Diarrhea in enterally fed patients: blame the diet?

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**Purpose of review**
Diarrhea has great impact on enteral nutrition. The purpose of this review is to identify the factors leading to diarrhea during enteral nutrition and to provide the published updates on diarrhea prevention through nutritional intervention.

**Recent findings**
Diarrhea in enterally fed patients is attributed to multiple factors, including medications (major contributor), infections, bacterial contamination, underlying disease, and enteral feeding. Diet management can alleviate diarrhea in enteral feeding. High content of fermentable oligosaccharides, disaccharides, and monosaccharides and polyols (FODMAPs) in enteral formula is postulated to induce diarrhea and lower FODMAPs formula may reduce the likelihood of diarrhea in enterally fed patients. Fiber-enriched formula can reduce the incidence of diarrhea and produce short-chain fatty acids for colonocytes. Ingesting prebiotics, nonviable probiotics or probiotic derivatives, and human lactoferrin may provide alternatives for reducing/preventing diarrhea.

**Summary**
Enteral feeding is not generally considered the primary cause of diarrhea, which is frequently linked to prescribed medications. When diarrhea is apparent, healthcare members should evaluate the possible risk factors and systematically attempt to eliminate the underlying causes of diarrhea before reducing or suspending enteral feeding. Lower FODMAPs formula, prebiotics, probiotic derivatives, and lactoferrin may be used to manage enteral feeding-related diarrhea.

**Keywords**
causes of diarrhea, enteral feeding, nosocomial diarrhea, nutritional intervention

**INTRODUCTION**
Diarrhea is a common complication in enteral nutrition. Its documented incidence ranges from 2 to 95% of cases due to differences in definition and ability to collect and measure stool samples [1]. Electrolyte imbalance, dehydration, perianal skin breakdown, wound contamination, and increased healthcare costs are complications associated with diarrhea [2]. Further, severe diarrhea may lead to the cessation of enteral nutrition, exacerbating pre-existing malnutrition [3].

Studies show that enteral nutrition may result in deleterious effects on gastrointestinal microbiota such as reducing bifidobacteria and key butyrate producers, causing abnormal water secretion into the ascending colon, and figuring in the risk of *Clostridium difficile* colonization and *C. difficile*-associated diarrhea [4–6]. Other factors implicated in causing diarrhea during enteral feeding include types and dosage of fiber used, formula osmolarity, delivery mode, enteral-feeding-equipment contamination, and the artificial nature of enteral formulas, which may alter digestion and absorption [7]. Apart from enteral feeding, diarrhea is associated with advanced age, prescription drugs, clinical conditions, length of hospitalization, and altered gastrointestinal anatomy [8,9\textsuperscript{a}]. Therefore, controversy remains over whether enteral nutrition is the main contributing factor to diarrhea. This article reviews recently published studies on the factors leading to diarrhea during enteral nutrition and discusses published updates on diarrhea prevention through nutritional intervention.

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CAUSES OF DIARRHEA

Diarrhea is an abnormal increase in frequency and fluidity of bowel movements. Traditionally, diarrhea is categorized as osmotic, secretory, exudative (inflammatory), and motility-related by the mechanism governing its occurrence [10]. However, most cases of nosocomial diarrhea are not due to enteral feeding per se. In a hospital setting, the pathophysiology of diarrhea may be attributable to multiple simultaneous factors including medications, infections, underlying disease, and enteral feeding [9*].

## MEDICATIONS

Medications are a major contributor to diarrhea via side-effects, toxicity, and disruption of the gut microbiota [9*]. The medicines that most frequently cause diarrhea include antibiotics (especially broad-spectrum antibiotics), proton pump inhibitors, osmotic or bulk laxatives, magnesium-containing antacids, potassium and phosphorus supplements, selective serotonin reuptake inhibitors, NSAIDs, prokinetic agents, and β-blockers. Additionally, sorbitol-containing and mannitol-containing medications also cause diarrhea, as they are not absorbed in the small bowel but metabolized in the colon (Table 1) [10,11]. The cause of diarrhea in the case of medications is closely related to onset time and commencement of drug treatment. Drug-induced diarrhea can be managed by withdrawing or reducing drug dosage, or replacement with a nondiarrhea causing agent [11].

### ENTERAL FEEDING

Enteral feeding can affect gut physiology by changing transit time, altering intestinal secretory/absorptive capacity, and modifying microbial ecology [5]. Metabolic activity of luminal microbiota can be

| Table 1. Common medications associated with diarrhea in enterally fed patients |
|---------------------------------|---------------------------------|
| **Drug**                        | **Examples (scientific name)**  |
| Gastrointestinal agents         | PPI: Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole, Rabeprazole |
|                                 | H-2 blockers: Ranitidine, Famotidine, Roxatidine |
|                                 | Magnesium-containing antacids: MgO |
|                                 | Others: Misoprostol |
| Antibiotics                     | Vancomycin (oral), Ampicillin, Amoxicillin, Cephalexin, Cefexime, Erythromycin, Azithromycin, Clarithromycin, Ciprofloxacin |
| Cholinergics                    | Donepezil, Rivastigmine, Galantamine, Bethanechol, Pyridostigmine |
| Antihypertensives               | β-Blockers: Propranolol, Bisoprolol |
| Laxatives                       | Liquid paraffin, Castor oil, Bisacodyl, Senna leaf, Lactulose, Polyethylene glycol, Sorbitol, Magnesium sulfate |
| NSAIDs                          | Indomethacin, Diclofenac, Ibuprofen, Tenoxicam, Nabumetone, Etodolac, Celecoxib |
| Potassium and phosphorus        | Neutral Phosphate |
| supplements                     | Prokinetics: Metoclopramide, Mosapride, Domperidone |
| Sedation                        | Zolpidem |
| Selective serotonin reuptake    | Fluoxetine, Sertraline, Escitalopram, Citalopram, Paroxetine |
| inhibitors                      | Intestinal anti-inflammatory agents: Mesalamine, Balsalazide |
| Glucose-lowering agents         | Metformin, Acarbose, Glipizide, Actosmet (Pioglitazone + Glimepiride), Repaglinide |
| Others                          | Betahistine, Colchicine, Digoxin, Strontium Ranelate |

H-2, histamine-2; PPI, proton pump inhibitors.

KEY POINTS

- Multiple factors may simultaneously contribute to diarrhea including medications, infections, underlying disease, and enteral feeding.
- Medications are the major contributor to nosocomial diarrhea via side-effects, toxicity, and disruption to gut microbiota.
- Caution should be taken when considering probiotics to treat or prevent diarrhea in critically ill patients.
- Human lactoferrin and probiotic derivatives may be helpful in reducing diarrhea in tube-fed patients, but more research is needed.
- Medical staff should be aware of what can cause diarrhea and take appropriate action to eliminate underlying causes before reducing or suspending enteral feeding.

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**Table 1. Common medications associated with diarrhea in enterally fed patients**

- Drug examples include PPIs (Proton Pump Inhibitors) such as Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole, and Rabeprazole.
- H-2 blockers like Ranitidine, Famotidine, and Roxatidine are also mentioned.
- Magnesium-containing antacids such as MgO are listed.
- Misoprostol is noted as another medication.
- Antibiotics include Vancomycin (oral), Ampicillin, Amoxicillin, Cephalexin, Cefexime, Erythromycin, Azithromycin, Clarithromycin, and Ciprofloxacin.
- Cholinergics include Donepezil, Rivastigmine, Galantamine, Bethanechol, and Pyridostigmine.
- β-Blockers such as Propranolol and Bisoprolol are included in the antihypertensives category.
- Laxatives like Liquid paraffin, Castor oil, Bisacodyl, Senna leaf, Lactulose, Polyethylene glycol, Sorbitol, and Magnesium sulfate are mentioned.
- NSAIDs include Indomethacin, Diclofenac, Ibuprofen, Tenoxicam, Nabumetone, Etodolac, and Celecoxib.
- Potassium and phosphorus supplements include Neutral Phosphate.
- Prokinetics such as Metoclopramide, Mosapride, and Domperidone are noted.
- Sedation medications like Zolpidem are included.
- Selective serotonin reuptake inhibitors like Fluoxetine, Sertraline, Escitalopram, Citalopram, and Paroxetine are listed.
- Intestinal anti-inflammatory agents such as Mesalamine and Balsalazide are mentioned.
- Glucose-lowering agents like Metformin, Acarbose, Glipizide, Actosmet (Pioglitazone + Glimepiride), and Repaglinide are noted.
- Others include Betahistine, Colchicine, Digoxin, and Strontium Ranelate.

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**Footnotes:**

- H-2, histamine-2; PPI, proton pump inhibitors.
disturbed during tube feeding, affecting colonization resistance, and contributing to the development of diarrhea [12,13]. Several feeding formula-related issues are consistently mentioned as causes of diarrhea including temperature, osmolality, fat content, caloric density, delivery rate, delivery location, and protein sources. However, direct links between enteral feeding and diarrhea are not supported by medical evidence and remain controversial [14].

**Osmolality of feeding formula**

It is thought that hypertonic feeding formulas can cause diarrhea and gastrointestinal intolerance via osmotic effects. However, studies have shown that osmolality of feeding formula does not affect the frequency or duration of diarrhea [14]. Formula osmolality itself is not the cause of diarrhea, but the combination of hypertonic feeding formula and cofactors such as hypoalbuminemia establish an environment for diarrhea and faster stool transit times through the gut [15]. There is no conclusive evidence that formula osmolality plays a significant role in causing diarrhea because the feeding formula can be changed to an isotonic formula, or infused at a slow rate to overcome the osmolality problems.

**FODMAPs**

Short-chain carbohydrates, fermentable oligosaccharides, disaccharides and monosaccharides and polyols (FODMAPs), are poorly absorbed, highly osmotic, and rapidly fermented by gut bacteria. Consequently, fermentation byproducts activate the feedback loop that regulates gut motility. This results in accelerated small bowel transit times and increased osmotic loading, leading to bloating, distension, cramping, and diarrhea [16,17]. Some studies indicate that impaired fermentation of poorly absorbed carbohydrates by altered intestinal microbiota can lead to diarrhea via osmotic effects [10,17]. It has been postulated that FODMAPs induce diarrhea during enteral nutrition [18]. Studies conducted by Halmos et al. [7] found that low FODMAPs formulas reduce the likelihood of diarrhea in enterally fed patients and most commercial enteral formulas appear to have high FODMAPs content [19]. Therefore, high content FODMAPs feeding formulas may play a role in diarrhea among patients treated with antibiotics experiencing altered intestinal microbiota. Nevertheless, more randomized controlled trials (RCTs) are needed to determine the effect of FODMAPs on enteral nutrition-associated diarrhea.

**INFECTION**

Most cases of nosocomial diarrhea result from noninfectious etiology. During hospitalization, infections cause diarrhea independent of enteral feeding [9]. Enteral fed patients taking antibiotics may experience diarrhea due to disruption of gut microbiota and normal host-microbiota interactions [20]. Generally, infections associated with antibiotic therapy relate to *C. difficile*, *Klebsiella oxytoca*, *Clostridium perfringens*, *Salmonella*, or *Staphylococcus aureus*. Infectious causes not associated with antibiotics include gastrointestinal viruses (e.g., rotavirus, adenovirus, and norovirus), enterotoxigenic *Bacteroides fragilis*, and so on [9,21]. The use of drugs to suppress gastric acid production, such as proton pump inhibitors and histamine-2 blockers, has been associated with increased risk of *C. difficile*, *Salmonella*, and *Campylobacter* infections [22,23]. In addition, parasites and bacteria typically associated with community-acquired diarrhea have been reported in transplant patients with nosocomial diarrhea and should be considered when related risk factors are present [24,25].

**BACTERIAL CONTAMINATION**

Enteral formulas have high nutritive values making them excellent growth media for microorganisms. Bacterial contamination can be caused by feeding formula contamination, or feeding delivery system contamination. Problems include poor cleaning of feeding equipment, improper use of disposable equipment (e.g., reusing syringes or administration sets), inappropriate storage of feed, poor manipulation techniques during setup and administration of feed, and poor hygiene, especially clean hands [26,27]. As feeding formulas are usually available as sterile ready-to-use products or dehydrated powdered forms, contamination during enteral feeding is more closely associated with the surrounding environment and cleanliness of hands [28]. Effective and thorough hand washing is the most important procedure in the prevention and control of infection. An infection-control program that educates, trains, and improves hygienic practices among healthcare workers is especially important in reducing the incidence of bacterial contamination during enteral feeding [29].

**HYPOALBUMINEMIA**

For two decades, studies have stated that hypoalbuminemia can cause malabsorptive diarrhea due to a decrease in oncotic pressure resulting in intestinal mucosal edema [14,29,30]. However, many studies over time have observed no significant
association between hypoalbuminemia and diarrhea [31,32,33]. Hypoalbuminemia appears to be a marker of illness severity and morbidity [34,35], the relationship between hypoalbuminemia and diarrhea may be related to a mechanism via illness severity rather than being a direct cause of diarrhea.

**ILLNESS SEVERITY**

Many studies indicate higher illness severity scores, including APACHE II scores, associated with increased frequency and duration of diarrhea [14,36,37]. Enterally fed patients, especially the critically ill, may experience hypermetabolic stress response, altered gastrointestinal physiology (increased intestinal lumen permeability and mucosal damage), and compromised immunity, resulting in higher incidences of diarrhea [14,37].

**PREVENTION OF DIARRHEA BY NUTRITIONAL INTERVENTION**

Several nutritional interventions to prevent or treat nosocomial diarrhea have been studied.

**FIBER-ENRICHED FORMULAS**

A systematic review and meta-analysis of 51 studies (43 RCTs) found that enteral formulas containing fiber can reduce the incidence of diarrhea [38]. Studies show that mixed fiber formulas can reduce diarrhea in critically ill patients receiving a broad spectrum of antibiotics [39] as well as increase fecal short-chain fatty acid (SCFA) concentrations [40]. The major antidiarheal mechanism comes from soluble fiber, such as pectin, fructo-oligosaccharides (FOS), inulin, and guar gum, which are fermented by colon anaerobic bacteria to produce SCFAs that feed colonocytes and stimulate the uptake of water and electrolytes [39,41]. SCFAs also have anti-inflammatory effects by inhibiting NF-κB and reducing pro-inflammatory cytokines [42,43]. Besides which, an increase in anaerobic bacteria growth in the gastrointestinal tract due to fiber supplementation may protect against the overgrowth of potential pathogens and prevent diarrhea occurrence. Therefore, guidelines of the Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition on nutrition support therapy in critically ill patients suggest that soluble fiber-containing or small-peptide formulations be considered if evidence of diarrhea exists [44]. Nevertheless, not all such clinical trials demonstrated beneficial effects on diarrhea [32]. This inconsistency may relate to patient characteristics, fiber sources, or the evaluation of confounding factors such as antibiotic types that may inhibit bacterial fermentation of fibers in the colon [38,45].

**PREBIOTICS**

Prebiotics such as Acacia gum, fructans (inulin, FOS), galacto-oligosaccharides, and β-glucans enhance the proliferation of beneficial intestinal bacteria such as bifidobacteria and lactobacilli, which ferment nondigestible carbohydrates in the colon to produce SCFAs. In addition, the growth of beneficial bacteria may suppress colonization of enteropathogens [12,46]. Studies have demonstrated that bifidobacteria and lactobacilli may regulate intestinal homeostasis, stimulate intestinal epithelium and the immune system to protect against microbial infection [47,48]. A growing body of evidence supports a role for prebiotics in reducing the prevalence of infectious pathogens and antibiotic-associated diarrhea (AAD) [47,49–51]. However, the results of a multicenter trial conducted by the Working Group for Probiotics and Prebiotics of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition concluded that the administration of prebiotics was not effective in preventing diarrhea and AAD in 105 children enrolled [52]. In addition, animal studies have shown that some prebiotics including FOS, inulin, and lactulose may act directly on intestinal cells by binding to specific receptors or act as irritants on epithelial cells, which might lead to higher mucosal permeability and increased susceptibility to pathogenic intestinal translocation [47]. Although there are many experimental animal studies and human trials demonstrating the evidence regarding prebiotic-induced health benefits [38,53,54,55], future large-scale, well designed, RCTs are still necessary in the prevention and management of diarrhea. These studies should aim at clarifying optimal dosage, treatment duration, and specific effects of prebiotics in different enteral feeding regimens as well as immunomodulation between intestinal microbiota and their human host.

**PROBIOTICS**

The role of gut microbiota and direct manipulation by probiotics may provide a novel method for the prevention and treatment of a variety of gastrointestinal disorders [20]. Probiotics, either as a single strain or in combination, can provide beneficial effects by enhancement of barrier function, stimulation of host cell antimicrobial peptides, production of antimicrobial factors, competition for intestinal wall adhesion sites, and immunomodulation [56]. Within studies of probiotics preventing...
AAD, *Saccharomyces boulardii*, *Lactobacillus rhamnosus* GG, and combination products appear to be the most effective treatments [28,40,57]. It has been demonstrated that the consumption of synbiotics, a mixture of probiotics and prebiotics, alters the composition of intestinal microbiota more effectively than the ingestion of probiotics alone [58]. However, the use of probiotics in the treatment of diarrhea is controversial in critically ill patients. Study has indicated that probiotic prophylaxis in patients with severe acute pancreatitis shows a significant increase in mortality [59]. A RCT also demonstrated that the *Lactobacillus rhamnosus* GG had no beneficial effect on the duration or severity of diarrhoea in critical illness [12]. Apart from, one animal study found that low doses of probiotic administration exerted poor immune modulating effects on T-cell immune responses than did high doses, a potentially detrimental situation in critical illness [60]. Notably, the ability of probiotics to induce cytokine secretions is largely mediated by cell wall components. Probiotics may produce their effects with viable as well as nonviable bacteria, suggesting that metabolic factors, secreted factors, structural components, or cellular components may mediate probiotic induced immunomodulatory activity [61–63]. There is growing interest in evaluating the beneficial effects induced by ingesting nonviable probiotics or probiotic derivatives by enteral/parenteral administration without being attendant on iatrogenic infections caused by probiotic agents. This may be of importance to critically ill or immune compromised patients. However, until definitive evidence has been gathered from well designed clinical trials on probiotic administration to critically ill patients, caution needs to be taken when considering probiotics to treat or prevent diarrhea [2,12,64].

**LACTOFERRIN**

Lactoferrin, an iron binding protein found in breast-milk and leukocytes, possesses antimicrobial, anti-inflammatory, and immunomodulatory functions. It binds not only to iron, which is essential for bacterial growth, but also to lipopolysaccharides on bacterial cell surfaces. Cell-surface bound lipopolysaccharide disrupts bacterial surface expressed virulence factors thereby decreasing the ability of enteropathogens to adhere or invade host cells [65]. Several clinical trials in children have stated that lactoferrin can reduce the duration of diarrhea [66,67]. One recent study concluded that human lactoferrin may reduce postantibiotic diarrhea in tube-fed long-term care patients and is well tolerated [68]. Lactoferrin is prepared by inserting the human gene into rice. This procedure produces large amounts of nearly identical human lactoferrin at a low cost [69]. It may offer an alternative for the prevention or management of nosocomial diarrhea and warrants further research.

**CONCLUSION**

Enteral feeding should not be considered a primary cause of diarrhea. Primary causes of diarrhea are frequently linked to prescription medicines [70]. When diarrhea is apparent, healthcare teams are recommended to consider all present risk factors, and systematically evaluate patients to determine the primary causes of diarrhea as well as take appropriate actions to eliminate the underlying causes before reducing or suspending enteral feeding.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 613).


This article enhances our knowledge about the mechanisms by which food triggers gastrointestinal symptoms, the structure, efficacy, and implementation of low FODMAPs diet. Food choice via low FODMAPs and potentially other dietary strategies seems to be a realistic and efficacious therapeutic approach to gut symptoms.


The author describes how a gut microbiome helps maintain intestinal health and how disturbances in this microbial community can lead to disease states.


This review article provides information about the role and safety of prebiotics and probiotics in gastrointestinal disorders.


Chang and Huang

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This is an excellent review article summarizing the existing data regarding the use of probiotics, prebiotics, and symbiotics in selected disorders encountered in ICU. The authors remind us that better identification of the ideal characteristics of effective probiotics coupled with improved understanding of mechanisms helps to delineate the true beneficial effects of probiotics in various disorders.


This community-based RCT determines the effect of bovine lactoferrin on the prevention of diarrhea in children. It leaves open the possibility that lactoferrin could have a role in the treatment of prolonged and persistent diarrhea.


Catafesta J, Francesconi C. Association between medication use and adverse gastroenterologic events in patients receiving enteral nutrition therapy at a University Hospital. Rev Gastroenterol Mex 2012; 77:161–166; doi:10.1016/j.rgmx.2012.06.003.