

## Peer Review File

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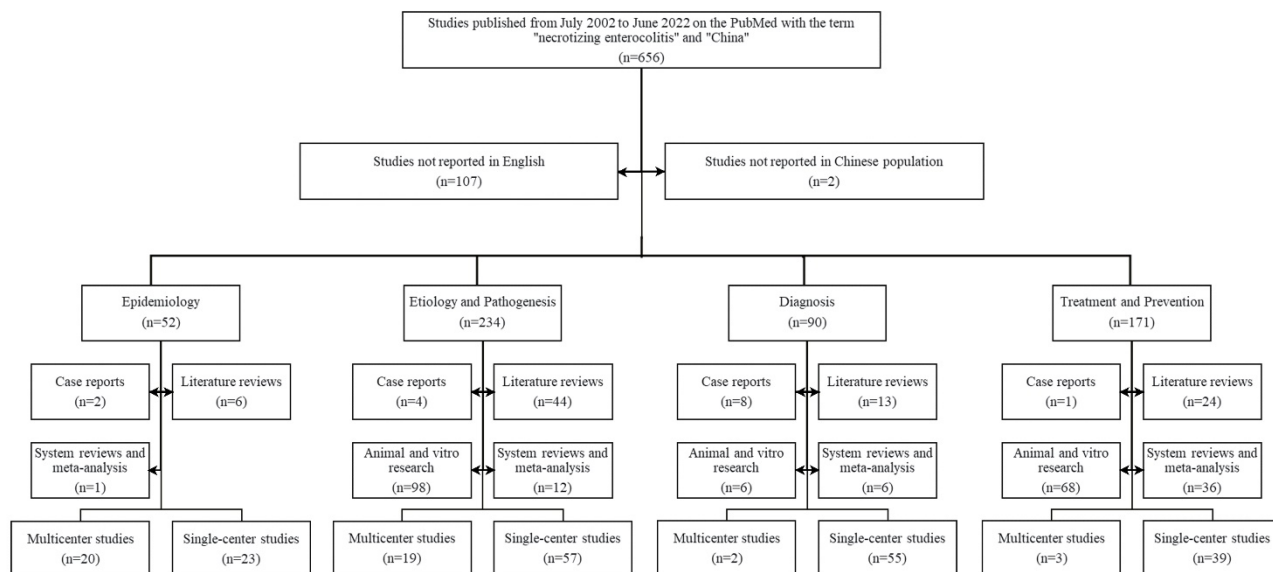
### Reviewer 1

Comment 1: The authors present a 20 year perspective on studies of NEC in the Chinese population. This approach has great potential to inform differences in NEC epidemiology, diagnosis, and treatment. However, even though the authors do not report that this is a systematic review, I am worried about the rigor of the search strategy, quality of reporting, and tendency towards overstatement of facts that comes without a rigorous and standardized approach to reviewing the literature.

**Reply 1:** Thanks for your suggestions and we have made some improvements in the Method section. As a narrative review, 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-analysis 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.

Comment 2: Major concerns include lack of a medical librarian assistance in designing the search, lack of reporting how many studies were found and how many were excluded, as well as the reasons why, and concerns for overstating differences based on small or single studies. For example, while the statement that mortality is higher in China than in developed countries may be true, the multicenter study cited for this fact was from data from a single year, and a different study cited in that same section states that a tertiary medical center actually had lower mortality from stage 3 NEC than developed countries. Anchoring each of the proposed themes according to the strength and certainty of evidence would make this a substantially stronger paper and more helpful to the reader. For example, in each section, the authors should report the number of papers found addressing each theme, the conclusions drawn, and the strength of that conclusion. Currently, the paper tends to list only conclusions without certainty as to how the authors arrived at them.

**Reply 2:** Thanks very much for your suggestions of evaluating the quality according to the strength and certainty of evidence and we have made some revisions to our description. Also, a figure of the retrieval and inclusion processes of the papers in our study has been provided as **Figure1**.



Comment 3: Additionally, there are concerns for statements posed as fact that are controversial or at a minimum, overstated (ie line 114: transfusions listed as an 'acknowledgeable risk factor', when in fact, observational studies show contradictory results to controlled trials; or line 142, "when imaging examinations are performed, the condition always worsens"; or lines 279-281, "by the time perforation develops, the inflammation... is life-threatening, and it is too late for surgery").

**Reply 3:** We have overviewed our manuscript and changed some of our statements. Also, some explanations were provided.

## Reviewer 2

Comment 1: Line 18, “the most life-threatening disease in neonates” suggest changing to “one of the most life-threatening diseases in neonates.”

**Reply 1:** It has been changed.

Comment 2: Line 26-27, “In China, the morbidity of NEC is comparable to that in developed countries.”, many would consider China a developed country so it may be best not to say "developed". Simply stating other countries would be reasonable.

**Reply 2:** It has been changed.

Comment 3: Line 31, “reacquainted” should be “re-evaluated”?

**Reply 3:** It has been changed.

Comment 4: Line 67, “The mortality in China is higher than that in developed countries”, and Line 292, “The morbidity of NEC in China is comparable to that in developed countries”

? "developed"

**Reply 4:** It has been changed.

Comment 5: Line 68, it is better to change “America” to “the United States”.

**Reply 5:** It has been changed.

Comment 6: Line 71, it should change “comparative” to “comparable”.

**Reply 6:** It has been changed.

Comment 7: Line 102-108, “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 neonate, and the *Bacillus cereus* group, a human pathogenic bacterium, have been found in infant formula milk in China.”

This is very interesting. Might it be possible to also mention that food protein intolerance (FPIES) also is often diagnoses as "NEC" and that some of cases diagnosed as "NEC" may actually be a form of food protein intolerance? This is an area that could and should be explored further.

**Reply 7:** We have added this in the “Diagnosis” section as the reason why the value of pneumatosis intestinalis and portal vein gas in the diagnosis of NEC should be reacquired. Shortly, in preterm infants with lower gestational age, NEC might be

easily misdiagnosed with feeding intolerance and pneumatosis intestinalis and portal vein gas can also be found in other diseases, such as food-protein induced enterocolitis and virus induced enterocolitis.

Comment 8: Line 132-134, “In addition, various invasive procedures, such 133 as catheterization, can block the microcirculation of intestinal vessels and lead to 134 intestinal ischemia(52).”

This is of major interest because intestinal ischemia may cause intestinal necrosis, but seems to be derived from a different pathophysiology than many other forms of "NEC" which appear to be more inflammatory.

**Reply 8:** Hypoxia and ischemia can lead to the redistribution of blood and the release of oxygen radicals and inflammatory factors. Thus, any factors related to these can be risk factors of NEC. In Chinese population, transfusion, intrahepatic cholestasis and meconium aspiration syndrome has been reported as risk factors for NEC related to hypoxia and ischemia. The potential mechanisms have been added in the manuscript.

Comment 9: Line 140, it is better to change “reacquainted” to “re-evaluated”.

**Reply 9:** It has been changed.

Comment 10: Line 296, “*the lack of breastfeeding one week after birth*”, this practice may require some explanation. Why is there a delay of one week?

**Reply10:** 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(1-4).

We have added the reasons in the manuscript.

1. Bai DL, Fong DYT, Lok KYW, et al. Practices, predictors and consequences of expressed breast-milk feeding in healthy full-term infants. *Public Health Nutrition* 2017;20:492-503.
2. Fan HSL, Wong JYH, Fong DYT, et al. Breastfeeding outcomes among early-term and full-term infants. *Midwifery* 2019;71:71-6.
3. Liu X-H, Han S-P, Wei Q-F, et al. The data and characteristics of the human milk banks in mainland China. *World Journal of Pediatrics* : WJP 2019;15:190-7.
4. Tian C, Li Y, Soowon L, et al. Lactating Women's Knowledge and Attitudes About Donor Human Milk in China. *Journal of Human Lactation* : Official Journal of International Lactation Consultant Association 2021;37:52-61.

### **Further comments**

Q1. Overall these authors have done a very nice job in editing their article. In fact on page 8, they hint at difficulties of diagnosing NEC versus feeding intolerance. It would be great if they could add a little more information perhaps in the introduction

and in the later part of the review about the difficulties defining NEC (there are at least 8 definitions in the literature) and how we need to redefine the different clusters of more specific diseases that are currently being called “NEC”.

A1. Thanks for your suggestions and we have added the difficulties in defining NEC in the “Dignosis” section and the opinions of how to difine NEC from different scholars are also showed. In addition, for the diagnosis are mainly based on imaging presentations nowadays, more information of pneumatosis intestinalis and portal vein gas are also provided in our revised edition.