Diarrhea in enterally fed patients: blame the diet?

Sue-Joan Chang[a] *and Hsiu-Hua Huang*[a,b]

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 enteral 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▪]. 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

[a]Department of Life Sciences, College of Bioscience and Biotechnology, National Cheng Kung University, Tainan and [b]Department of Food and Nutrition, Taipei Veterans General Hospital, Taipei, Taiwan

Correspondence to Sue-Joan Chang, Department of Life Sciences, College of Bioscience and Biotechnology, National Cheng Kung University, No.1, University Road, Tainan City 701, Taiwan. Tel: +886 6 2757575x65542; fax: +886 6 2742583; e-mail: sjchang@mail.ncku.edu.tw

Curr Opin Clin Nutr Metab Care 2013, 16:588–594
DOI:10.1097/MCO.0b013e328363bcaf

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.

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 supplements	Neutral Phosphate
Prokinetics	Metoclopramide, Mosapride, Domperidone
Sedation	Zolpidem
Selective serotonin reuptake inhibitors	Fluoxetine, Sertraline, Escitalopram, Citalopram, Paroxetine
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.

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▪]. Enterally fed patients taking antibiotics may experience diarrhea due to disruption of gut microbiota and normal host-micobiota 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 antidiarrheal 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 proinflammatory 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 diarrhea 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 priobiotic 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 breastmilk 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.

Acknowledgements

We gratefully acknowledge the Director Pi-Lai Tseng of Pharmacy at Kaohsiung Veterans General Hospital for her valuable suggestions.

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).

1. Whelan K. Enteral-tube-feeding diarrhoea: manipulating the colonic microbiota with probiotics and prebiotics. Proc Nutr Soc 2007; 66:299–306.
2. Jack L, Coyer F, Courtney M, Venkatesh B. Probiotics and diarrhoea management in enterally tube fed critically ill patients: what is the evidence? Intensive Crit Care Nurs 2010; 26:314–326; doi: 10.1016/j.iccn.2010.07.001.
3. Majid HA, Emery PW, Whelan K. Definitions, attitudes, and management practices in relation to diarrhea during enteral nutrition: a survey of patients, nurses, and dietitians. Nutr Clin Pract 2012; 27:252–260; doi:10.1177/0884533611431986.
4. O'Keefe SJD. Tube feeding, the microbiota, and Clostridium difficile infection. World J Gastroenterol 2010; 16:139–142.
5. Whelan K, Judd PA, Tuohy KM, *et al.* Fecal microbiota in patients receiving enteral feeding are highly variable and may be altered in those who develop diarrhea. Am J Clin Nutr 2009; 89:240–247.
6. Bowling TE, Raimundo AH, Grimble GK, Silk DB. Colonic secretory effect in response to enteral feeding in humans. Gut 1994; 35:1734–1741.
7. Halmos EP, Muir JG, Barrett JS, *et al.* Diarrhoea during enteral nutrition is predicted by the poorly absorbed short-chain carbohydrate (FODMAP) content of the formula. Aliment Pharmacol Ther 2010; 32:925–933; doi:10.1111/j.1365-2036.2010.04416. x.
8. Turner P. Providing optimal nutritional support on the intensive care unit: key challenges and practical solutions. Proc Nutr Soc 2010; 9:574–581; doi:10.1017/S002966511000385X.
9. ▪ Polage CR, Solnick JV, Cohen SH. Nosocomial diarrhea: evaluation and treatmen of causes other than Clostridium difficile. Clin Infect Dis 2012; 55:982–989; doi:10.1093/cid/cis551.

This article provides a practical approach to the evaluation and management of nosocomial diarrhea when tests for *C. difficile* are negative.

10. Deepak P, Ehrenpreis ED. Diarrhea. Dis Mon 2011; 57:490–510; doi:10.1016/j.disamonth.2011.05.005.
11. Sweetser S. Evaluating the patient with diarrhea: a case-based approach. Mayo Clin Proc 2012; 87:596–602; doi: 10.1016/j.mayocp.2012.02.015.

12. Ferrie S, Daley M. Lactobacillus GG as treatment for diarrhea during enteral feeding in critical illness: randomized controlled trial. JPEN J Parenter Enteral Nutr 2011; 35:43–49; doi:10.1177/0148607110370705.

13. Whelan K, Schneider SM. Mechanisms, prevention, and management of diarrhea in enteral nutrition. Curr Opin Gastroenterol 2011; 27:152–159; doi:10.1097/MOG.0b013e32834353cb.

14. Jack L, Coyer F, Courtney M, Venkatesh B. Diarrhoea risk factors in enterally tube fed critically ill patients: a retrospective audit. Intensive Crit Care Nurs 2010; 26:327–334; doi:10.1016/j.iccn.2010.08.001.

15. Burns PE, Jairath N. Diarrhea and the patient receiving enteral feedings: a multifactorial problem. J Wound Ostomy Continence Nurs 1994; 21:257–263.

16. Barrett JS, Gibson PR. Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) and nonallergic food intolerance: FODMAPs or food chemicals? Therap Adv Gastroenterol 2012; 5:261–268; doi:10.1177/1756283X11436241.

17. ■■ Gibson PR, Shepherd SJ. Food choice as a key management strategy for functional gastrointestinal symptoms. Am J Gastroenterol 2012; 107:657–666; doi:10.1038/ajg.2012.49.

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.

18. Barrett JS, Shepherd SJ, Gibson PR. Strategies to manage gastrointestinal symptoms complicating enteral feeding. JPEN J Parenter Enteral Nutr 2009; 33:21–26.

19. Halmos EP, Liels KL, Rosella O, *et al.* Enteral nutritional formulas deliver laxative doses of FODMAPs which cannot be predicted by ingredients lists. J Gastroenterol Hepatol 2011; 26:S73.

20. ■ Young VB. The intestinal microbiota in health and disease. Curr Opin Gastroenterol 2012; 28:63–69; doi:10.1097/MOG.0b013e32834d61e9.

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

21. Simakachorn N, Bibiloni R, Yimyaem P, *et al.* Tolerance, safety, and effect on the faecal microbiota of an enteral formula supplemented with pre and probiotics in critically ill children. J Pediatr Gastroenterol Nutr 2011; 53:174–181; doi:10.1097/MPG.0b013e318216f1ec.

22. Bavishi C, Dupont HL. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. Aliment Pharmacol Ther 2011; 34:1269–1281; doi:10.1111/j.1365-2036.2011.04874.x.

23. Khanna S, Pardi DS. Clostridium difficile infection: new insights into management. Mayo Clin Proc 2012; 87:1106–1117; doi:10.1016/j.mayocp.2012.07.016.

24. Maes B, Hadaya K, de Moor B, *et al.* Severe diarrhea in renal transplant patients: results of the DIDACT study. Am J Transplant 2006; 6:1466–1472.

25. Kamboj M, Mihu CN, Sepkowitz K, *et al.* Work-up for infectious diarrhea after allogeneic hematopoietic stem cell transplantation: single specimen testing results in cost savings without compromising diagnostic yield. Transpl Infect Dis 2007; 9:265–269.

26. Lyman B, Gebhards S, Hensley C, *et al.* Safety of decanted enteral formula hung for 12 h in a pediatric setting. Nutr Clin Pract 2011; 26:451–456; doi:10.1177/0884533611413891.

27. Best C. Enteral tube feeding and infection control: how safe is our practice? Br J Nurs 2008; 17:1036–1041.

28. ■ Ho SS, Tse MM, Boost MV. Effect of an infection control programme on bacterial contamination of enteral feed in nursing homes. J Hosp Infect 2012; 82:49–55; doi:10.1016/j.jhin.2012.05.002.

This study investigates the effectiveness of an infection control program (ICP) on knowledge and practice of enteral feeding by nursing home staff, and concludes that an effective ICP can significantly reduce the contamination of enteral feed.

29. Bockus S. Troubleshooting your tube feedings. Am J Nurs 1991; 91:24–30.

30. Brinson RR, Kolts BE. Hypoalbuminemia as an indicator of diarrheal incidence in critically ill patients. Crit Care Med 1987; 15:506–509.

31. ■ Bittencourt AF, Martins JR, Logullo L, *et al.* Constipation is more frequent than diarrhea in patients fed exclusively by enteral nutrition: results of an observational study. Nutr Clin Pract 2012; 27:533–539; doi:10.1177/0884533612449488.

This observational study analyzes the frequency of diarrhea and constipation in patients receiving enteral nutrition.

32. Heimburger DC, Geels VJ, Bilbrey J, *et al.* Effects of small-peptide and whole-protein enteral feedings on serum proteins and diarrhea in critically ill patients: a randomized trial. JPEN J Parenter Enteral Nutr 1997; 21:162–167.

33. Eisenberg P. An overview of diarrhea in the patient receiving enteral nutrition. Gastroenterol Nurs 2002; 25:95–104.

34. Viasus D, Garcia-Vidal C, Simonetti A, *et al.* Prognostic value of serum albumin levels in hospitalized adults with community-acquired pneumonia. J Infect 2013; 66:415–423.

35. Vijapur SM, Varghese GK. Hypoalbuminaemia: a marker of disease severity in acute febrile illnesses. Rec Res Sci Tech 2011; 3:134–138.

36. Lopez-Herce J. Gastrointestinal complications in critically ill patients: what differs between adults and children? Curr Opin Clin Nutr Metab Care 2009; 12:180–185.

37. Huang HH, Hsu CW, Kang SP, *et al.* Association between illness severity and timing of initial enteral feeding in critically ill patients: a retrospective observational study. Nutr J 2012; 11:30; doi:10.1186/1475-2891-11-30.

38. Elia M, Engfer MB, Green CJ, Silk DB. Systematic review and meta-analysis: the clinical and physiological effects of fibre-containing enteral formulae. Aliment Pharmacol Ther 2008; 27:120–145.

39. Chittawatanarat K, Pokawinpudisnun P, Polbhakdee Y. Mixed fibers diet in surgical ICU septic patients. Asia Pac J Clin Nutr 2010; 19:458–464.

40. Schneider SM. Microbiota and enteral nutrition. Gastroenterol Clin Biol 2010; 34:S57–61. doi:10.1016/S0399-8320(10)70022-1.

41. Kato Y, Nakao M, Iwasa M, *et al.* Soluble fiber improves management of diarrhea in elderly patients receiving enteral nutrition. Food Nutr Sci 2012; 3:1547–1552; doi:10.4236/fns.2012.311202.

42. Vinolo MA, Rodrigues HG, Hatanaka E, *et al.* Suppressive effect of short-chain fatty acids on production of proinflammatory mediators by neutrophils. J Nutr Biochem 2011; 22:849–855; doi:10.1016/j.jnutbio.2010.07.009.

43. Liu T, Li J, Liu Y, *et al.* Short-chain fatty acids suppress lipopolysaccharide-induced production of nitric oxide and proinflammatory cytokines through inhibition of NF-κB pathway in RAW264.7 cells. Inflammation 2012; 35:1676–1684; doi:10.1007/s10753-012-9484-z.

44. McClave SA, Martindale RG, Vanek VW, *et al.* Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr 2009; 33:277–316; doi:10.1177/0148607109335234.

45. Majid HA, Emery PW, Whelan K. Faecal microbiota and short-chain fatty acids in patients receiving enteral nutrition with standard or fructo-oligosaccharides and fibre-enriched formulas. J Hum Nutr Diet 2011; 24:260–268; doi:10.1111/j.1365-277X.2011.01154.x.

46. Brownawell AM, Caers W, Gibson GR, *et al.* Prebiotics and the health benefits of fiber: current regulatory status, future research, and goals. J Nutr 2012; 142:962–974; doi:10.3945/jn.112.158147.

47. Licht TR, Ebersbach T, Frøkiær H. Prebiotics for prevention of gut infections. Trends Food Sci Technol 2012; 23:70–82.

48. Wells JM. Immunomodulatory mechanisms of lactobacilli. Microb Cell Fact 2011; 10:S17; doi:10.1186/1475-2859-10-S1-S17.

49. Drakoularakou A, Tzortzis G, Rastall RA, Gibson GR. A double-blind, placebo-controlled, randomized human study assessing the capacity of a novel galacto-oligosaccharide mixture in reducing travellers' diarrhoea. Eur J Clin Nutr 2010; 64:146–152.

50. Waligora-Dupriet AJ, Campeotto F, Nicolis I, *et al.* Effect of oligofructose supplementation on gut microflora and well being in young children attending a day care centre. Int J Food Microbiol 2007; 113:108–113.

51. Lewis S, Burmeister S, Brazier J. Effect of the prebiotic oligofructose on relapse of Clostridium difficile-associated diarrhea: a randomized, controlled study. Clin Gastroenterol Hepatol 2005; 3:442–448.

52. Szajewska H, Weizman Z, Abu-Zekry M, *et al.,* ESPGHAN Working Group on Probiotics and Prebiotics. Inulin and fructo-oligosaccharides for the prevention of antibiotic-associated diarrhea in children: report by the ESPGHAN Working Group on Probiotics and Prebiotics. J Pediatr Gastroenterol Nutr 2012; 54:828–829; doi:10.1097/MPG.0b013e31824e5f95.

53. ■ Quigley EM. Prebiotics and probiotics: their role in the management of gastrointestinal disorders in adults. Nutr Clin Pract 2012; 27:195–200; doi:10.1177/0884533611423926.

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

54. Giannini EG, Mansi C, Dulbecco P, Savarino V. Role of partially hydrolyzed guar gum in the treatment of irritable bowel syndrome. Nutrition 2006; 22:334–342.

55. Macfarlane S, Macfarlane GT, Cummings JH. Review article: prebiotics in the gastrointestinal tract. Aliment Pharmacol Ther 2006; 24:701–714.

56. Morrow LE, Gogineni V, Malesker MA. Probiotics in the intensive care unit. Nutr Clin Pract 2012; 27:235–241; doi:10.1177/0884533612440290.

57. Corinaldesi R, Stanghellini V, Barbara G, *et al.* Clinical approach to diarrhea. Intern Emerg Med 2012; 7:S255–S262; doi:10.1007/s11739-012-0827-4.

58. Preidis G, Versalovic J. Targeting the human microbiome with antibiotics, probiotics, and prebiotics: Gastroenterology enters the metagenomics era. Gastroenterology 2009; 136:2015–2031.

59. Besselink MGH, van Santvoort HC, Buskens E, *et al.* Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo controlled trial. Lancet 2008; 371:651–659.

60. Wen K, Li G, Bui T, *et al.* High dose and low dose Lactobacillus acidophilus exerted differential immune modulating effects on T cell immune responses induced by an oral human rotavirus vaccine in gnotobiotic pigs. Vaccine 2012; 30:1198–1207.

61. Taverniti V, Guglielmett S. The immunomodulatory properties of probiotic microorganisms beyond their viability (ghost probiotics: proposal of paraprobiotic concept). Genes Nutr 2011; 6:261–274; doi: 10.1007/s12263-011-0218-x.

62. Sharifuzzaman SM, Abbass A, Tinsley JW, Austin B. Subcellular components of probiotics Kocuria SM1 and Rhodococcus SM2 induce protective immunity in rainbow trout (Oncorhynchus mykiss, Walbaum) against Vibrio anguillarum. Fish Shellfish Immunol 2011; 30:347–353; doi:10.1016/j.fsi.2010.11.005.

63. Benson KF, Redman KA, Carter SG, *et al.* Probiotic metabolites from *Bacillus coagulans* GanedenBC30 support maturation of antigen-presenting cells *in vitro*. World J Gastroenterol 2012; 18:1875–1883; doi:10.3748/wjg.v18.i16.1875.

64. ■■ Morrow LE, Gogineni V, Malesker MA. Probiotic, prebiotic, and synbiotic use in critically ill patients. Curr Opin Crit Care 2012; 18:186–191; doi:10.1097/MCC.0b013e3283514b17.

This is an excellent review article summarizing the existing data regarding the use of probiotics, prebiotics, and synbiotics 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.

65. Ochoa TJ, Cleary TG. Effect of lactoferrin on enteric pathogens. Biochimie 2009; 91:30–34; doi:10.1016/j.biochi.2008.04.006.

66. Zavaleta N, Figueroa D, Rivera J, *et al.* Efficacy of rice-based oral rehydration solution containing recombinant human lactoferrin and lysozyme in Peruvian children with acute diarrhea. J Pediatr Gastroenterol Nutr 2007; 44:258–264.

67. ■ Ochoa TJ, Chea-Woo E, Baiocchi N, *et al.* Randomized double-blind controlled trial of bovine lactoferrin for prevention of diarrhea in children. J Pediatr 2013; 162:349–356.

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.

68. Laffan AM, McKenzie R, Forti J, *et al.* Lactoferrin for the prevention of postantibiotic diarrhoea. J Health Popul Nutr 2011; 29:547–551.

69. Nandi S, Suzuki YA, Huang JM, *et al.* Expression of human lactoferrin in transgenic rice grains for the application in infant formula. Plant Sci 2002; 163:713–722.

70. 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.