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## BAPEN Symposium 2 on ‘Pre- and probiotics’

# Enteral-tube-feeding diarrhoea: manipulating the colonic microbiota with probiotics and prebiotics

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Diarrhoea is a common and serious complication of enteral tube feeding. Its pathogenesis involves antibiotic prescription, enteropathogenic colonization and abnormal colonic responses, all of which involve an interaction with the colonic microbiota. Alterations in the colonic microbiota have been identified in patients receiving enteral tube feeding and these changes may be associated with the incidence of diarrhoea. Preventing negative alterations in the colonic microbiota has therefore been investigated as a method of reducing the incidence of diarrhoea. Probiotics and prebiotics may be effective because of their suppression of enteropathogenic colonization, stimulation of immune function and modulation of colonic metabolism. Randomized controlled trials of probiotics have produced contrasting results, although *Saccharomyces boulardii* has been shown to reduce the incidence of diarrhoea in patients in the intensive care unit receiving enteral tube feeding. Prebiotic fructo-oligosaccharides have been shown to increase the concentration of faecal bifidobacteria in healthy subjects consuming enteral formula, although this finding has not yet been confirmed in patients receiving enteral tube feeding. Furthermore, there are no clinical trials investigating the effect of a prebiotic alone on the incidence of diarrhoea. Further trials of the efficacy of probiotics and prebiotics, alone and in combination, in preventing diarrhoea in this patient group are warranted.

### Enteral nutrition: Microflora: Diarrhoea: Pro- and prebiotics

Enteral tube feeding (ETF) is a method of artificial nutritional support for patients who are unable to achieve their nutritional requirements through an oral diet. Although recent data on its use in general hospitalized patients are scarce, a national survey in 1994 has reported that each hospital in the UK provided ETF to an average of 213 patients per year (Payne-James *et al.* 1995). ETF is used increasingly in the intensive care unit (ICU), where  $\leq 77\%$  of patients receive ETF (Preiser *et al.* 1999), and in the community, where in the UK between 20 000 and 25 000 patients currently receive ETF (Elia, 2003).

Alterations in faecal output can occur during ETF that result in the diagnosis of diarrhoea. The incidence of diarrhoea reported in the literature ranges from 2% (Cataldi-Betcher *et al.* 1983) to 95% (DeMeo *et al.* 1998) of patients. This wide range of incidence is a result of differences in the patient groups investigated and

differences in the definition of diarrhoea used. One review of the literature (Lebak *et al.* 2003) has identified the use of thirty-three different definitions of diarrhoea in studies of ETF.

Diarrhoea during ETF may result in a number of problematic complications. For example, patients may develop fluid and electrolyte abnormalities and require fluid support or anti-diarrhoeal medication (Stroud *et al.* 2003). Patients with diarrhoea are at greater risk of faecal incontinence (Bliss *et al.* 2000), which may contribute to infection of surgical or pressure wounds. However, there is limited evidence that diarrhoea impedes formula delivery in patients in the ICU (Reid, 2006) or in general hospital wards (Whelan *et al.* 2006b) who receive ETF. Furthermore, although diarrhoea during ETF may seem unpleasant, there is little information about the burden of diarrhoea to the patient, the nurse or the carer. Indeed, in a

study of patients receiving ETF via percutaneous endoscopic gastrostomy at home, only a small minority of patients perceived diarrhoea to be a major difficulty (Brotherton *et al.* 2006). Further investigation of the impact of diarrhoea on the patient receiving ETF is required.

Diarrhoea is a common and problematic complication during ETF. The aim of the present review is to discuss the pathogenesis of diarrhoea during ETF, with a particular focus on the colonic microbiota, and to discuss the use of probiotics and prebiotics in the prevention of diarrhoea during ETF.

### Pathogenesis of diarrhoea during enteral tube feeding

Several factors have been identified that contribute to the pathogenesis of diarrhoea in patients receiving ETF, including antibiotic prescription, enteropathogenic colonization and abnormal colonic responses to ETF.

Antibiotic prescription is common in the hospital setting, with one study (Bliss *et al.* 1998) reporting that 93% of patients receiving ETF were also prescribed at least one antibiotic. Some prospective studies in patients receiving ETF (Keohane *et al.* 1984; Guenter *et al.* 1991; Bleichner *et al.* 1997) report the incidence of diarrhoea to be higher in those patients prescribed antibiotics than in those not prescribed antibiotics, whilst other studies (Kelly *et al.* 1983; Schultz *et al.* 2000) report no difference in the incidence of diarrhoea. One potential explanation for these conflicting results may be that it is not antibiotic prescription *per se*, but the duration of antibiotic prescription that is relevant. An association between the duration of antibiotic prescription and the incidence of diarrhoea has been demonstrated in studies in hospitalized patients (Wistrom *et al.* 2001) and those receiving ETF (Heimbürger *et al.* 1994).

Enteropathogenic colonization, particularly with *Clostridium difficile*, is also a cause of diarrhoea during ETF. *Clostridium difficile* is a Gram-positive spore-forming enteropathogen that can cause *C. difficile*-associated diarrhoea (CDAD) and pseudomembranous colitis (Mylonakis *et al.* 2001). One prospective cohort study of residents in a long-term care facility (Simor *et al.* 1993) has demonstrated that ETF is an independent risk factor for *C. difficile* colonization (OR 6.5,  $P = 0.006$ ). Meanwhile, a case-control study of seventy-six patients receiving ETF who were matched for age, ward and disease severity with seventy-six patients not receiving ETF (Bleichner *et al.* 1997) has demonstrated that ETF is a risk factor for *C. difficile* colonization (OR 3.1,  $P = 0.03$ ) and CDAD (OR 9.0,  $P = 0.049$ ).

The causes of an increased risk of enteropathogenic colonization are unclear. One suggestion is that contamination of the enteral formula may be responsible. Contamination has been associated with decanting of formula (Beattie & Anderton, 2001), the absence of adequate quality-control protocols (Oliveira *et al.* 2001) and home ETF (Anderton *et al.* 1993). However, there is contrasting evidence of a link between formula contamination and enteropathogenic colonization or diarrhoea. For example,

one prospective cohort study of twenty-five patients receiving ETF (Okuma *et al.* 2000) has demonstrated that those patients with diarrhoea ( $n = 2$ ) are more likely to be receiving contaminated formula, whereas other studies (Belknap *et al.* 1990; Mathus-Vliegen *et al.* 2000) have found no such association. In addition, the redesign of formula delivery systems has dramatically reduced exogenous contamination (McKinlay *et al.* 2001), indicating that any remaining contamination is now likely to be endogenous (e.g. retrograde contamination from the patient's stomach or lungs; Mathus-Vliegen *et al.* 2006). Further research is required to identify the exact causes of enteropathogenic colonization in patients receiving ETF.

Abnormal colonic responses to ETF have been demonstrated in a number of *in vivo* segmental colonic perfusion studies. For example, intra-gastric ETF causes an abnormal secretion of water into the ascending colon (Bowling *et al.* 1994), which in the absence of compensatory absorptive mechanisms is likely to contribute to diarrhoea. Interestingly, when SCFA are infused into the caecum this abnormal water secretion is reversed (Bowling *et al.* 1993).

The mechanism of this abnormal colonic water secretion is still unclear, but is likely to involve neuro-humoral mechanisms initiated in the proximal gastrointestinal tract. The production of peptide YY, a polypeptide that promotes colonic water absorption (El-Salhy *et al.* 2002), is not stimulated during intra-gastric ETF (Bowling & Silk, 1996). It has been suggested (Bowling & Silk, 1998) that whatever causes the abnormal colonic water secretion during intra-gastric ETF may be inhibited by peptide YY. Interestingly, an ileal infusion of SCFA stimulates peptide YY production (Cuhe *et al.* 2000), thus providing a potential mechanism through which SCFA can reverse the abnormal colonic water secretion during ETF.

Antibiotic prescription, enteropathogenic colonization and abnormal colonic responses all contribute to the pathogenesis of diarrhoea in patients receiving ETF. Each of these mechanisms is likely to involve an interaction with the colonic microbiota. For example, concentrations of colonic microbiota (Sullivan *et al.* 2001) and SCFA (Clausen *et al.* 1991) undergo substantial alterations during antibiotic prescription. The colonic microbiota may prevent enteropathogenic infection via colonization inhibition and competitive exclusion, whilst they also ferment carbohydrates and proteins to produce SCFA that reverse abnormal colonic water secretion. Thus, it is possible that alterations to the colonic microbiota are involved in the pathogenesis of diarrhoea in patients receiving ETF.

### Enteral tube feeding and the colonic microbiota

The colonic microbiota is a complex and diverse microbial ecosystem. Although there may be >500 species present, forty different species contribute to approximately 99% of bacterial numbers (Mai & Morris, 2004).

In view of their potential role in the pathogenesis of diarrhoea during ETF a number of studies have investigated the impact of enteral formula on the colonic microbiota of healthy subjects and of patients receiving ETF (Whelan *et al.* 2004a). However, many of these early

studies report conflicting results, perhaps as a result of major methodological weaknesses, including small sample sizes, the additional use of enemas or laxatives and the reliance on traditional bacterial culture (Winitz *et al.* 1970; Attebery *et al.* 1972; Bornside & Cohn, 1975). Thus, more-recent studies have sought to accurately quantify the effects of an enteral formula on the colonic microbiota.

One study of ten healthy subjects consuming standard (fibre-free) enteral formula as the only source of nutrition for 2 weeks (Whelan *et al.* 2005) has demonstrated large reductions in faecal bacteria and total SCFA, acetate, propionate and butyrate concentrations, together with an increase in faecal pH. This reduction in total bacteria would be likely to reduce the ability of the colonic microbiota to perform colonization inhibition and competitive exclusion, whilst the reduction in SCFA may impact on colonocyte water absorption.

In another study (Schneider *et al.* 2000) eight patients receiving long-term standard ETF were shown to have higher concentrations of aerobes, lower concentrations of anaerobes and yet similar concentrations of faecal SCFA compared with ten healthy controls. However, this difference in aerobe:anaerobe may be partly explained by differences in age between the patients and the controls (Hopkins *et al.* 2001).

Enteral formula may therefore result in alterations to the colonic microbiota. Such alterations have been shown in some studies to be associated with the incidence of diarrhoea in patients receiving ETF. For example, the resolution of diarrhoea in twenty patients receiving ETF was shown to result in a reduction in the concentration of faecal aerobes and an increase in the concentrations of total faecal SCFA, acetate and propionate following supplementation with  $\leq 28$  g galactomannan soluble fibre/d (Nakao *et al.* 2002). However, whether these changes are associated with the resolution of diarrhoea or the treatment with galactomannan, or are merely a result of less-dilute faeces is unclear (Whelan *et al.* 2002). More recently, a study of twenty patients in general hospital wards (Whelan *et al.* 2004b) has demonstrated no systematic changes in the major faecal bacteria during the first 2 weeks of standard ETF. However, higher concentrations of faecal clostridia were reported in those patients who developed diarrhoea and there was a trend towards lower concentrations of bifidobacteria in those who developed diarrhoea or CDAD (Whelan *et al.* 2004b). These differences in colonic microbiota may be directly involved in the pathogenesis of diarrhoea and CDAD during ETF, or may merely be indicative of antibiotic prescription.

Alterations in the colonic microbiota occur during ETF, and these changes may be associated with the incidence of diarrhoea. There has therefore been much interest in the use of probiotics and prebiotics to prevent such alterations in the colonic microbiota and to reduce the incidence of diarrhoea.

### Probiotics in enteral tube feeding

A probiotic can be defined as a 'preparation of, or a product containing, viable, defined micro-organisms in

sufficient numbers, which alter the microbiota by implantation or colonization in a compartment of the host and by that exert beneficial health effects in this host' (Schrezenmeir & de Vrese, 2001). Probiotic preparations and products most commonly contain strains of lactobacilli, bifidobacteria or saccharomyces, or mixtures of these strains. Probiotics should fulfill strict criteria before consideration for use in patients receiving ETF, including safety, viability during processing and storage, gastrointestinal survival and function (Tuomola *et al.* 2001).

Safety is an essential characteristic for probiotic use in patients receiving ETF and, although rare, a number of case reports of infection or sepsis following probiotic use have been reported (Munoz *et al.* 2005). Those individuals at particular risk of probiotic sepsis include immunocompromised patients, premature infants, patients with a central venous catheter and those in whom the probiotic is delivered via jejunostomy (Boyle *et al.* 2006). However, the clinical safety of *Lactobacillus casei* Shirota ( $10^7$  colony-forming units/d) was demonstrated in twenty-eight paediatric patients in the ICU who received ETF, none of whom developed positive lactobacillus growth in any of the bodily fluids (e.g. blood, urine, endotracheal aspirates) or surface swabs (e.g. skin, central catheter tips) analysed (Srinivasan *et al.* 2006).

Strain viability is also essential, particularly as the probiotic preparation may spend much time stored in hospital wards or in the patient's home or nursing home before use. In the UK some capsule and powdered probiotics have been shown to have low bacterial concentrations (Hamilton-Miller, 1996; Hamilton-Miller *et al.* 1999), whereas in general fermented milks have been shown to have satisfactory bacterial concentrations even after storage (Whelan *et al.* 2006a).

A probiotic must also be able to survive gastrointestinal transit, as its major site of action is in the colon. Although a number of probiotics have been shown to survive gastrointestinal transit in healthy subjects, few studies have investigated survival in patients receiving ETF. The composition of the enteral formula and its mode of delivery may alter gastric acid (Hsu *et al.* 2006) and biliary secretions (O'Keefe *et al.* 2003), both of which will impact on probiotic survival. *Bifidobacterium longum* ( $5 \times 10^9$  colony-forming units/d, together with 2.5 g fructo-oligosaccharides (FOS)) when administered to seven patients receiving long-term standard ETF was found to result in an increase in faecal bifidobacteria in some, but not all, patients (Del Piano *et al.* 2004). Meanwhile, in the study of paediatric patients receiving ETF on the ICU (Srinivasan *et al.* 2006), *Lactobacillus casei* Shirota ( $10^7$  colony-forming units/d) was shown to survive gastrointestinal transit in five of six patients tested.

Once a probiotic has survived gastrointestinal transit it must then function to reduce the incidence of diarrhoea, possibly through the suppression of enteropathogenic colonization, immune stimulation and modulation of colonic metabolism (Whelan *et al.* 2001; Table 1).

In view of the mechanisms of diarrhoea during ETF, the alterations in colonic microbiota that may exist in these patients and the potential functions of probiotics (Table 1), a number of clinical trials have investigated the effect of

**Table 1.** Examples of potential mechanisms through which probiotics and prebiotics may prevent diarrhoea in patients receiving enteral tube feeding (ETF)

Mechanism	Examples in probiotics	Examples in prebiotics
Suppression of enteropathogens		
(a) Lumen colonization resistance		
Antimicrobial production	Some bifidobacteria, and their products, inhibit <i>Salmonella typhimurium</i> infection in mice (Lievin <i>et al.</i> 2000)	–
Reduction in pH	<i>Lactobacillus johnsonii</i> La1 decreases faecal pH in healthy human subjects (Yamano <i>et al.</i> 2006)	Oligosaccharides reduce faecal pH in infants (Knol <i>et al.</i> 2005)
(b) Mucosal competitive exclusion		
Steric and chemical hindrance	Some lactobacilli, and their products, inhibit adhesion of <i>Escherichia coli</i> and <i>S. typhimurium</i> to Caco-2 and HT29 cell lines (Bernet-Camard <i>et al.</i> 1997)	Potential for oligosaccharides to act as a 'decoy' to enteropathogenic adhesion to enterocytes (Gibson <i>et al.</i> 2005)
Immune stimulation		
Non-specific immunity	Some lactobacilli and bifidobacteria enhance phagocytosis against <i>E. coli</i> in human blood (Schiffrin <i>et al.</i> 1997)	Possible effects, although too few human studies (Watzl <i>et al.</i> 2005)
Specific immunity	Specific IgA production in healthy human subjects (Link-Amster <i>et al.</i> 1994)	Possible effects, although too few human studies (Watzl <i>et al.</i> 2005)
Colonic metabolism		
SCFA production	<i>S. boulardii</i> increases butyrate and total SCFA in patients receiving ETF (Schneider <i>et al.</i> 2005)	FOS enhance SCFA production in pure and faecal culture (Rossi <i>et al.</i> 2005)

FOS, fructo-oligosaccharides.

probiotics in preventing diarrhoea in patients receiving ETF.

Heimbürger *et al.* (1994) have conducted a randomized controlled trial in forty-one patients starting ETF. Eighteen patients were randomly assigned to receive *Lactobacillus acidophilus* and *Lactobacillus bulgaricus* (1 g three times daily), with the remaining patients receiving an identically-packaged placebo (lactose and dextrose). However, when comparing patients in the probiotic group with those in the control group there were no significant differences in faecal weight or the incidence of diarrhoea (31 and 11% of patients developed diarrhoea respectively;  $P = 0.21$ ).

Bleichner *et al.* (1997) have conducted a multi-centre randomized controlled trial of 128 patients in the ICU starting ETF. Sixty-four patients were randomly assigned to receive *Saccharomyces boulardii* (500 mg four times daily), with the remaining patients receiving an identically-packaged placebo. There were 25% fewer diarrhoea days in those patients receiving *S. boulardii* compared with placebo (14 and 19% of patient days with diarrhoea respectively;  $P = 0.0069$ ).

The explanation for these contrasting results is likely to be a result of differences in methodology and the probiotic used. For example, Heimbürger *et al.* (1994) measured the incidence as the percentage of patients with diarrhoea, rather than the preferred method of the percentage of patient days with diarrhoea (Bliss *et al.* 1992) as used by Bleichner *et al.* (1997). Furthermore, lactobacilli produce lactate as the main fermentation product, whereas *S. boulardii* has been shown to increase faecal concentrations of total SCFA and butyrate in patients receiving long-term ETF (Schneider *et al.* 2005).

### Prebiotics in enteral tube feeding

A prebiotic is defined as a 'non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improving host health' (Gibson & Roberfroid, 1995). In order to be classified as a prebiotic a compound must resist digestion by human enzymes, undergo colonic fermentation and result in the selective growth of beneficial bacteria (Roberfroid, 2001).

The most extensively studied prebiotics are the FOS oligofructose and inulin. They are resistant to small intestinal digestion because of the inability of human gastrointestinal enzymes to hydrolyse the  $\beta$ 2–1 glycosidic bonds between the fructose monomers (Oku & Nakamura, 2003). FOS have therefore shown high recovery rates in ileostomy effluent (Ellegard *et al.* 1997).

Although resistant to small-intestinal digestion, FOS are not recovered from the faeces of healthy subjects, suggesting rapid colonic fermentation (Alles *et al.* 1996). *In vitro* studies have demonstrated that FOS are fermented into lactate and acetate, some of which is then converted into butyrate (Morrison *et al.* 2006).

A number of studies have shown that FOS increase the concentration of faecal bifidobacteria when provided as a dietary supplement (Kolida *et al.* 2002). Their selectivity in stimulating bifidobacterial growth is considered to be more effective than that of any of the other candidate prebiotics (Palframan *et al.* 2003).

The effect on the colonic microbiota of supplementing an enteral formula with FOS has been investigated in a number of studies in both healthy subjects and patients

receiving ETF (Whelan *et al.* 2004a). Consumption of an enteral formula supplemented with FOS (10 g/l) was shown to result in an increase in faecal bifidobacteria in nine healthy subjects (Garleb *et al.* 1996). Meanwhile, consumption of an enteral formula supplemented with short-chain FOS (5.1 g/l) and fibre (8.9 g/l) was found to result in an increase in bifidobacteria and a reduction in clostridia whilst maintaining faecal concentrations of total SCFA in ten healthy subjects (Whelan *et al.* 2005). This finding is particularly important as patients with diarrhoea during ETF have been shown to have a trend towards lower concentrations of bifidobacteria, higher concentrations of clostridia (Whelan *et al.* 2004b) and lower concentrations of total SCFA (Nakao *et al.* 2002).

Surprisingly, the promising effects of FOS on the colonic microbiota have not been confirmed in studies in patients receiving ETF. Schneider *et al.* (2006) have conducted a prospective randomized cross-over trial in fifteen patients receiving long-term ETF. Formula supplemented with a mixture of fibres (including FOS at an intake of 2.4–3.8 g/d) was found to result in an increase in faecal concentrations of total bacteria and bacteroides, but had no effect on faecal bifidobacteria. It is possible that the quantity of FOS was insufficient to selectively stimulate growth of bifidobacteria (Bouhnik *et al.* 1999). However, increases in acetate, butyrate and total SCFA were found following ETF with the fibre–FOS formula (Schneider *et al.* 2006).

Prebiotics that undergo colonic fermentation and stimulate the growth of bifidobacteria may, like probiotics, function to reduce the incidence of diarrhoea through the suppression of enteropathogenic colonization, immune stimulation and modulation of colonic metabolism (Table 1). For example, oligofructose has recently been shown to reduce the incidence of recurrent CDAD in hospitalized inpatients, albeit in those not receiving ETF (Lewis *et al.* 2005).

Despite the existence of alterations in the colonic microbiota of patients with diarrhoea during ETF (Nakao *et al.* 2002; Whelan *et al.* 2004b) and the potential mechanisms through which prebiotics may prevent diarrhoea, there are few trials that have investigated the effect of prebiotics on its incidence. Those studies that have been conducted have used fibre formulas containing an additional but unspecified quantity of FOS (Vandewoude *et al.* 2005) or have used a compound with uncertain prebiotic characteristics (Spapen *et al.* 2001; Rushdi *et al.* 2004).

Vandewoude *et al.* (2005) randomly assigned seventy older patients to receive an enteral formula containing fibre (30 g/d, including an unspecified amount of inulin) and eighty-five patients to receive a standard formula. The patients who received the fibre–inulin formula were found to have a lower faecal frequency (4.1 *v.* 6.3 faeces per week;  $P = 0.008$ ) and more formed faeces (31% *v.* 21% formed faeces;  $P = 0.001$ ) than the patients who received standard formula. However, this finding may be partly explained by the greater use of laxatives in the control group. A number of studies have demonstrated that guar gum (Rushdi *et al.* 2004) or partially-hydrolysed guar gum (Spapen *et al.* 2001) reduces the incidence of diarrhoea

in patients receiving ETF. However, whether these compounds are able to selectively stimulate the growth of beneficial bacteria (e.g. bifidobacteria) in patients receiving ETF, and therefore can be defined as prebiotic, is uncertain.

### Other effects of probiotics and prebiotics in enteral tube feeding

A number of randomized controlled trials in patients receiving ETF have investigated the effect of probiotics and prebiotics on clinical outcomes other than the incidence of diarrhoea. For example, probiotics have been shown to result in reductions in bacterial translocation following liver transplantation (Rayes *et al.* 2005), pancreatic sepsis in patients with acute pancreatitis (Olah *et al.* 2002) and antibiotic prescription in patients following gastrointestinal surgery (Rayes *et al.* 2002). Only one of these studies (Rayes *et al.* 2005) has measured the incidence of diarrhoea as an outcome, demonstrating no difference in incidence between patients receiving a formula supplemented with a prebiotic and those receiving a formula supplemented with both a probiotic and a prebiotic. However, the incidence of diarrhoea was not a primary outcome of this study and the criteria for its definition were not provided. Finally, a recent meta-analysis (Watkinson *et al.* 2007) has found that in the ICU the delivery of probiotics, prebiotics or both probiotics and prebiotics (synbiotics) has no impact on length of stay, mortality or the risk of nosocomial infections or pneumonia.

### Conclusion

The pathogenesis of diarrhoea in patients receiving ETF involves an interaction between antibiotic prescription, enteropathogenic colonization, abnormal colonic responses and alterations in the colonic microbiota. Methods of manipulating the colonic microbiota may therefore reduce the incidence of diarrhoea in this patient group, and probiotics and prebiotics have been investigated to this end. However, conclusive results from clinical trials are lacking. The yeast *S. boulardii* has been shown to reduce the incidence of diarrhoea in patients in the ICU receiving ETF. However, although FOS have prebiotic effects in healthy subjects, their ability to increase faecal bifidobacteria and reduce the incidence of diarrhoea in patients receiving ETF has not been demonstrated. Thus, the recent Guidelines on Enteral Nutrition from the European Society of Parenteral and Enteral Nutrition recommend that 'a combination of different fibers, probiotics and prebiotics should be studied because of synergistic effects in different diseases' (Lochs *et al.* 2006).

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