Nutritional Interventions for Necrotizing Enterocolitis

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Necrotizing enterocolitis (NEC), which is characterized by severe intestinal inflammation and in advanced stages necrosis, is a gastrointestinal emergency in the neonate with high mortality and morbidity. Despite advancing medical care, effective prevention strategies remain sparse. Factors contributing to the complex pathogenesis of NEC include immaturity of the intestinal immune defense, barrier function, motility and local circulatory regulation and abnormal microbial colonization. Interestingly, enteral feeding is regarded as an important modifiable factor influencing NEC pathogenesis. Moreover, breast milk, which forms the currently most effective prevention strategy, contains many bioactive components that are known to support neonatal immune development and promote healthy gut colonization. This systematic review describes the effect of different enteral feeding interventions on the prevention of NEC incidence and severity and the effect on pathophysiological mechanisms of NEC, in both experimental NEC models and clinical NEC. Besides, pathophysiological mechanisms involved in human NEC development are briefly described to give context for the findings of altered pathophysiological mechanisms of NEC by enteral feeding interventions.

Keywords: necrotizing enterocolitis ; enteral nutrition ; inflammation ; intestinal barrier function

1. Introduction

Necrotizing enterocolitis (NEC) is a multifactorial disease, characterized by severe intestinal inflammation and, in advancing disease, gut necrosis, that mainly affects premature neonates [1]. Around 5 to 10% of very low birth weight (VLBW) infants develop NEC, with the highest incidence among neonates with an extremely low birth weight (ELBW) [2]. Despite advancing medical care, NEC incidence has not substantially decreased over time, mainly due to increased early survival of neonates [3][4][5]. NEC mortality is inversely correlated with birth weight and generally ranges from 15% to 30% [2][6]. However, case fatality can increase up to 50% for ELBW infants treated surgically [6][7]. Being responsible for 10% of NICU deaths, NEC represents an important cause of death in this setting [8]. Moreover, infants that do recover from NEC suffer from several long-term morbidities such as growth retardation [9], short bowel syndrome [10], intestinal failure [11], intestinal failure-associated liver disease and neurodevelopmental delays [12]. Although the precise healthcare costs of NEC are difficult to estimate [13], the costs undoubtedly exceed those of matched controls, with estimates of around $70,000 extra hospital costs for medical NEC and around $180,000 for surgical NEC [14]. Moreover, life-long care for patients with morbidities following NEC will impose an even higher financial burden on both society and the individual patient [15]. NEC thus forms an important health issue that has high impact on the patient and its parents and also leads to a significant economic burden.

Due to its complex pathophysiology and fulminant nature, NEC treatment remains, despite advancing medical care, largely symptomatic [1]. Moreover, effective prevention strategies are sparse [1]. Factors contributing to the excessive intestinal inflammation in NEC include immaturity of the intestinal immune defense, barrier function, motility and local circulatory regulation and abnormal microbial colonization [1][6]. Interestingly, NEC almost exclusively develops in infants that have been enterally fed and the NEC risk increases with delay of enteral feeding, indicating enteral feeding is an important target to modify NEC pathogenesis [16][17][18]. Breast milk contains many bioactive components that are known to shape neonatal (intestinal) immune development [19] and promote healthy gut colonization [20], thereby preventing intestinal inflammation [19]. Consequently, although not completely effective, breast milk is highly protective against NEC development and is currently considered the most effective preventive strategy [21][22]. Accordingly, several enteral feeding interventions that use donor breast milk or feeding components derived from breast milk have been studied over the past years as potential strategies for prevention of NEC [1][23]. This systematic review aims to describe the effect of different enteral feeding interventions on the prevention of NEC incidence and severity and the effect on pathophysiological mechanisms of NEC (intestinal inflammation, systemic inflammation, intestinal barrier function, vascular dysfunction/hypoxia-ischemia/free radical formation, intestinal epithelial cell death/altered proliferation, microbial dysbiosis, disturbed digestion and absorption and enteric nervous system alterations), in both experimental NEC models

and clinical NEC. Besides, pathophysiological mechanisms involved in human NEC development are briefly described to contextualize the findings of altered pathophysiological mechanisms of NEC by enteral feeding interventions.

2. Development and Findings

Experiments in animal models of NEC provide a large amount of evidence of the beneficial effect of enteral nutritional interventions for preventing NEC incidence, severity, signs and symptoms, and mortality, as well as for ameliorating several pathophysiological processes related to NEC development including intestinal inflammation and intestinal barrier loss. A broad range of nutritional substances has been reported to be effective in several complementary experimental models, e.g., in different species and with different ways of inducing NEC. Especially HMO and growth factor-based interventions such as HB-EGF and EGF are promising as they have been shown to be effective in many experimental studies in which they target a broad range of pathophysiological mechanisms. Although some studies provide excellent insight in the underlying working mechanisms, addressing this for a broader range of interventions could be of great benefit to predict potential synergistic action between different substances of interest. This should therefore be subject of further research.

Despite the large amount of evidence from animal models, remarkably few enteral feeding interventions (e.g., arginine and probiotics) have been shown to be effective in meta-analyses of clinical trials. To date, only probiotics have reduced NEC incidence in adequately powered clinical studies and these interventions thereby form a promising preventive therapy, although even for these interventions certainty of evidence is at best moderate. Hence, the translation from preclinical findings in animal models to clinical practice remains challenging. Several underlying problems may be responsible for this arduous translation.

First, animal experiment related factors are in play. The current evidence from animal studies needs to be interpreted with caution, primarily due to the difficulty to adequately assess risk of bias in most animal studies and to determine certainty of evidence. Dissemination bias is likely present in animal studies of NEC, as researchers estimate that, in general, only around 50–60% of conducted animal studies [24][25] and data of only 26% of animals used are published [25]. Importantly, one of the main reasons for not publishing a study appears to be non-statistically significant results [24]. Moreover, other sources of bias may be present in experimental animal studies and are difficult to detect as many methodological aspects of the studies that are important for assessment of bias are poorly reported, both in studies incorporated in this systematic review and animal experiments in general [26]. Additionally, adequately assessing certainty of evidence from animal studies [27] is currently hampered, since amongst others confidence intervals and power calculations are often not reported. Due to (dissemination) bias, reports in literature of successful enteral feeding interventions in animal models may not reflect the true biological potential of the tested substance. Thus, based on the current evidence, it difficult to establish which preclinically studied interventions are most promising (considered safe, clinically relevant effect size, moderate to high certainty of evidence) and, hence, should be pursued in clinical trials. Besides, a smooth transition from animal research to clinical practice is hampered by the fact that experimental NEC modeling is still suboptimal. Notwithstanding the fact that many disease characteristics and a number of pathophysiological mechanisms involved in NEC are included in the current animal models of NEC, it is likely at least part of its complex pathophysiology is not adequately covered by the current models [28]. In addition, animal models are inherently limited due to the difficulty of using animals that are preterm and have bacterial colonization of the gut comparable to the human situation and differences between human and animal physiology [28][29][30][31].

Second, factors related to the conduct of clinical trials are involved. Many clinical trials are not designed with NEC incidence as primary outcome and are underpowered to convincingly prove a clinically significant beneficial effect. As Xiong et al. have nicely ascertained, the number of neonates required to prove a 20% relative risk reduction with 80% power assuming a 5% incidence of NEC is over 10,000 [32]. Including this amount of neonates in a study requires multi-center and international collaboration, which is logistically challenging and expensive. Moreover, NEC is not clearly defined and NEC diagnoses likely consist of a mixture of ‘classical’ NEC and closely related pathologies such as transfusion-related NEC, ischemic intestinal necrosis, spontaneous intestinal perforation and food protein intolerance enterocolitis syndrome [33][34]. It is likely that NEC(-like) diseases require a different treatment and that poorer effects of treatment will be found in clinical trials in which all these disease entities are pooled as one group.

Third, it is challenging to determine the optimal therapeutic regimen (dose, frequency, timing). Even though dose is of clear importance for the therapeutic effect [35][36], most animal studies only test a single dose and frequency of administration and it is therefore unclear how the dose and administration regimen used in animal studies should be translated to the human neonate. Of note, the optimal dose for the human neonate may be very well dependent on individual baseline levels, e.g., an infant with baseline deficit of a specific nutritional component may benefit from a higher

dosage than an infant with baseline values within the normal range. Furthermore, timing of the feeding intervention often differs between animal studies and clinical trials. Due to the rapid nature of NEC progression following its onset, the value of nutritional interventions lies in prevention of NEC rather than treatment of ongoing NEC and as such, enteral feeding interventions are used as prevention in clinical trials. However, in animal models, enteral feeding interventions are almost always started in parallel to a NEC inducing protocol, and can therefore probably not be (fully) regarded as preventive. Studies looking at interventions at an earlier moment, such as in utero nutritional interventions, are in this context valuable [37].

Last, surprisingly few animal studies have looked at enteral feeding interventions with a combination of several bioactive substances, although this is, in light of the complex composition of breastmilk and the multifactorial nature of NEC pathogenesis, likely to be of pivotal importance.

Considering the abovementioned factors that hinder development of successful clinically applicable enteral nutritional interventions to reduce NEC incidence, several aspects should be improved. Future clinical trials investigating the potential of enteral feeding interventions to reduce NEC incidence should be adequately powered to at least be able to fairly estimate effect size and preferably reach statistical significance. In addition, clinical researchers should strive for the use of a clearer definition of NEC, ideally after international consensus regarding this definition in the field of NEC research. To this end, international collaboration between (pre)clinical NEC researchers and clinicians is essential.

Preclinical studies remain important to further understand NEC pathophysiology and optimize the current experimental models of NEC. In addition, the development of new human tissue based experimental models such as intestinal organoids, NEC-in-a-dish and gut-on-a-chip models is of importance [31][38][39]. In future preclinical experiments issues such as timing of intervention and dose/treatment regimen should be taken into account. Negative findings should be published, which could be stimulated by voluntary or mandatory registration of conducted (animal) studies as is more and more common practice in the clinical research field [25]. Moreover, the reporting quality of methodological aspects in experimental studies should be significantly improved to enable fair assessment of risk of bias and certainty of evidence. Finally, studying combinations of the most promising single substances based on findings in single component supplementation studies and on biological working mechanisms is likely to be of pivotal importance for finding effective enteral nutritional interventions that reduce clinical NEC incidence.

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