecule of the bacterial quorum sensing system and plays an important role in microbiota communication, changes before the microbiota changes and can be used as a new biomarker for NEC diagnosis and monitoring (111).

### **Treatment**

#### **The duration of fasting and decompression are clinically controversial**

Fasting and decompression are important treatments of NEC and can reduce the pressure from the intestinal contents, and decompression can promote intestinal rest. There are few studies on the duration of fasting and decompression based on the Chinese population, and we still adopt the standard that is recommended worldwide (30,112). Fasting should last for 7-10 days (30), and once the patient's vital signs are stable and the clinical symptoms are improved, enteral nutrition should be reintroduced immediately, which benefits intestinal recovery (113,114). It has been pointed out that fasting for less than 7 days did not increase recurrence, death, or sequela-like stenosis in NEC infants (115), and shortening the duration of fasting can reduce the incidence of catheter-related sepsis (116). No uniform standard is recognized for the start and end of decompression. Early decompression is recommended (117) and should not stop until the relief of intestinal paralysis and until there is no PI on abdominal imaging (112). However, there has been no clinical evidence that has been identified for the duration of fasting and

decompression in NEC infants in China.

### **The choices of antibiotics differ in clinical practice**

For antibiotic treatment in NEC, a length of 7–14 days is mostly recommended, and the length of antibiotic therapy depends on the stage of disease (118). A questionnaire survey of 284 pediatricians in tertiary hospitals in 29 provinces and cities in China found that 77.5% of pediatricians choose a time frame of 5–10 days for the treatment of stage II NEC, and 79.6% choose a time frame of 7–14 days for stage III NEC (119). However, there is currently a lack of high-quality evidence-based evidence for the choice of antibiotics, and no antibiotic has been reported to have specific efficacy in the treatment of NEC (120). In developed countries, broad-spectrum antibiotics like vancomycin, aminoglycosides and metronidazole are the most choices (30,121). While in the Chinese survey, beta-lactamase inhibitors, carbapenems and cephalosporins are the top three single-antibiotic regimens and twenty combinations of two antibiotics were identified (119). Anti-anaerobic treatment was not first chosen as single-antibiotic regimens in China for carbapenems can be regarded as treatment of most anaerobic infections (122). However, in this survey, the combination of beta-lactamase inhibitors and anti-anaerobic agents was the top combination (119), while there are some controversies among Chinese neonatologists. A single-center cohort study on term NEC infants in Southwest China showed that the combined use of metronidazole could not prevent the progression of NEC (123). The best choice of antibiotics and whether anti-anaerobic treatment is necessary in the treatment of NEC in China still require further study.

### **The efficacy of probiotics in the treatment and prevention of NEC needs to be further clarified**

Dysbiosis presenting with a lower abundance of *Firmicutes* and a higher abundance of *Proteobacteria* in NEC infants has been previously indicated by previous studies (103,104). Because most probiotics belong to the *Firmicutes* phylum, in theory, probiotic supplementation may be beneficial for the treatment and prevention of NEC. Many recent studies have shown that probiotics play an important role in the treatment and prevention of NEC (124–127). However, few prospective or multicenter studies regarding the efficacy have been performed up to the present, and some clinically recognized probiotics have been suggested to be ineffective in the prevention and progression of NEC. A randomized controlled trial

performed in very preterm infants found that intervention with *Bifidobacterium breve* BBG-001 did not benefit the prevention of NEC (128), and a retrospective cohort study in China also showed that probiotic supplementation may not prevent the deterioration of NEC from stage I to II/III (129). Therefore, more clinical studies evaluating the use of probiotics in the treatment and prevention of NEC still need to be conducted in the Chinese population.

### **Exploration of ideal surgery indications still has a long way to go**

Perforation is considered an absolute indication for surgery of NEC infants, but by the time perforation develops, the inflammation caused by intestinal perforation as well as septic shock or other fatal complications are life-threatening (130–133). Therefore, the ideal surgical indication of full-thickness intestinal wall necrosis but no perforation has been proposed in recent years (4). However, it has been difficult to find the most ideal time point. Scoring systems that include clinical symptoms and signs and imaging and laboratory indicators have been constructed and found to be effective in surgery decision making (134–136). Our preliminary study found that a serum Relm $\beta$  concentration >19.7  $\mu\text{mol/L}$  combined with abdominal wall tenseness and abdominal tenderness may be useful in determining the surgical timing in neonates with NEC (137). But there is still no prediction model of surgical timing clinically available recommended by the guidelines and there is still a long way to go for the exploration of the ideal surgical indications for the Chinese population.

### **Strengths and limitations**

As a populous country with quantities of preterm infants, there were many researches of NEC in the Chinese population and we present a 20-year perspective on these studies according to the evidence-based level. This approach has great potential to inform differences in NEC epidemiology, diagnosis, and treatment and shows the current status of NEC in China. However, there are still some limitations. These studies should be scored with the scoring system for different types of researches for the strength of evidence level. And those conclusions from single-center studies with small sample size might be subjective and cannot reflect the overall status of NEC in China. And we only searched the studies on PubMed and included those reported in English and some studies performed in Chinese population might be missed.

## Conclusions

The morbidity and mortality of NEC in China is comparable to that in other countries, and they can range based on the level of medical institutions and the regional economic development in China. Although premature birth is considered to be the most important risk factor for NEC, many term cases are reported in China due to the large population and the lack of breastfeeding one week after birth. In addition, transfusion, intrahepatic cholestasis and meconium aspiration syndrome have been reported as risk factors for NEC in the Chinese population. For the diagnosis, the value of pneumatosis intestinalis and portal vein gas should be reacquainted because these two presentations can also be found in food-protein induced enterocolitis, which is easily misdiagnosed as NEC. Ultrasound examination is given more attention for its advantage of finding minor disease changes in the intestine, and new imaging presentations on supine abdominal X-rays are helpful in the diagnosis of perforation and surgery decision-making. In addition, new biomarker exploration, including microbiota and metabolites derived from the Chinese population, has been a new focus, and more evidence based on clinical practice is needed for further application. There is a lack of widely accepted standards for the duration of fasting and decompression, and the choices of antibiotics, especially the usage of anti-anaerobic treatment, differ based on clinical experience. The safety and efficacy of probiotics in the treatment and prevention of NEC still need to be further clarified. The exploration of the ideal surgery indications based on the clinical symptoms and signs and the imaging and laboratory indicators will be a new direction in the future. In summary, although great success in NEC exploration based on the Chinese population has been achieved, there is still a long and difficult road ahead for the clinical application of these new findings, and further research is needed.

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