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Review

The role of xanthan gum in necrotizing enterocolitis: clinical implications and safety for preterm neonates

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ABSTRACT

Necrotizing enterocolitis (NEC) is severe inflammatory disease that predominantly affects preterm infants and is closely related to shaping the gut microenvironment and immune system. Early-life feeding plays a critical role in the pathophysiology of NEC. Xanthan gum (XG) has viscosity-stabilizing properties and resistance to breast milk amylase. Therefore, XG has therefore been used in the management of dysphagia in infants. However, its safety in the intestines of premature infants remains controversial. This study aims to review current scientific evidence on the use of XG in NEC and to evaluate potential pathophysiological mechanisms from a clinical perspective. Current data suggest that fermentation of XG by the colonic microbiota into short-chain fatty acids may contribute to mucosal injury in the immature gut, although a causal relationship has not been established. Clinical studies show that NEC cases associated with XG-based thickeners have a later onset than classical NEC, with approximately half of cases developing post-discharge. Therefore, regulatory authorities such as the FDA, EFSA, and JECFA have published restrictive guidelines on the use of XG in neonates. In this context, it is crucial that XG-based products be carefully evaluated, especially in at-risk infants, and that the decision to thicken the product be made through a multidisciplinary, individualized approach that considers the infant's intestinal maturity.

Keywords: food additives, necrotizing enterocolitis, preterm infants, xanthan gum

Introduction

Food additives have been used for many years to enhance the appearance, taste, texture, and shelf life of food products (1,2). The impact of additives on intestinal health is a frequently addressed topic in research. Studies suggest that food additives can modulate the gut microbiota, which are essential for maintaining the intestinal barrier (2). In addition to their effects on the microbiota, various studies have shown that several food additives may induce intestinal damage (3).

Necrotizing enterocolitis (NEC) is characterised by severe intestinal inflammation, particularly in preterm neonates (4). Frequently encountered in neonatal intensive care units, this condition carries a high risk of mortality (5). NEC can rapidly worsen, leading to serious complications such as damage to intestinal tissue, perforation, sepsis, or shock. Major risk factors are prematurity and very low birth weight (VLBW) (4). Consistently, gut bacterial imbalance and intestinal immaturity also contribute to the problem (6). In addition, hypoxia, reduced blood flow, invasive breathing support, and

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prolonged antibiotic use can increase the risk. From a practical standpoint, feeding premature infants formula rather than breast milk is another important risk factor. This highlights the importance of components in formula, especially thickeners among food additives (7).

To prevent NEC, various preventive strategies have been developed or implemented in clinical practice. These include breastfeeding, nutritional strategies, and the use of specific food additives in breast milk, including probiotics, prebiotics, glutamine, arginine, and lactoferrin (8-10). Apart from that, the effects of gum-based thickeners, such as Xanthan Gum (XG), among additives commonly used in premature infants with dysphagia, on intestinal health are a subject of considerable debate (11). Clinical findings indicate that XG-associated NEC cases have a later onset and more pronounced colonic involvement. On the other hand, multiple observational studies report no increased risk of NEC with XG-based thickeners (12,13). These conflicting findings highlight the need to reassess the safety of XG-based thickeners in neonatal nutrition. Already, the potential implications of XG for NEC and the current regulatory perspectives on this substance have not yet been adequately discussed in the literature. This study aims to critically evaluate the potential physiological effects of XG relevant to NEC pathogenesis in preterm neonates. In addition, legal regulations regarding XG over the last 20 years have also been examined.

Preterm Infant Physiology

The suboptimal development of the intestinal barrier in preterm infants arises from both deficiencies in structural proteins and an imbalance in the microbial population. This issue becomes more pronounced as birth weight and gestational age decrease (14). Preterm infants have a less developed and permeable intestinal barrier. This immaturity, along with their weaker immune systems and less developed gut bacteria, makes them more vulnerable to serious health issues like NEC (15,16). In preterm infants, the expression of epithelial barrier-supporting proteins such as mucin-5AC (MUC5AC), trefoil factors (TFF2 and TFF3), and neutrophil defensin 3 (DEFA3) is lower in the fecal proteome compared to term infants. This deficiency in preterm infants indicates a thinner, less stable mucus layer, weakening the intestinal barrier (14). Intestinal barrier development is also closely related to the microbiota (17). An inverse relationship has been observed between the deficiency of barrier proteins in preterm infants and the production of bacterial oxidative stress proteins by opportunistic pathogens (e.g., *Enterococcus spp.* and *Klebsiella spp.).* In term infants, beneficial bacteria such as *Bifidobacterium*, which are more abundant, protect by producing short-chain fatty acids (SCFAs) that stimulate barrier function. However, colonization by these bacteria is generally delayed in preterm infants (18).

In preterm infants, reduced intestinal motility and impaired carbohydrate absorption may promote excessive lactose fermentation by potentially pathogenic bacteria, such as *Clostridium butyricum*, leading to overproduction of butyric acid and subsequent mucosal injury. This excessive production is thought to upregulate inducible nitric oxide synthase (iNOS) gene expression, which is associated with mucosal damage, thereby contributing to the development of NEC (19-21).

At normophysiological concentrations, butyrate exerts protective effects by activating the Notch Receptor 1 (Notch1) signaling pathway and enhancing the expression of key negative regulators of intestinal inflammation, such as Single Ig IL-1 Related Receptor (SIGIRR) and Tumor Necrosis Factor Alpha-Induced Protein 3 (A20) (22). Furthermore, butyrate, acetate, and propionate have been shown to have anti-inflammatory effects in intestinal tissue. These effects involve suppressing proinflammatory cytokines interleukin-6 (IL-6) and interleukin-8 (IL-8) and inhibiting inflammatory signaling

pathways, such as Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (NF-κB) (23,24). Consistently, clinical evidence indicates that levels of butyrate, propionate, and acetate are significantly reduced in infants diagnosed with NEC (23). This situation suggests that the impact of butyrate on intestinal health is highly dose- and context-dependent.

Physicochemical Properties and Digestibility of Xanthan Gum in Infant Feeding

XG is a high molecular weight, naturally occurring heteropolysaccharide produced by the aerobic fermentation of *Xanthomonas campestris*, a Gram-negative bacterial species. Described in the literature as a non-toxic, biodegradable, and biocompatible polymer, XG has a wide range of applications in medicine and pharmaceutical sciences due to these properties. XG was cleared for food use in the United States by the US Food and Drug Administration (FDA) in 1969 and is currently regulated as a direct food additive under 21 CFR 172.695 (25).

XG is used in patients' nutritional and therapeutic processes primarily due to its thickening and stabilizing properties. As a high molecular weight polysaccharide, XG has the capacity to significantly increase the viscosity of liquids even at low concentrations (26). XG solutions exhibit pseudoplastic flow behavior. This property means that their fluidity increases when a mechanical force, such as mixing or swallowing, is applied, and they thicken again when the force is removed. This rheological property facilitates the control of food in the mouth, especially during oral intake. Furthermore, XG maintains high elasticity and structural stability under shear stress (27).

XG's high stability to pH and ionic strength changes ensures it retains its structural integrity when combined with various food and beverage matrices (26,28). Finally, XG is entirely resistant to the amylase enzyme found in human saliva and breast milk. While rice cereal-based thickeners rapidly degrade when added to breast milk, XG can remain stable for hours.

XG is not digested in the human stomach or small intestine and therefore reaches the colon intact. In the colon, it is fermented by anaerobic microbiota, producing SCFAs and serving as an energy source for colonic bacteria. This property makes XG a suitable carrier for targeted colon drug-delivery systems (29). In a study involving healthy adults, daily consumption of 15 g of XG for 10 days significantly increased SCFA production in stool samples than basal levels (30).

Clinical Evidence Linking Xanthan Gum to NEC Risk

In clinical settings, NEC cases have been reported in infants receiving specific XG-based commercial thickening agents. These cases appear to have a later onset than classical NEC. While typical NEC cases generally occur around day 45 of life, the median age of onset in XG-associated cases has been reported as 66 days (12). In addition, whereas most NEC cases develop in the hospital setting, approximately 50% of XG-associated cases have been reported to occur after hospital discharge, representing a distinctive clinical pattern. These cases have also been characterized by greater colonic involvement (12,31,32).

A retrospective study conducted at Boston Children's Hospital evaluated 20 infants who received XG-based thickening agents and reported no cases of NEC. The authors attributed this finding to the low baseline incidence of NEC within the studied population (33).

Similarly, a 2022 retrospective cohort study by Abdulezer and colleagues compared the safety of XG-based commercial thickeners and rice cereal-based thickeners in 53 infants with dysphagia. The results showed no statistically significant differences between the two groups regarding the incidence of diarrhea, constipation, excessive weight gain, or obesity during the 3-6 month and 6-12 month follow-up periods. Both types of thickeners exhibited comparable safety profiles; however, prolonged use of rice cereal-based products was linked to a

higher prevalence of constipation. Importantly, no cases of NEC were reported among the infants (13).

Proposed Mechanisms Potentially Linking Xanthan Gum to Necrotizing Enterocolitis

The mechanisms proposed to link XG exposure to NEC are summarised in Figure 1. These comprise altered fermentation kinetics, bile acid accumulation, and activation of inflammatory signalling pathways. It should be emphasised that these pathways are hypothesised on the basis of preclinical and indirect clinical data and do not establish a causal relationship (Figure 1).

Fermentation Kinetics and Short-Chain Fatty Acid (SCFA) Accumulation

XG provides superior stability compared with rice cereal for thickening breast milk and infant formula. However, its use involves clinically relevant considerations. Through colonic fermentation, XG may modulate SCFA production, with implications for NEC risk. Therefore, clinical decision-making regarding thickener use should consider not only safety outcomes but also technical and feeding-related factors, including variability in preparation, time to achieve the desired viscosity, and infant oral sensory responses (34). The current lack of robust randomized controlled trials underscores the need for individualized risk–benefit assessment and for further high-quality clinical studies to inform evidence-based recommendations.

XG is broken down by anaerobic bacteria, including *Bacteroides*, *Bifidobacterium*, and *Eubacteria*, when it reaches the colon. It produces sugars, hydrogen gas, and SCFAs such as acetate, propionate, and butyrate at the end of fermentation in the colon (32,35). Consistent with these findings, XG increased acetate, propionate, butyrate, and total SCFAs in the gut of male mice in an *in vivo* study (36).

The role of SCFAs in NEC pathogenesis is controversial, as excessive levels may be toxic to intestinal tissue. High doses of SCFAs can cause intestinal mucosal damage, similar to NEC. For instance, high levels of butyric acid may contribute to the development of NEC by increasing the expression of the iNOS gene, which is responsible for mucosal injury (37). Similarly, intraluminal SCFA administration in neonatal rats consistently triggers mucosal damage. These injuries bear a striking resemblance to the clinical features of human NEC (38).

Although the information presented so far suggests that SCFAs are harmful to NEC pathogenesis, studies have shown that premature infants, who are more susceptible to NEC, have lower SCFA concentrations in their intestines than full-term infants (22). SCFAs mitigate inflammatory damage by reducing the production of IL-6, IL-8, and tumor necrosis

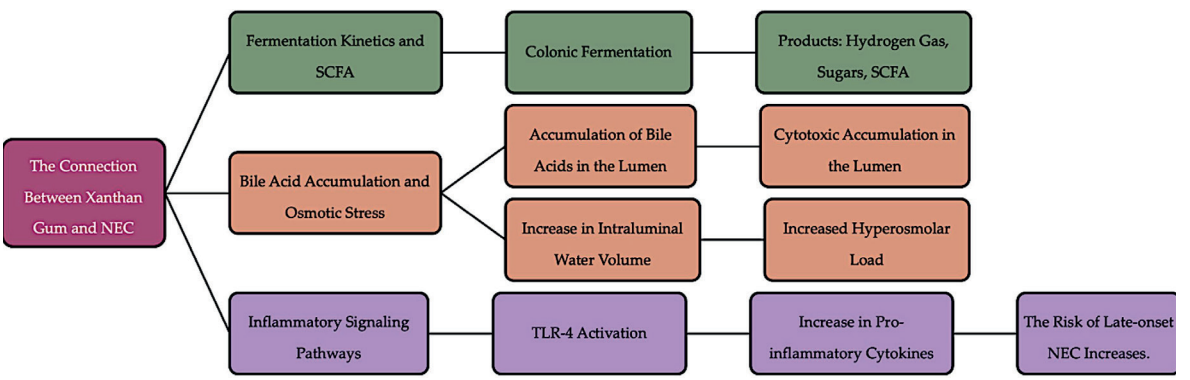

Figure 1. Conceptual framework of the proposed mechanisms potentially linking XG exposure to NEC in preterm infants.

factor-alpha (TNF-α), and so strengthening intestinal barrier integrity (37). For example, butyrate activates the Notch1 signaling pathway in the intestinal epithelium and suppresses pro-inflammatory Toll-like receptor (TLR) signaling. This process helps develop immune tolerance to bacterial colonization in the newborn gut and reduces the risk of NEC (22).

In brief, the relationship between SCFAs and NEC is complex, described in the literature as both a protective shield and a disease-triggering factor under certain conditions. The conclusion drawn from the reviewed scientific literature is that SCFAs produced under controlled conditions via beneficial bacteria have a protective function against NEC. Uncontrolled SCFA accumulation resulting from pathogenic overgrowth or the addition of exogenous fermentable substances, such as XG, increases the risk of tissue necrosis. However, the current findings were contradictory. Given the limited number of randomized controlled clinical trials, further research is needed in this area.

Bile Acid–Induced Toxicity and Osmotic Stress

XG consumption has been found to enhance bile acid excretion in humans via fecal matter (32). For instance, in a study conducted on rats, those fed an XG diet had a higher bile acid pool than the control group ($p<0.001$) (39). This increase leads to the accumulation of bile acids in the intestinal lumen. The accumulation of cytotoxic bile acids in the intestine has been identified as a critical component for NEC development in neonatal mouse models.

XG, a high-molecular-weight polysaccharide, also has a strong water-retaining capacity (40). According to sources, it increases the amount of water in the intestinal lumen of infants (32). This property leads to strong osmotic effects within the intestine. For example, studies on rats have shown that XG causes a 400% increase in intraluminal water and a 150% increase in sugar in the distal part of the small intestine. The underdeveloped intestines of premature infants may not tolerate this hyperosmolar load within the lumen, potentially leading to intestinal injury (41). In addition, the accumulation of intraluminal sugars, leading to the production of SCFA and hydrogen gas, further enhances the effect of the generated osmotic load. However, XG use does not always result in NEC among neonates (33).

XG increases the amount of water, sugars, bile acids, and SCFAs in the intestinal lumen, creating excessive stimulation and osmotic stress on the sensitive intestinal tissue of premature infants, which plays a role in NEC pathogenesis. However, given conflicting findings, well-designed randomized controlled clinical trials and cohort studies are needed in this area.

Activation of TLR-4 and Pro-inflammatory Signaling Pathways

XG can induce the production of pro-inflammatory cytokines, such as TNF-α and interleukin-12 (IL-12), in macrophages by acting as a TLR4 ligand. Overactivation of the TLR-4 signaling pathway is directly linked to mucosal damage and tissue necrosis, which are key components of NEC. It has been proposed that XG may contribute to the risk of late-onset NEC in preterm infants through this pathway (32).

The anti-inflammatory effect of XG appears to differ between paediatric and adult populations. XG, which is used in the treatment of osteoarthritis, a disease characterized by intense inflammation, decreased the Osteoarthritis Research Society International Score (OARSI) and inflammatory cytokine concentration after intra-articular injection (42). In support of these findings, pediatric gastroenterology authorities approach the use of thickeners cautiously. XG is not recommended for use in premature infants due to the risk of NEC, especially in the late-onset form (43).

Aside from underlying inflammation mechanisms, excessive accumulation of SCFAs in the lumen from XG intake can lead to mucosal

damage, irritation, and an inflammatory cascade. At the end of this, the risk of NEC can be increased (12,32).

The pro-inflammatory activity of XG on NEC is antithetical to its effect on osteoarthritis, where inflammation is intense. Studies on osteoarthritis have demonstrated that XG exhibits a high binding affinity for the TLR4 receptor, thereby significantly reducing cytokine release and the synthesis of inflammatory proteins (44). This discrepancy may be due to differences in age between patient groups with NEC and osteoarthritis.

Although some studies have demonstrated that XG has pro-inflammatory effects on NEC, studies in adults have shown the contrary. Therefore, more clinical research is needed in this area.

Regulatory and Legal Considerations

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition / European Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN/ESPGHAN) (2009) guidelines focus on the use of rice, corn, and potato starches, as well as guar gum and locust bean gum, as thickeners in commercial antiregurgitation formulas. The guidelines state that while thickeners reduce vomiting, they do not reduce acid reflux attacks and that their long-term use in infants requires special attention. Additionally, at the time the study was published, the risk of NEC in premature infants was associated not with XG (45).

The use of a specific XG-based thickening agent in premature infants has been subjected to extensive safety review and resulted in severe restrictions by the FDA. The FDA issued its first formal warning in May 2011 regarding reports of potentially related adverse events such as NEC. The warning concerned 17 reported cases of NEC in premature infants born before 37 weeks, 5 of which were fatal. The agency's investigations determined that some of the cases occurred after the infants were discharged from the hospital and transitioned to a feeding regimen containing the product. Consequently, the product was strongly discouraged both in the hospital and for the first 30 days after discharge. The FDA is actively investigating whether other thickening agents pose similar risks and is requesting prompt reporting of symptoms such as bloating or bloody stools. XG-based thickeners are contraindicated for *ad libitum* (addition at home or in the hospital) use in infants born before 37 weeks (46).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) first evaluated XG in 1974. In 1986, the committee assigned it a status of "not specified" for Acceptable Daily Intake (ADI). This decision was made due to the absence of any observed adverse effects, which eliminated the need for a specific numerical value for ADI. During its 82nd meeting in 2016, JECFA concluded that the use of XG in infant formulas, follow-on formulas, and special medical purpose infant formulas at a maximum concentration of 1,000 mg/L does not raise any safety concerns. This scientific data supports the use of the substance in food as a thickener, stabilizer, emulsifier, and foaming agent (47).

The 2017 EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) assessment found that XG (E 415) is safe for infants and children older than 12 weeks. Its use in special medical purpose infant formulas at concentrations up to 1,500 mg/L was found to be clinically well tolerated, not affecting infant growth characteristics, and not disrupting mineral balance. The report emphasized that this additive is not absorbed from the intestines and does not pose any genotoxic risk. However, it was explicitly noted that these 2017 results did not include infants younger than 12 weeks at that time, and a separate risk assessment is needed for this age group (48). Additionally, the 2018 NASPGHAN/ESPGHAN guidelines recommend thickening milk as a first-line treatment for regurgitation. While rice grains are recommended for formula milk, it is emphasized that breast milk cannot be

thickened with grains because of enzymes, and that commercial products with age restrictions, varying by brand, should be used (43).

In 2023, EFSA re-evaluated the safety of XG. The published report concluded that its use is safe up to a concentration of 1200 mg/L in special medical-purpose infant formulas. Technical updates included recommendations to ensure that the bacteria used in production do not contain live cells, that the product is free of residual enzyme activity, to add the *Cronobacter sakazakii* test to the microbiological criteria, and to change the substance description to "water-dispersible". Furthermore, it was reaffirmed that the risk of NEC in premature infants is associated not with XG added as a controlled food additive at the factory, but with thickeners added directly and in high doses (*ad libitum*) to breast milk or formula (49).

Conclusion

Nutrition in the early stages of life is important for establishing a healthy intestinal environment at the cellular and molecular levels. Dietary additives influence the delicate balance of this microenvironment and can affect intestinal barrier integrity and gut microbiota composition. In this context, the potential impact of XG-based thickeners, commonly used in dysphagia management, on the pathophysiology of NEC in premature infants is a critical area of investigation.

Because the neonatal intestine is physiologically unique, nutritional modifications must prioritize intestinal maturity and safety over the technical ease of application. The available evidence argues specifically against using XG-based thickening agents added directly, and in uncontrolled amounts, to human milk or infant formula in preterm infants and in infants younger than 12 weeks of corrected age, particularly in the home setting. This caution should not be generalized as a universal contraindication to all XG-containing products: XG incorporated at controlled, regulator-approved concentrations during the industrial manufacture of formulas for special medical purposes has not been associated with the same risk. Decisions regarding feed thickening should therefore be made on an individual basis. In addition, a multidisciplinary approach involving pediatricians and dietitians is required to assess the infant's specific microbial and developmental requirements. Furthermore, parents must be educated to monitor for symptoms like abdominal distension and bloody stools, particularly when products are used in a home setting. Ultimately, the preferred clinical approach must protect the immunological and microbial integrity of human milk while focusing future research on personalized feeding protocols and precise dosage ranges based on intestinal maturity.

Author contribution

The authors confirm contribution to the paper as follows: Review conception and design: GT, EG; literature review: GT, EG; draft manuscript preparation: GT, EG. All authors reviewed the results and approved the final version of the manuscript.

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