

Mechanisms, prevention, and management of diarrhea in enteral nutrition

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Purpose of review

Diarrhea is a common and problematic complication of enteral nutrition, about which there has been considerable recent research. This article briefly reviews the mechanisms of diarrhea during enteral nutrition and then critically appraises the recent and emerging evidence for the prevention and management of this distressing complication.

Recent findings

For many years, fiber was extensively investigated for its role in preventing diarrhea; however, a more recent focus has been the investigation of specific fiber blends, including soluble fibers and prebiotics, for which there is now considerable quality evidence. Enteral nutrition may result in deleterious effects on the gastrointestinal microbiota, including reductions in bifidobacteria and key butyrate producers. Their modulation by prebiotics has been confirmed in studies on healthy individuals, but convincing evidence in acutely ill patients is required. Probiotics have undergone extensive recent research and their effect on preventing diarrhea in enteral nutrition would seemingly be strain dependent. Further research is required on systematic approaches to treating diarrhea during enteral nutrition.

Summary

A number of factors contribute to the pathogenesis of diarrhea in enteral nutrition, meaning that approaches to its prevention and management are necessarily multifaceted. Approaches to prevent diarrhea during enteral nutrition, and a clinical algorithm to manage it, are now presented.

Keywords

diarrhea, enteral nutrition, fiber, prebiotics, probiotics, short-chain fatty acids

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Introduction

Enteral nutrition is a method of artificial nutritional support commonly used in patients in the hospital or community setting. Diarrhea can occur in 2–95% of patients, the wide range resulting from differences in the patient populations and the definition of diarrhea adopted [1]. It may result in a number of negative clinical sequelae, including fluid and electrolyte abnormalities, fecal incontinence, and pressure sores. This may result in the cessation of enteral nutrition, which may exacerbate undernutrition and its associated consequences of increased morbidity and mortality. Importantly, diarrhea is also distressing and burdensome for both patients and their carers [2]. The article briefly reviews the mechanisms of diarrhea during enteral nutrition and then critically appraises recent and emerging evidence on the prevention and management of this distressing complication.

Pathogenesis of diarrhea

A number of factors contribute to the pathogenesis of diarrhea in enteral nutrition, including altered

physiological response, antibiotics, and enteropathogenic infection.

Altered physiological responses may occur during enteral nutrition. Studies on healthy individuals found that intragastric enteral nutrition results in abnormal water secretion into the ascending colon [3]. This may be exacerbated by suppression of distal colonic motor activity that accelerates colonic transit and reduces the opportunity for water absorption [4]. If these occur in patients receiving enteral nutrition, then in the absence of compensatory absorptive mechanisms, diarrhea may result.

Many patients receiving enteral nutrition also receive concomitant antibiotics, and a number of studies have shown that diarrhea is associated with the prescription, number, or duration of antibiotics [5,6]. However, it is unclear whether this is merely antibiotic-associated diarrhea, or whether there is a particular interaction between antibiotics, enteral nutrition, and diarrhea. A number of studies support the latter hypothesis, including that diarrhea during enteral nutrition is in part associated with

Table 1 Potential mechanisms through which prebiotics and probiotics may influence gastrointestinal physiology of relevance to enteral nutrition diarrhea

Physiological effect	Examples of prebiotic mechanisms	Examples of probiotic mechanisms
Enteropathogenic suppression Luminal colonization resistance	Oligosaccharides reduce fecal pH in infants	Some bifidobacteria inhibit <i>Salmonella typhimurium</i> infection in mice, whereas some lactobacilli decrease fecal pH
Mucosal competitive exclusion	Inulin may prevent recurrent CDAD	Some lactobacilli, and their products, inhibit adhesion of <i>Escherichia coli</i> and <i>S. typhimurium</i> to cell lines
Colonic fermentation SCFA production	Inulin enhances SCFA production in pure culture and fecal culture	<i>Saccharomyces boulardii</i> increases butyrate and total SCFA in patients receiving EN
Immune activity Immune regulation	Possible effects, limited human studies	Lactobacilli reduce IL-6 production in patients receiving nutrition support on the ICU
Immune stimulation	Possible effects, limited human studies	Some lactobacilli and bifidobacteria enhance phagocytosis and specific IgA production. One study has shown they may enhance IgA and IgG production in patients receiving EN on the ICU

CDAD, *Clostridium difficile*-associated diarrhea; EN, enteral nutrition; SCFA, short-chain fatty acid. Data from [1].

deleterious alterations in luminal microbiota. For example, in a small cohort study that monitored the fecal microbiota in patients during the first 2 weeks of enteral nutrition, those who developed diarrhea had higher clostridia and lower bifidobacteria, and interestingly, these alterations were present even at the start of enteral nutrition [7[•]]. Although there is convincing evidence for the role of antibiotics in predisposing to higher risk of diarrhea during enteral nutrition, it is unclear whether other factors associated with gastrointestinal dysbiosis (e.g., ageing, disease) may also predispose to such risks.

There is evidence of elevated risk of enteropathogenic infection in patients receiving enteral nutrition. For example, one case–control study found that *Clostridium difficile* colonization was three-fold higher, and *C. difficile*-associated diarrhea (CDAD) was nine-fold higher, in patients receiving enteral nutrition, and this is despite similar antibiotic use [8]. More recently, in an analysis of 233 patients undergoing percutaneous endoscopic gastrostomy (PEG), 15 (6.4%) patients developed CDAD within 1 month, six (2.6%) of whom entered a cycle of recurrent CDAD, resulting in a major interruption to the delivery of enteral nutrition [9[•]]. Prophylactic antibiotics are frequently given during PEG insertion, and following multivariate analysis, the duration of antibiotic prescription (but not actual antibiotic prescription) was an independent predictor of subsequent development of CDAD [9[•]].

Prevention of diarrhea

A number of factors contribute to the pathogenesis of diarrhea in enteral nutrition, meaning that approaches to its prevention and management are necessarily multifaceted, many of which are nutritional interventions. For example, some fibers undergo fermentation and produce short-chain fatty acids (SCFAs) that reverse the abnormal

colonic water secretion in enteral nutrition [3] and some fibers can alter colonic motor activity [10]. In addition, prebiotics and probiotics may suppress enteropathogenic colonization, alter colonic fermentation, and modulate immune function (Table 1) and, therefore, minimize the risks from antibiotics and *C. difficile*. The evidence to support these nutritional interventions is reviewed.

Fiber

Fibers can exert a number of gastrointestinal effects, depending on their solubility in water and fermentability by the colonic microbiota, with some being categorized as prebiotics. They may prevent diarrhea through reducing the rate of gastric emptying, improving gut barrier function, increasing epithelial cell turnover or regeneration, and increasing colonic fluid and electrolyte absorption [11]. Previously, many fiber-enriched enteral formulas contained poorly fermentable soy polysaccharides; however, these increased formula viscosity and tended to sediment. More recently, the composition of fiber-enriched formulas has evolved toward the use of blends of soluble and insoluble fibers. Formulas containing such blends have been reported to increase fecal SCFA concentrations in adult patients receiving enteral nutrition [12], whereas this was not confirmed in one study on children, though perhaps due to the small numbers involved [13[•]].

Partially hydrolyzed guar gum is a soluble fiber added to enteral formulas and has the largest body of evidence supporting its use in diarrhea prevention when compared against fiber-free formulas (Table 2) [14–25]. A systematic review and meta-analysis of prospective randomized controlled trials (RCTs) of fiber-enriched formulas in the prevention of diarrhea has recently been reported [11]. Although it statistically aggregated the results of RCTs of different fibers, it reported a preventive effect of fiber-enriched enteral nutrition on diarrhea, with a significant reduction in the percentage of patients with

Table 2 Randomized controlled trials that measure the preventive impact of fiber on stool output or diarrhea

Reference	Patient group	Number	Fiber studied	Results
Vandewoude <i>et al.</i> [14]	Geriatrics	155	Cellulose, hemicelluloses, pectin, inulin	Reduced number of stools, improved stool consistency
Hart and Dobb [15]	ICU	68	Isphaghula husk	No effect
Homann <i>et al.</i> [16]	Medicine/surgery	100	Partially hydrolyzed guar gum	Reduced diarrhea incidence
Spapen <i>et al.</i> [17]	ICU (sepsis)	25	Partially hydrolyzed guar gum	Reduced diarrhea incidence
Schultz <i>et al.</i> [18]	ICU	44	Pectin/fiber mixture ^a	No effect
Belknap <i>et al.</i> [19]	Medicine/surgery/ICU	60	Psyllium	No effect
Dobb and Towler [20]	ICU	91	Soy polysaccharides	No effect
Frankenfield and Beyer [21]	ICU	9	Soy polysaccharides	No effect
Guenter <i>et al.</i> [22]	ICU	100	Soy polysaccharides	No effect
Reese <i>et al.</i> [23]	Postoperative	80	Soy polysaccharides	Reduced diarrhea incidence in men only
de Kruif and Vos [24]	Postoperative	60	Soy polysaccharides	Reduced diarrhea score
Khalil <i>et al.</i> [25]	Postoperative	16	Soy polysaccharides + oat fiber	No effect

^a Oat, soy, gum arabic, carboxymethylcellulose, fructooligosaccharides.

diarrhea [odds ratio (OR) 0.68, 95% confidence interval (CI) 0.48–0.96; 16 datasets] and a tendency for a reduction in the percentage of days with diarrhea [11].

Few studies have directly compared different fibers for their impact on diarrhea in enteral nutrition. A 12-week RCT of enteral nutrition in diabetic patients compared two formulas: a 'conventional' fiber-enriched formula (55% of energy as carbohydrate; 30% lipids; 15% protein; and 2 g/l of undefined fiber) and a 'diabetes-specific' fiber-enriched formula (45% of energy as carbohydrates; 38% lipids – mostly monounsaturated; 17% protein; and 1.5 g/l of a mixture of soluble and insoluble fibers) [26]. Stool frequency during the first week was significantly reduced in the 'diabetes-specific' fiber-enriched group (0.8 ± 0.3 stools/day) compared with the 'conventional' fiber-enriched group (1.8 ± 0.3 stools/day, $P = 0.034$) and this did not significantly change over time [26].

Recent American Society for Parenteral and Enteral Nutrition (ASPEN) ICU guidelines highlight the interest in partially hydrolyzed guar gum and the lack of interest in insoluble fiber in preventing enteral nutrition-associated diarrhea [27]. They go as far as to advise against the use of insoluble fiber, arguing that it may increase the risk of bowel obstruction in the critically ill. However, the evidence to support this recommendation is very limited (five cases of bowel obstruction in surgical and trauma patients) and it is largely based on expert opinion. Meanwhile, European Society for Parenteral and Enteral Nutrition guidelines on enteral nutrition refer to fibers and their properties (or lack thereof), but fail to give any recommendation on the matter [28].

Prebiotics and fermentable carbohydrates

Studies have shown that standard formulas (no fiber, no prebiotics) result in negative alterations to the colonic microbiota, including lower total bacteria [29], higher aerobes [30], and lower numbers of the butyrate-producing *Faecalibacterium prausnitzii* [31[•]], with subsequent

reductions in total SCFA and butyrate [29,31[•]] and higher fecal pH [29]. In view of this, some formulas now have prebiotics added to them. Prebiotics are defined as 'the selective stimulation of growth and/or activity of one or a limited number of microbial genera/species in the gut microbiota that confer health benefits to the host' [32[•]]. The most commonly used prebiotics are inulin-type fructans (inulin, oligofructose, fructooligosaccharides).

When added to enteral formulas, prebiotics have been shown to increase fecal bifidobacteria in healthy individuals [29]; however, whether such effects occur in patients receiving enteral nutrition remains as yet unclear. For example, in one RCT of 15 patients receiving long-term home enteral nutrition, a mixed fiber/prebiotic formula increased fecal SCFAs, but had no effect on fecal bifidobacteria [12]. However, a recent pilot RCT of 16 patients receiving long-term home enteral nutrition investigated the impact of a standard formula (no fiber, no prebiotic) compared with a fiber/prebiotic formula on stool output [33]. Fecal microbiota were compared between a subgroup of patients ($n = 10$) and there was shown to be a reduction in bifidobacteria in the standard formula, which did not occur in the fiber/prebiotic formula. Although diarrhea was not measured *per se*, there were no differences in the number of soft stools between groups [33]. Meanwhile, no studies have investigated the ability of prebiotic formulas to stimulate growth of bifidobacteria in in-patients with acute illness.

No studies have specifically investigated the effect of a prebiotic alone in the prevention of diarrhea during enteral nutrition; however, a small number have investigated the effect of a fiber/prebiotic formula [11]. The most notable study is a RCT of 155 older patients who received a standard (no fiber, no prebiotic) or a fiber/prebiotic formula. In those receiving the prebiotic, there was lower stool frequency (4.1 vs. 6.3 stools per week, $P = 0.008$) and more formed stools (31 vs. 21% formed

stools, $P=0.001$) than patients receiving standard formula [14].

Recently, a number of small cross-over RCTs comparing fiber/prebiotic formulas with standard formulas have been undertaken in children receiving long-term enteral nutrition. In one, there was no difference in stool consistency or frequency in 27 children irrespective of which formula was used, despite increases in number of bifidobacteria during the fiber/prebiotic formula [13[•]]. In addition, a study of 25 children found no difference in the number of days with diarrhea between patients when receiving a standard or a fiber/prebiotic formula [34[•]]. However, in a recent study that was limited by small numbers ($n=14$) and heterogeneous disease categories requiring subgroup analysis, children with neurological impairment experienced fewer watery stools when receiving a fiber/prebiotic formula (11%) compared with the standard formula (26%, $P<0.05$) [35[•]]. Stool frequency did not differ between formulas [35[•]]. Studies investigating the effects of formulas enriched with prebiotics alone on the luminal microbiota and prevalence of diarrhea are required. This is particularly important in the hospital setting, in which the prevalence of diarrhea is more of a burden.

Finally, a recent retrospective case-note review of 160 hospitalized patients who had received enteral nutrition hypothesized that fermentable carbohydrates may actually be associated with the development of diarrhea [6[•]]. Following logistic regression analysis that adjusted for clinical factors associated with diarrhea (length of stay, duration of enteral nutrition, antibiotic use), it was shown that one formula was associated with a lower diarrhea risk ($OR=0.18$, $P=0.029$) and that this was low in fermentable oligosaccharide, disaccharide, monosaccharides, and polyols (FODMAPs). The mechanism may relate to the osmotic potential of these carbohydrates in the small intestine, which have been shown to increase water delivery to the colon [36], which in the absence of compensatory colonic absorption, may contribute to diarrhea pathogenesis. The authors are careful to point out that the limitations of the study design impede a conclusion of a cause and effect relationship, but RCTs are to follow [6[•]].

Probiotics

Probiotics are 'live microorganisms which when administered in adequate amounts confer a health benefit on the host' [37]. Commonly used strains include lactobacilli, bifidobacteria, and saccharomyces (and commercial mixtures) and are available in capsules, powders, yoghurts, and fermented milks.

Over the past 20 years, a number of RCTs investigating probiotics in patients receiving enteral nutrition have

recorded diarrhea as an outcome measure (Table 3) [38–40,41^{••}–43^{••}]. Two small studies demonstrated no impact of probiotics on diarrhea prevalence. In the first, 41 patients received *Lactobacillus acidophilus*/*Lactobacillus bulgaricus* or placebo and there were no significant differences in fecal weight or diarrhea [38]. In the second, 28 patients on the ICU received VSL#3, sonicated VSL#3, or placebo, without any significant differences in diarrhea duration between groups, although this study was probably underpowered to detect such outcomes [39]. For some time, the largest study in the area has been a trial of 128 patients receiving enteral nutrition on the ICU who received *Saccharomyces boulardii* or placebo, and those in the probiotic group experienced 25% fewer diarrhea days than placebo [40].

Over the last year, there has been rapid expansion in trials investigating probiotics in patients receiving enteral nutrition wherein stool output and/or diarrhea have been recorded as an outcome (Table 3). First, a trial of 45 patients starting enteral nutrition on the ICU demonstrated a reduction in liquid stools in patients receiving VSL#3 (mean 0.5 liquid stools/day) compared with placebo (1.1 liquid stools/day; $P=0.03$) [41^{••}]. Compared with the previous trial of VSL#3 [39], this study was powered to detect differences in stool output [41^{••}]. A small trial in 36 adults receiving enteral nutrition on the ICU who currently had diarrhea found that *Lactobacillus rhamnosus* GG in addition to a small dose of inulin (560 mg/day) did not have benefit over the same dose of inulin alone in treating patients [42^{••}]. Finally, the largest trial to date is now an RCT of 167 patients receiving placebo or the commercial product Ergyphilus (consisting mainly of *L. rhamnosus* GG) [43^{••}]. Although not the primary outcome, there were no differences in the proportion of patients developing diarrhea (defined as 3 liquid stools/day) between the probiotic (55%) and the placebo (53%) group. Interestingly, the probiotic had differential effects on mortality between those with severe sepsis (probiotics reduced mortality, $OR=0.38$, $P=0.035$) and those with nonsevere sepsis (probiotics increased mortality, $OR=3.09$, $P=0.08$).

Clearly, safety is an important consideration prior to using probiotics in the clinical setting. This is particularly relevant in patients receiving enteral nutrition as increased gastric pH (due to enteral formula or gastric acid suppressing drugs) or postpyloric administration (e.g., nasojejunal tube) will result in increased probiotic survival into the small intestine. Safety was highlighted following an RCT of probiotics in patients with severe acute pancreatitis that reported increased mortality in the probiotic group [44]. However, in that study, the probiotic was a novel product with little previous data on human applications and was delivered via nasojejunal tube.

Table 3 Randomized controlled trials that measure the impact of probiotics on stool output or diarrhea in patients receiving enteral nutrition

Reference	Patient group	Probiotic intervention and placebo	Sample size	Results	P value
Heimbürger <i>et al.</i> [38]	41 adults starting EN	<i>Lactobacillus acidophilus</i> and <i>L. bulgaricus</i> (3 g/day)	18	31% developed diarrhea	0.21
Alberda <i>et al.</i> [39]	28 adults starting EN on ICU	Placebo	23	11% developed diarrhea	NS
		VSL#3 – live cells (9×10^{11} bacteria/day)	10	14% of days with diarrhea	
		VSL#3 – DNA only (9×10^{11} bacteria/day)	9	12% of days with diarrhea	
Bleichner <i>et al.</i> [40]	128 adults starting EN on ICU	Placebo	9	23% of days with diarrhea	0.0069
		<i>Saccharomyces boulardii</i> (2 G/D)	64	14% of days with diarrhea	
Frohman <i>et al.</i> [41**]	45 adults starting EN on ICU	Placebo	64	19% of days with diarrhea	0.03
		VSL#3 (9×10^{11} bacteria/day)	20	0.5 liquid stools/day	
Ferrie and Daley [42**]	36 adults with diarrhea during EN on ICU	Placebo	25	1.1 liquid stools/day	0.08
		<i>L. rhamnosus</i> GG (2×10^{10} cells/day) and inulin (560 mg/day)	18	3.8 days duration of diarrhea	
Barraud <i>et al.</i> [43**]	167 adults starting EN on ICU	Inulin (560 mg/day)	18	2.6 days duration of diarrhea	NS
		Ergyphilus (2×10^{10} cells/day)	87	55% developed diarrhea	
		Placebo	80	53% developed diarrhea	

VSL#3 consists of *Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus acidophilus*, *Lactobacillus delbrueckii*, *Bifidobacterium longum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, and *Streptococcus salivarius*. Ergyphilus consists of mainly *Lactobacillus rhamnosus* GG, *Lactobacillus casei*, *Lactobacillus acidophilus*, and *Bifidobacterium bifidum*. EN, enteral nutrition; NS, not significant.

Safety was investigated in a systematic review of case reports and clinical trials of probiotics in patients receiving nutritional support [45*]. Case reports of 32 patients receiving nutritional support (enteral nutrition or parenteral nutrition) who developed an infection caused by probiotics were found. Risk factors included increased risk of bacterial translocation and the presence of a central venous catheter, which enables direct access to the systemic circulation when it is handled by contaminated hands. Despite this, the systematic review identified 50 trials of probiotics in patients receiving nutritional support (>4000 patients) that did not report negative clinical sequelae [45*]. A risk-benefit analysis and routine monitoring for adverse events should, therefore, be undertaken when considering probiotic use in patients receiving enteral nutrition.

There is contrasting evidence of efficacy of probiotics in preventing diarrhea in patients receiving enteral nutrition [46*]. This is likely due to variations in trial methodology, but in particular due to differences in functional characteristics of the various probiotics. Therefore, experts in nutritional support should be cautious when extrapolating the results from one probiotic to that of another.

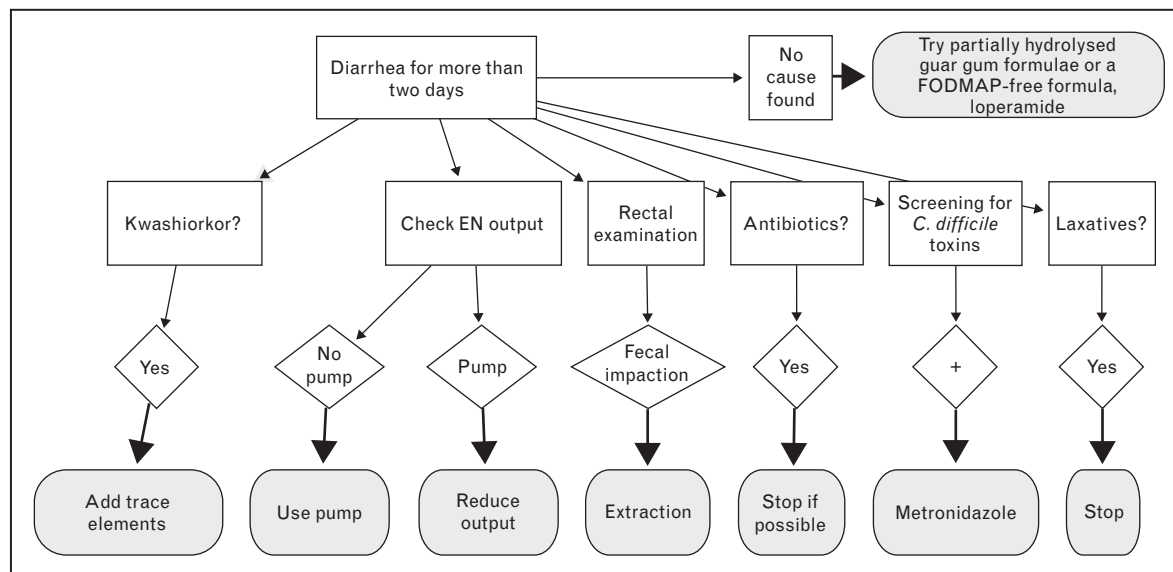
Management of diarrhea

Most episodes of nosocomial diarrhea are mild and will usually spontaneously abate after 72 h, even though exacerbation of preexisting diarrhea may persist. Should diarrhea continue for 72 h or more, an abdominal examination should be performed, a stool sample should be

tested for *C. difficile* enterotoxins, blood samples should be taken for a serum electrolyte panel (to evaluate excessive electrolyte losses or dehydration), and medications should be reviewed. As discussed, antibiotics (especially broad spectrum and those effective against anaerobes) are renowned for causing diarrhea [5,6*], whereas syrup or liquid preparations of medications often have a very high osmolar load or contain sorbitol leading to an osmotic laxative effect. Lactose (as an excipient in numerous tablets) and FODMAPs in enteral formulas may have the same effect [6*].

Water and electrolyte replenishment is crucial and can be achieved orally, enterally, or parenterally, as appropriate. Antimotility agents such as loperamide, loperamide oxide, and codeine can be used; however, this must wait until fecal impaction and, most importantly, *C. difficile* infection have been excluded [47]. There is no evidence to support the use of probiotics [42**] or prebiotics in treating patients who already have diarrhea. An example of clinical algorithm for the management of diarrhea in enteral nutrition is shown in Fig. 1. Research is required to investigate the effectiveness of a cadre of interventions to treat diarrhea in patients receiving enteral nutrition.

The composition of the enteral formula may also be adapted. Although only two studies are available, the use of soluble fiber may prove useful in treating diarrhea in patients receiving enteral nutrition. In an open-labeled study, galactomannans (7–28 g/day) were provided to 20 elderly in-patients with diarrhea during enteral nutrition and resulted in a significant decrease in the stool-water

Figure 1 Algorithm for clinical management of enteral nutrition-associated diarrhea

EN, enteral nutrition.

content and stool frequency [48]. Although this was not a controlled trial, the beneficial effects disappeared after fiber was discontinued [48]. In a RCT in 20 ICU patients with diarrhea during enteral nutrition, the use of a formula containing partially hydrolyzed guar gum (compared to a standard formula) led to a significant decrease in the number of liquid stools, while allowing a higher volume of formula to be delivered [49]. The addition of sodium chloride and trace elements to the formula may counteract the effects of active gastrointestinal water secretion and prevent specific deficiencies. Another approach to treating diarrhea is to minimize the residue reaching the colon and some authors recommend predigested enteral formulas containing peptides and medium-chain triglycerides rather than whole proteins and long-chain triglycerides [27]. Outside situations of major pancreatic exocrine insufficiency, this approach is not supported by any evidence. ASPEN combined these different approaches and stated that if there is evidence of diarrhea, soluble fiber-enriched formulas or predigested formulas may be utilized. The lack of conclusive high-quality evidence to support this recommendation resulted in it being given a grade E [27].

Despite these approaches to modifying the composition of the enteral formula, most importantly, enteral nutrition should not be interrupted or stopped. In the clinical setting, diarrhea is a frequently cited cause for enteral nutrition to be interrupted or stopped [50]. However, continued bowel rest exacerbates bacterial overgrowth and gastrointestinal dysmotility, which perpetuates the

diarrhea. Furthermore, protein and energy goals will not be reached, which will predispose or exacerbate undernutrition and its associated consequences of increased morbidity, mortality, length of stay, and of course cost. Reducing the delivery rate, while still achieving target volume is one possibility. Another option is to reduce enteral nutrition provision and to replace protein and energy with supplementary parenteral nutrition, which can subsequently be tapered down once diarrhea abates and the volume of enteral nutrition is increased.

Conclusion

Diarrhea is a major concern in enteral nutrition and may represent a limitation to the broad use this therapy deserves. Recent research shows the main causal factor to be dysbiosis, related to the initial disease, antibiotics, and also the formula composition (lack of certain fibers, presence of poorly absorbed fermentable compounds). Future progress will come from new techniques in bacterial stool analysis as well as the progress in describing the microbiota, which may allow us to screen prospective enteral nutrition patients in order to determine which ones are at risk for diarrhea; this will allow us to start them on a specific formula, and such approaches need to be studied further [51]. The priority in treating patients with enteral nutrition-associated diarrhea is to keep the provision of their water, electrolyte, protein, and energy needs. For both prevention and treatment, a number of new fiber blends now available may be of interest; however, the need for clinical studies remains.

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 (pp. 196–197).

- 1 Whelan K. Enteral tube feeding diarrhoea: manipulating the colonic microbiota with probiotics and prebiotics. *Proc Nutr Soc* 2007; 66:299–306.
 - 2 Majid HA, Emery PW, Whelan K. Attitudes of patients and nurses towards diarrhoea during enteral tube feeding. *J Hum Nutr Diet* 2008; 21:395.
 - 3 Bowling TE, Raimundo AH, Grimble GK, Silk DBA. Reversal by short chain fatty acids of colonic fluid secretion induced by enteral feeding. *Lancet* 1993; 342:1266–1268.
 - 4 Bowling TE, Silk DB. Colonic responses to enteral tube feeding. *Gut* 1998; 42:147–151.
 - 5 Trabal J, Leyes P, Hervás S, *et al.* Factors associated with nosocomial diarrhea in patients with enteral tube feeding. *Nutr Hosp* 2008; 23:500–504.
 - 6 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.
- An investigation of the independent risk factors for diarrhea in enteral nutrition. The first study to report that formulas low in fermentable carbohydrates may prevent diarrhea in enteral nutrition.
- 7 Whelan K, Judd PA, Tuohy KM, *et al.* The 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.
- This is the first study to undertake secular monitoring of luminal microbiota in patients receiving enteral nutrition and to link dysbiosis (higher clostridia, lower bifidobacteria) with the presence of diarrhea.
- 8 Bliss DZ, Johnson S, Savik K, *et al.* Acquisition of *Clostridium difficile* and *Clostridium difficile*-associated diarrhea in hospitalised patients receiving tube feeding. *Ann Intern Med* 1998; 129:1012–1019.
 - 9 Yokohama S, Aoshima M, Asama T, *et al.* *Clostridium difficile*-associated enteric disease after percutaneous endoscopic gastrostomy. *J Gastroenterol* 2009; 44:121–125.
- This study used multivariate analysis to link antibiotic use during PEG insertion with subsequent development of CDAD.
- 10 Silk DB, Walters ER, Duncan HD, Green CJ. The effect of a polymeric enteral formula supplemented with a mixture of six fibres on normal human bowel function and colonic motility. *Clin Nutr* 2001; 20:49–58.
 - 11 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.
 - 12 Schneider SM, Girard-Pipau F, Anty R, *et al.* Effects of total enteral nutrition supplemented with a multifibre mix on faecal short-chain fatty acids and microbiota. *Clin Nutr* 2006; 25:82–90.
 - 13 Guimber D, Bourgeois B, Beghin L, *et al.* Effect of multifibre mixture with prebiotic components on bifidobacteria and stool pH in tube-fed children. *Br J Nutr* 2010; 104:1514–1522.
- A small, but well conducted, RCT of the effect of a fiber and prebiotic-enriched formula on stool output, luminal microbiology, and markers of fermentation.
- 14 Vandewoude MF, Paridaens KM, Suy RA, *et al.* Fibre-supplemented tube feeding in the hospitalised elderly. *Age Ageing* 2005; 34:120–124.
 - 15 Hart GK, Dobb GJ. Effect of a fecal bulking agent on diarrhoea during enteral feeding in the critically ill. *JPEN J Parenter Enteral Nutr* 1988; 12:465–468.
 - 16 Homann HH, Kemen M, Fuessenich C, *et al.* Reduction in diarrhoea incidence by soluble fibre in patients receiving total or supplemental enteral nutrition. *JPEN J Parenter Enteral Nutr* 1994; 18:486–490.
 - 17 Spapen H, Diltoer M, Van Malderen C, *et al.* Soluble fibre reduces the incidence of diarrhoea in septic patients receiving total enteral nutrition: a prospective, double-blind, randomized, and controlled trial. *Clin Nutr* 2001; 20:301–305.
 - 18 Schultz AA, Ashby-Hughes B, Taylor R, *et al.* Effects of pectin on diarrhoea in critically ill tube-fed patients receiving antibiotics. *Am J Crit Care* 2000; 9:403–411.
 - 19 Belknap D, Davidson LJ, Smith CR. The effects of psyllium hydrophilic mucilloid on diarrhoea in enterally fed patients. *Heart Lung* 1997; 26:229–237.
 - 20 Dobb GJ, Towler SC. Diarrhoea during enteral feeding in the critically ill: a comparison of feeds with and without fibre. *Intensive Care Med* 1990; 16:252–255.
 - 21 Frankenfield DC, Beyer PL. Soy-polysaccharide fibre: effect on diarrhoea in tube-fed, head-injured patients. *Am J Clin Nutr* 1989; 50:533–538.
 - 22 Guenter PA, Settle RG, Perlmutter S, *et al.* Tube feeding-related diarrhoea in acutely ill patients. *JPEN J Parenter Enteral Nutr* 1991; 15:277–280.
 - 23 Reese JL, Means ME, Hanrahan K, *et al.* Diarrhoea associated with naso-gastric feedings. *Oncol Nurs Forum* 1996; 23:59–66.
 - 24 de Kruijff JT, Vos A. The influence of soy fibre supplemented tube feeding on the occurrence of diarrhoea in postoperative patients. *Clin Nutr* 1993; 12:360–364.
 - 25 Khalil L, Ho KH, Png D, Ong CL. The effect of enteral fibre-containing feeds on stool parameters in the postsurgical period. *Singapore Med J* 1998; 39:156–159.
 - 26 Vaisman N, Lansink M, Rouws CH, *et al.* Tube feeding with a diabetes-specific feed for 12 weeks improves glycaemic control in type 2 diabetes patients. *Clin Nutr* 2009; 28:549–555.
 - 27 McClave SA, Martindale RG, Vanek VW, *et al.*; A.S.P.E.N. Board of Directors, American College of Critical Care Medicine, Society of Critical Care Medicine. 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* 2009; 33:277–316.
 - 28 Lochs H, Allison SP, Meier R, *et al.* Introductory to the ESPEN guidelines on enteral nutrition: terminology, definitions and general topics. *Clin Nutr* 2006; 25:180–186.
 - 29 Whelan K, Judd PA, Preedy VR, *et al.* Fructo-oligosaccharides and fiber partially prevent the alterations in fecal microbiota and SCFA concentrations caused by standard enteral formula in healthy humans. *J Nutr* 2005; 135:1896–1902.
 - 30 Schneider SM, Le Gall P, Girard-Pipau F, *et al.* Total artificial nutrition is associated with major changes in the fecal flora. *Eur J Nutr* 2000; 39:248–255.
 - 31 Benus RF, van der Werf TS, Welling GW, *et al.* Association between *Faecalibacterium prausnitzii* and dietary fibre in colonic fermentation in healthy human subjects. *Br J Nutr* 2010; 104:693–700.
- This study is the first to demonstrate the interaction between the absence of fiber in an enteral formula and lower *F. prausnitzii* and butyrate.
- 32 Roberfroid M, Gibson GR, Hoyle L, *et al.* Prebiotic effects: metabolic and health benefits. *Br J Nutr* 2010; 104 (Suppl 2):S1–S63.
- The most recent and comprehensive review of the application of prebiotics in health and disease, including state-of-the-art analysis and integration of prebiotic research.
- 33 Wierdsma NJ, van Bodegraven AA, Uitdehaag BM, *et al.* Fructo-oligosaccharides and fibre in enteral nutrition has a beneficial influence on microbiota and gastrointestinal quality of life. *Scand J Gastroenterol* 2009; 44:804–812.
 - 34 Evans S, Daly A, Davies P, MacDonald A. Fibre content of enteral feeds for the older child. *J Hum Nutr Diet* 2009; 22:414–421.
- One of the first RCT to investigate the effect of fiber/prebiotic formulas on stool output and diarrhea in children receiving home enteral nutrition.
- 35 Khoshoo V, Sun SS, Storm H. Tolerance of an enteral formula with insoluble and prebiotic fiber in children with compromised gastrointestinal function. *J Am Diet Assoc* 2010; 110:1728–1733.
- Although a limited sample size, this study investigated the effect of a fiber/prebiotic formula on stool output in children requiring long-term enteral nutrition.
- 36 Barrett JS, Geary RB, Muir JG, *et al.* Dietary poorly absorbed, short-chain carbohydrates increase delivery of water and fermentable substrates to the proximal colon. *Aliment Pharmacol Ther* 2010; 31:874–882.
 - 37 Food and Agriculture Organization of the UN and World Health Organization Working Group. Guidelines for the evaluation of probiotics in food. Rome/Geneva: FAO/WHO; 2002.
 - 38 Heimbürger DC, Sockwell DG, Geels WJ. Diarrhea with enteral feeding: prospective reappraisal of putative causes. *Nutrition* 1994; 10:392–396.
 - 39 Alberda C, Gramlich L, Meddings J, *et al.* Effects of probiotic therapy in critically ill patients: a randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr* 2007; 85:816–823.
 - 40 Bleichner G, Blehaut H, Mentec H, Moysé D. *Saccharomyces boulardii* prevents diarrhea in critically ill tube fed patients. *Intensive Care Med* 1997; 23:517–523.
 - 41 Frohmader TJ, Chaboyer WP, Robertson IK, Gowardman J. Decrease in frequency of liquid stool in enterally fed critically ill patients given the multi-species probiotic VSL#3: a pilot trial. *Am J Crit Care* 2010; 19:e1–11.
- This excellent RCT used careful monitoring of stool frequency, consistency and weight to demonstrate a reduction in liquid stools using VSL#3.

- 42 Ferrie S, Daley M. Lactobacillus GG as treatment for diarrhea during enteral feeding in critical illness: randomized controlled trial. *J Parenter Enteral Nutr* 2010 [Epub ahead of print]. doi:10.1177/0148607110370705.

The first RCT to use the established probiotic *L. rhamnosus* GG as a single strain to actively treat diarrhea during enteral nutrition.

- 43 Barraud D, Blard C, Hein F, *et al.* Probiotics in the critically ill patient: a double blind, randomized, placebo-controlled trial. *Intensive Care Med* 2010; 36:1540–1547.

The largest RCT of probiotics in enteral nutrition thus far to measure diarrhea as an endpoint, indicating a lack of efficacy of the particular commercial probiotic. The probiotic had differential effects on mortality between those with severe sepsis (probiotics reduced it) and those with nonsevere sepsis (probiotics increased it).

- 44 Besselink MG, van Santvoort HC, Buskens E, *et al.*; the Dutch Acute Pancreatitis Study Group. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; 371:651–659.

- 45 Whelan K, Myers CE. Safety of probiotics in patients receiving nutritional support: a systematic review of case reports, randomized controlled trials and nonrandomized trials. *Am J Clin Nutr* 2010; 91:687–703.

An extensive systematic review of the case reports of adverse events of probiotics in nutritional support and of the clinical trials in that area. A detailed discussion of the potential risk factors associated with probiotics in this patient group.

- 46 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.

This article reviews the current evidence on various probiotic strains in the prevention of diarrhea in enteral nutrition.

- 47 O'Keefe SJ. A guide to enteral access procedures and enteral nutrition. *Nat Rev Gastroenterol Hepatol* 2009; 6:207–215.

- 48 Nakao M, Ogura Y, Satake S, *et al.* Usefulness of soluble dietary fibre for the treatment of diarrhoea during enteral nutrition in elderly patients. *Nutrition* 2002; 18:35–39.

- 49 Rushdi TA, Pichard C, Khater YH. Control of diarrhoea by fibre-enriched diet in ICU patients on enteral nutrition: a prospective randomized controlled trial. *Clin Nutr* 2004; 23:1344–1352.

- 50 Meyer R, Harrison S, Sargent S, *et al.* The impact of enteral feeding protocols on nutritional support in critically ill children. *J Hum Nutr Diet* 2009; 22:428–436.

- 51 Schneider SM. Microbiota and enteral nutrition. *Gastroenterol Clin Biol* 2010; 34:S57–S61.