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Diarrhoea during enteral nutrition is predicted by the poorly absorbed short-chain carbohydrate (FODMAP) content of the formula

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SUMMARY

Background
Although it is recognized that diarrhoea commonly complicates enteral nutrition, the causes remain unknown.

Aim
To identify factors associated with diarrhoea in patients receiving enteral nutrition with specific attention to formula composition.

Methods
Medical histories of in-patients receiving enteral nutrition were identified by ICD-10-AM coding and randomly selected from the year 2003 to 2008. Clinical and demographic data were extracted. Formulas were classified according to osmolality, fibre and FODMAP (fermentable oligo-, di- and mono-saccharides and polyols) content.

Results
Formula FODMAP levels ranged from 10.6 to 36.5 g/day. Of 160 patients receiving enteral nutrition, 61% had diarrhoea. Univariate analysis showed diarrhoea was associated with length of stay >21 days (OR 4.2), enteral nutrition duration >11 days (OR 4.0) and antibiotic use (OR 2.1). After adjusting for influencing variables through a logistic regression model, a greater than five-fold reduction in risk of developing diarrhoea was seen in patients initiated on Isosource 1.5 ($P = 0.029$; estimated OR 0.18). The only characteristic unique to this formula was its FODMAP content, being 47–71% lower than any other formula.

Conclusions
Length of stay and enteral nutrition duration independently predicted diarrhoea development, while being initiated on a lower FODMAP formula reduced the likelihood of diarrhoea. As retrospective evaluation does not support a cause–effect relationship, an interventional study investigating FODMAPs in enteral formula is indicated.

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INTRODUCTION

Diarrhoea commonly complicates hospital admission, resulting in increased health care costs, in addition to impacting patient's quality of life.[1–3] While it is known that certain medications cause or contribute to non-infectious diarrhoea,[1, 3–5] defining mechanisms that underlie the common occurrence of diarrhoea in patients receiving enteral nutrition (EN) remains poorly explored.[6–10]

Frequently, the enteral formula is blamed for inducing diarrhoea. Fibre has received the most attention with 13 controlled studies reported. Meta-analysis concluded that fibre significantly reduces the incidence of diarrhoea (OR 0.68), but the types of fibre used and the dosage of fibre varied considerably. Furthermore, the positive effect was not seen in populations from an intensive care setting and was mainly observed where the incidence of diarrhoea was very high in both the fibre and no-fibre control groups.[11] The strategy of offering low osmolality enteral formulas to decrease the risk of diarrhoea remains unexplored. Other factors implicated in the cause of diarrhoea in EN include the mode of delivery,[12, 13] contamination of EN equipment with micro-organisms,[7] colonization of bacteria and fungi along enteral feeding tubes, acquisition of *Clostridium difficile* (*C. difficile*) from postpyloric feeding[14] and the artificial nature of EN itself which alters digestion and possibly absorption.[12]

A recently presented but untested hypothesis is that diarrhoea may be induced by the presence in enteral formula of poorly absorbed short-chain carbohydrates, which have been collectively termed FODMAPs (fermentable oligo-, di- and mono-saccharides and polyols[15]).[16] FODMAPs are found in a wide variety of foods including lactose (in milk), fructose in excess of glucose (in mango and honey), fructans (in onion, garlic, wheat and rye), galacto-oligosaccharides (in legumes), and polyols (in stone fruit and some artificial sweeteners).[17] Restricting the intake of dietary FODMAPs has been shown to improve gastrointestinal symptoms, including diarrhoea, in a majority of patients with irritable bowel syndrome (IBS)[18, 19] and inflammatory bowel disease.[20] A randomized, placebo-controlled rechallenge trial confirmed that this response was not a placebo effect and was due to the reduction of FODMAPs.[19] The mechanism by which restriction of FODMAPs provides this benefit is through their small molecular size and osmotic activity.[21, 22] FODMAPs are also rapidly fermented by bacteria and the subsequent luminal distension might lead to secondary motility disturbance and diarrhoea.[23]

The current study aimed to examine the clinical predictors of diarrhoea in patients receiving EN, with specific attention to the association of the composition of the enteral formulas.

METHODS

Patients

The medical histories of adult patients, admitted to Box Hill Hospital, were selected over three random time periods between 2003 and 2008: 1 March to 30 September 2003, 1 June to 31 December 2005, and 1 April 2007 to 30 June 2008. Patients receiving EN were identified by ICD-10-AM coding (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification). Patients less than 18 years of age, with inflammatory bowel disease, receiving postpyloric EN and receiving EN for less than 3 days were excluded. The study protocol was approved by the Eastern Health Research and Ethics Committee.

Data collection

Clinical and demographic data were collected from the histories in addition to all documentation of EN regimens, faecal output and methods of treating diarrhoea. Details of faecal consistency and weight were described through documentation by nursing staff. For the purpose of this study, diarrhoea was defined as four or more bowel actions daily and/or bowel actions described as 'loose' or 'ooze'.

Formula composition

All enteral formulas used in this study were supplied by Novartis Medical Nutrition (Novartis Consumer Health Australasia Pty. Ltd., Mulgrave, Vic., Australia), overtaken by Nestlé Nutrition July 2007 (Nestlé Healthcare Nutrition, Notting Hill, Vic., Australia), with the exception of two Abbott Nutrition formulas (Abbott Australasia Pty. Ltd., Botany, NSW, Australia), each of which was used in one study participant when the Novartis Medical Nutrition equivalent formula was unavailable. The composition of formulas was obtained from published nutrition information[24, 25] and categorized into components that might potentially influence faecal output; fibre-containing or fibre-free (no fibre) and low (<500 mOsm/L) or high osmolality (≥500 mOsm/L).

To determine FODMAP content of the main formulas used, formulas were prepared according to the Food Standards Australia New Zealand (Canberra, Australia) food sampling procedure. Samples were extracted and

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analysed in triplicate. From each formula, 5 g was accurately weighed and diluted with 80 mL of distilled water, which was heated to 80 °C. The solution was then placed on a magnetic stirrer and temperature was maintained at 80 °C for 15 min so that the sample was completely dispersed. The solution was then cooled slightly, adjusted to 100 mL and filtered through 0.22 μm sterile Millex GP syringe driven filler units (Millipore, Carrigtwohill, Co. Cork, Ireland). High-performance liquid chromatography (HPLC) was used to quantify all FODMAPs, except total fructans, as described in detail in Muir *et al.*[17, 26] Identified FODMAPs include galacto-oligosaccharides (raffinose, stachyose and verbascose), fructose (in excess of glucose), lactose and polyols (sorbitol and mannitol).[17, 26] Total fructan content was determined by commercially available enzymatic kits (Megazyme Fructan HK Assay Kit; Megazyme International Ireland Ltd., Wicklow, Ireland), also described in Muir *et al.*[17, 26]

Statistical analyses

All descriptive data, including patient demographics, were non-parametric and presented as median and interquartile range. Comparison with matching subgroups was made using Kruskal–Wallis with *post hoc* Dunn's multiple comparison analysis. Incidence of diarrhoea from differing variables underwent univariate analysis and was presented as chi-square *P* value and an odd's ratio (OR) with 95% confidence intervals (CI). Multivariate analysis of the same variables was performed by logistic regression. All statistical tests were analysed with GraphPad Prism or EViews programs. A *P* value of ≤0.05 was considered statistically significant.

RESULTS

Composition of formulas

Published nutrition information for all the formulas used in the study lacked FODMAP content, except lactose. All formulas were advertised as lactose-free, which was confirmed via HPLC analysis (Table 1). FODMAP content was based on the daily volume of formula required to provide the recommended dietary intake and adequate intake for micronutrients.[27] Qualitative and quantitative FODMAP analyses of the formulas most commonly used in this study are shown in Table 1. The common types of FODMAPs found in the enteral formulas were fructans and the galacto-oligosaccharides (GOS) raffinose and verbascose. Fructose, in excess of glucose, and polyols (sorbitol and mannitol) were present in two formulas (Table 1). Levels of FODMAPs per daily volume ranged from 10.6 g (Isosource 1.5, Novartis Medical Nutrition, Mulgrave, Vic., Australia) to 36.5 g (Novasource 2.0, Novartis Medical Nutrition, Mulgrave, Vic., Australia). Fibre content and clinical indications of formulas are also illustrated in Table 1.

Patients and the development of diarrhoea

Of 310 patient histories assessed for entry into the study, 150 were excluded as per defined exclusion criteria. Of the remaining 160, 65 underwent EN following a stroke and 46 were treated in intensive care for various reasons including respiratory distress, cardiac arrest and ruptured abdominal aortic aneurysm. The most common reason for EN in intensive care was nutrition support for ventilator-dependent patients (>85% of patients in intensive care subgroup). All remaining patients required EN to support their hypermetabolic state which was commonly secondary to cancer, sepsis or pneumonia. The details of the patients, including a comparison of the subgroups, are shown in Table 2. Diarrhoea occurred in 98 of the 160 patients receiving EN (61%). This incidence was similar in the stroke (55%) and intensive care subgroups.

The clinical response to managing diarrhoea varied. Microbiological testing of faecal specimens was conducted in 38 of the 98 EN patients with diarrhoea. The presence of *C. difficile* was demonstrated in only two patients and no other infective cause was identified. Antidiarrhoeal medication was prescribed in five, drug therapy (mainly antibiotics) was manipulated in seven. The EN regimens were altered 47 patients, specifically as a response to diarrhoea in 10. No therapeutic intervention was attempted in 74 patients.

Predictors of diarrhoea

Associations with the development of diarrhoea in the period during which EN was initiated are shown in Table 3. Diarrhoea was more common in patients with LOS greater than 21 days, patients receiving EN for greater than 11 days and patients receiving antibiotics or proton pump inhibitors. There were no significant associations between the mode of delivery, formula components or even individual formulas and the development of diarrhoea. The incidence of diarrhoea among the most commonly used formulas and the formula compositions are shown in Figure 1.

To adjust for confounding factors, thereby identifying independent predictors of diarrhoea, all variables that underwent univariate analysis were also applied to a multivariate analysis model. Initiated enteral formulas were grouped according to qualitative content of

Table 1 | Fermentable oligo-, di- and mono-saccharides and polyols content and fibre content of the most commonly used enteral formulas. FODMAPs were measured via high-performance liquid chromatography and enzymatic assays. All formulas were lactose-free

		FODMAP content (g/day)									
			Galacto-oligosaccharides					Polyols			
Formula*	Clinical indications†	Total fructans	Raffinose	Stachyose	Verbascose	Free fructose‡	Lactose	Mannitol	Sorbitol	Total	Fibre content† (g/day) Total
Isosource 1.5	Standard formula/higher nutritional requirements	7.9	2.7	nd	nd	nd	nd	nd	nd	10.6	7.4
Fibersource HN	Standard formula	10.5	13.1	nd	9.4	nd	nd	nd	nd	33.0	12
Isosource HN	Standard formula	13.7	10.2	nd	7.1	nd	nd	nd	nd	31.0	0
Isosource	Standard formula	13.2	nd	nd	10.6	7.6	nd	0.6	nd	32.0	0
Resource Diabetic TF	Diabetic patients	11.9	nd	nd	nd	7.4	nd	nd	0.84	20.1	17.8
Novasource Renal	Renal failure	7.4	15.6	nd	nd	nd	nd	nd	nd	23.0	0
Novasource 2.0	Cachexia/fluid restriction/very high nutritional requirements	14.3	13.1	nd	9.1	nd	nd	nd	nd	36.5	0

nd, not detected.

* Supplied by Novartis Medical Nutrition (Novartis Consumer Health Australasia Pty. Ltd., Mulgrave, Vic., Australia).

† Published by Novartis Medical Nutrition[25].

‡ Fructose in excess of glucose.

Table 2 | Comparison of subgroups of patients receiving enteral nutrition (EN) categorized as patients receiving EN after suffering a stroke, in intensive care unit (ICU) or for other reasons

Variable	All (n = 160)	Stroke (n = 65)	ICU (n = 46)	Other (n = 49)
Male	77 (48%)	22 (34%)	27 (59%)	28 (57%)
Age (years)	76 (66–92)*	79 (71–84)†	70 (56–79)†	75 (66–82)
Length of stay (days)	22 (15–35)*	21 (16–34)	21 (14–35)	23 (16–36)
Duration of EN (days)	11 (6–20)*	13 (7–24)	9 (5–17)	11 (7–19)
Texture modified diet	52 (33%)	31 (48%)	6 (13%)	15 (31%)
Antibiotics	97 (61%)	39 (60%)	41 (89%)	17 (35%)
Proton pump inhibitors	44 (28%)	6 (9%)	23 (50%)	15 (31%)
Laxatives	83 (52%)	47 (72%)	18 (39%)	18 (37%)

* Median (interquartile range).

† P = 0.004, comparing stroke and ICU subgroups using Kruskal–Wallis with *post hoc* Dunn's multiple comparison analysis.

FODMAPs, fibre and osmolality combinations to ensure that formulas were not analysed multiple times. For the purpose of analysis, 'low FODMAP' was arbitrarily classified as ≤10.6 g FODMAPs per daily volume of enteral formula. This cut-off represents the formula with the lowest FODMAP content per daily volume. The incidence of diarrhoea across those formula groupings, in addition to all non-formula variables that underwent univariate analysis, was applied to a logistic regression model. The multivariate analysis identified only three independent predictors of the development of diarrhoea (Table 4): LOS >21 days, EN duration >11 days and initiation with the low FODMAP, fibre-containing, high osmolality formula Isosource 1.5.

DISCUSSION

Diarrhoea is a frequent complication of EN as shown by almost two in three patients being affected in the present series. Diarrhoea is a major nursing problem in ill patients, including those in intensive care or with mobility problems following a stroke, and may compromise other management such as maintaining fluid and electrolyte balance. There is therefore a definite need to prevent its development in patients receiving EN.

There are many risk factors for hospitalized patients developing diarrhoea. Antibiotic use is one example, and the likelihood of these risk factors influencing patients increases with increasing LOS. Thus, to determine associations of enteral formula with the development of diarrhoea, all possible influences on diarrhoea had to be taken into account. Indeed, there was a four-fold increased risk of diarrhoea when LOS was greater than 21 days and the duration of EN more than 11 days, and two-fold increased risk when antibiotics were used. No clear associations with enteral formula and mode of delivery were identified.

Given that univariate analysis identified several factors apparently associated with the development of diarrhoea, it is important to adjust for potentially confounding variables. This was particularly important in the current study, as many patients were taking medications that are well documented to cause diarrhoea[2, 3] (including antibiotics and laxatives). Multivariate analysis that included all variables, as shown in Table 4, was performed. One enteral formula was identified as protective, with a greater than five-fold reduction in risk of complicating diarrhoea, independent of other variables. The only characteristic that was unique to that protective formula was its lower FODMAP content.

Most previous works on the characteristics of EN that are associated with diarrhoea have concentrated on the risk of infectious diarrhoea due either to the enteral feeding equipment and sterility of the formula,[7] or to the fibre content of the formula itself.[28–31] Other issues often discussed, but with minimal evidence base, are the osmolality of the formulas and mode of EN delivery (bolus vs. continuous feeding). In the current study, strict adherence to EN hygiene practice protocols was maintained and this has been shown to decrease risk of diarrhoea associated with micro-organisms acquired from external sources.[7] Mode of delivery, osmolality and fibre content of the formulas showed no association with the risk of developing diarrhoea. It might have been anticipated that fibre-supplemented formulas were

Table 3 | Univariate analysis of associations with diarrhoea in patients receiving enteral nutrition

Variable	Diarrhoea present (%)	*P* value	OR (95% CI)
Age >65 years	77/123 (63)	0.522	1.28 (0.605–2.69)
Age ≤65 years	21/37 (57)		
Stroke unit	36/65 (55)	0.208	0.661 (0.346–1.26)
Not stroke unit	62/95 (65)		
Intensive care unit	32/46 (70)	0.170	1.66 (0.801–3.45)
Not Intensive care unit	66/114 (58)		
Length of stay >21 days	**62/80 (78)**	**<0.001**	**4.21 (2.12–8.35)**
Length of stay ≤21 days	**36/80 (45)**		
EN duration >11 days	**61/79 (77)**	**<0.001**	**4.03 (2.03–7.99)**
EN duration ≤11 days	**37/81 (46)**		
Antibiotics	**72/107 (67)**	**0.026**	**2.14 (1.09–4.19)**
No antibiotics	**26/53 (49)**		
Proton pump inhibitors	**33/45 (73)**	**0.050**	**2.12 (0.993–4.51)**
No proton pump inhibitors	**65/115 (57)**		
Laxatives	49/83 (59)	0.551	0.824 (0.435–1.56)
No laxatives	49/77 (64)		
Texture modified diet	35/52 (67)	0.966	1.03 (0.271–3.90)
No texture modified diet	8/12 (67)		
Initiated bolus delivery	16/32 (50)	0.208	1.65 (0.754–3.59)
Initiated continuous delivery	79/127 (62)		
Initiated fibre-containing	35/67 (52)	0.899	1.04 (0.554–1.96)
Initiated fibre-free	49/92 (53)		
Initiated low osmolality	18/37 (49)	0.589	0.816 (0.391–1.71)
Initiated high osmolality	65/121 (54)		
Initiated Isosource 1.5	7/20 (35)	0.093	2.28 (0.856–6.06)
Not initiated Isosource 1.5	76/139 (55)		
Initiated Fibersource HN	34/61 (56)	0.522	0.811 (0.426–1.54)
Not initiated Fibersource HN	49/98 (50)		
Initiated Isosource HN	22/46 (48)	0.420	1.33 (0.667–2.64)
Not initiated Isosource HN	62/113 (55)		
Initiated Resource Diabetic TF	7/10 (70)	0.252	0.452 (0.113–1.82)
Not initiated Resource Diabetic TF	77/150 (51)		

Statistically significant variables (chi-square analysis) are shown in bold.

protective of diarrhoea, especially since a meta-analysis of interventional studies of fibre in the feed indicated a reduction of 30% in the incidence of diarrhoea in hospitalized patients.[11] Reasons for the lack of association in the present study remain uncertain. Furthermore, contrary to the meta-analysis findings, the only formula that was associated with a reduced risk of diarrhoea (Isosource 1.5) had a relatively low fibre content of 7.4 g per specified daily volume to meet recommended dietary and adequate intake for micronutrients. While the required amount of fibre needed to decrease the incidence of diarrhoea has not been determined, most stud-

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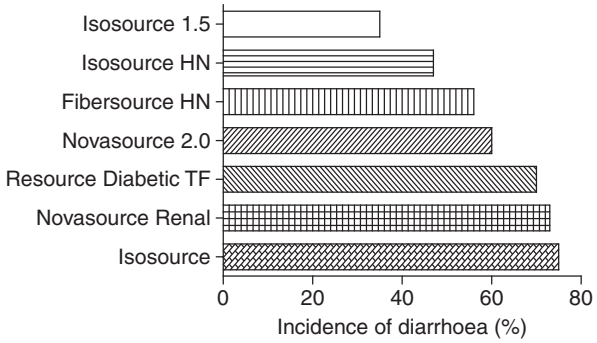

FODMAP content (g)	Fibre content (g)	Osmolality (mOsm/L)
10.6	7.4	650
31.0	0	490
33.0	12	490
36.5	0	790
20.1	17.8	400
23.0	0	700
31.0	0	490

Figure 1 | Incidence of diarrhoea among enterally fed patients while on initiating formula. Osmolality, FODMAP content and fibre content of each formula are shown.

Table 4 | Results of multivariate analysis, using logistic regression model, showing the incidence of diarrhoea and estimated odds ratio (OR) among enterally fed patients. Formulas were grouped into combinations of low and high FODMAP, fibre-free and fibre-containing, and low and high osmolality. For the purpose of this analysis, low FODMAP was defined as ≤10.6 g per daily volume of enteral formula

Variable	*n*	Diarrhoea present (%)	*P* value	Estimated OR
Age >65 years	123	77 (63)	0.840	1.10
Stroke unit	65	36 (55)	0.637	0.785
Intensive care unit	42	32 (76)	0.505	1.46
Length of stay >21 days	**80**	**62 (78)**	**0.026**	**2.70**
EN duration >11 days	**79**	**61 (77)**	**0.021**	**2.91**
Antibiotics	107	72 (67)	0.443	1.39
Proton pump inhibitors	45	33 (73)	0.642	1.25
Laxatives	83	49 (59)	0.784	0.90
Texture modified diet	52	35 (67)	0.515	1.36
Initiated bolus delivery	32	16 (50)	0.982	1.00
Initiated Isosource 1.5*	**20**	**7 (35)**	**0.029**	**0.18**
Initiated Fibersource HN/Resource Diabetic TF†	71	41 (58)	0.273	0.49
Initiated Isosource HN/Isosource‡	50	25 (50)	0.213	0.44
Initiated Novasource Renal/Novasource 2.0§	16	11 (69)	0.938	1.07

Statistically significant predictors are shown in bold.

* Low FODMAP, fibre-containing, high osmolality.

† High FODMAP, fibre-containing, low osmolality.

‡ High FODMAP, fibre-free, low osmolality.

§ High FODMAP, fibre-free, high osmolality.

ies included in the meta-analysis used a daily fibre intake of at least 14 g.[11]

Fermentable oligo-, di- and mono-saccharides and polyols are a recently described group of short-chain carbohydrates that are poorly absorbed. In high enough doses, they are laxatives in most people; sorbitol is an example of a FODMAP that is utilized as a laxative. A role of FODMAPs in enteral formulas in the induction of diarrhoea has recently been hypothesized.[16] While lactose, the FODMAP most recognized in the induction of

gastrointestinal symptoms (including diarrhoea), is routinely omitted from all enteral formulas, other FODMAPs are not similarly identified. As no other data existed on FODMAP content in enteral formulas, this was examined using well-established techniques[17, 26] on the common formulas used in the present study. The formula with the lowest FODMAP content, of 10.6 g per daily volume, was Isosource 1.5, which contained nearly one half or less of the other formulas. Interestingly, this formula was the only one associated with a considerable reduction in risk of developing diarrhoea. Whether this association was due to lower load of FODMAPs could not be addressed in the study design, but the lower FODMAP content was the only feature unique to this formula. Clearly, a randomized controlled trial will need to address if this association is indeed due to FODMAP content.

To date, the impact of FODMAPs has only been investigated in food. Translating this concept into an EN model is based on theory and therefore must be put into practice to be substantiated. Furthermore, the theory of reducing FODMAPs to prevent or control diarrhoea has only been investigated in the presence of IBS.[19] The FODMAP load known to control IBS symptoms, ≤0.5 g per sitting,[16, 32] would equate to ≤4.0 g per daily volume of enteral formula, if a sitting were a 3-h interval (to represent the average time between a meal and snack). Ideally, a low FODMAP enteral formula would be comparable to this value to be suitable for an IBS population. As no formula in the present series is ≤4.0 g FODMAPs per daily volume, Isosource 1.5 is the most reflective of a low FODMAP formula. As most patients receiving EN would probably not require as stringent a restriction as in IBS populations, the lower FODMAP content of Isosource 1.5 would still highlight its protective feature of reduced FODMAP content in preventing diarrhoea. Only excessive doses of FODMAPs, as seen in most of the formulas in this study, are expected to trigger diarrhoea in those ordinarily asymptomatic. FODMAP loading is important in predicting diarrhoea and as such, arbitrary classifications are only guides in preventing diarrhoea rather than known therapeutic measures.

There are inherent weaknesses in the design of the current study. Its retrospective nature implies dependence on the completeness and quality of documentation. A second major issue is the definition and assessment of diarrhoea, which have been a troublesome aspect for all studies examining the complications of EN. While faecal frequency could be accurately monitored by the nursing staff, faecal consistency and weight did not undergo quantitative testing. The descriptions of bowel consistency and quantity are subject to the attending nurse's opinion and relied on regular reporting. Varying opinions will result in inconsistent descriptions of faecal consistency and weight and therefore inaccuracies in the results. Auditing diarrhoea in these patients would be facilitated by the use of a validated system of reporting such as the King's Stool Chart.[33]

Another limitation of the study design is the inability to exclude infectious diarrhoea in patients that did not have microbiological investigations. Testing of faecal specimens was conducted in only one-third of patients included in the study and *C. difficile* was confirmed in only two patients (5% of patients tested). This incidence is lower than anticipated on comparison with previous studies investigating sources of diarrhoea[34, 35] and may be as a result of the preferred treatment method of the medical team. Ideally, all patients should be investigated for infectious diarrhoea and treated accordingly. A potential opportunity for treatment may have been lost in this current study. The suggested algorithm published by Barrett *et al.*[16] would best guide management strategies for EN-associated diarrhoea.

The present study's definition of diarrhoea (four or more bowel actions daily and/or descriptions of 'loose' or 'ooze' bowel actions) was chosen to favour bowel frequency and consistency. This definition reflects the two most important characteristics in determining diarrhoea[33] and the most commonly documented information. The potential to under- or over-estimate its presence must be considered in the interpretation of the findings.

In conclusion, retrospective evaluation of patients receiving EN showed that long LOS and duration of EN were independent risk factors for the development of diarrhoea. The only independent protective factor was initiation of EN with the formula comprising lowest FODMAP content. While theoretical considerations regarding the effect of FODMAPs on bowel function support a cause–effect relationship, this can only be addressed by a placebo-controlled interventional study investigating FODMAP content of the enteral formula and controlling for all other EN regimen characteristics.

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REFERENCES

1. Bishara J, Peled N, Pitlik S, Samra Z. Mortality of patients with antibiotic-associated diarrhoea: the impact of Clostridium difficile. *J Hosp Infect* 2008; **68**: 308–14.
2. Bliss DZ, Johnson S, Savik K, Clabots CR, Gerding DN. Fecal incontinence in hospitalized patients who are acutely ill. *Nurs Res* 2000; **49**: 101–8.
3. Garey KW, Graham G, Gerard L, *et al.* Prevalence of diarrhea at a university hospital and association with modifiable risk factors. *Ann Pharmacother* 2006; **40**: 1030–4.
4. Howitt JR, Grace JW, Schaefer MG, *et al.* Clostridium difficile-positive stools: a retrospective identification of risk factors. *Am J Infect Control* 2008; **36**: 488–91.
5. Raveh D, Rabinowitz B, Breuer GS, Rudensky B, Yinnon AM. Risk factors for Clostridium difficile toxin-positive nosocomial diarrhoea. *Int J Antimicrob Ag* 2006; **28**: 231–7.
6. Bleichner G, Thomas O, Sollet JP. Diarrhea in intensive care: diagnosis and treatment. *Int J Antimicrob Ag* 1993; **3**: 33–48.
7. Luft VC, Beghetto MG, de Mello ED, Polanczyk CA. Role of enteral nutrition in the incidence of diarrhea among hospitalized adult patients. *Nutrition* 2008; **24**: 528–35.
8. Montejo JC. Enteral nutrition-related gastrointestinal complications in critically ill patients: a multicenter study. The Nutritional and Metabolic Working Group of the Spanish Society of Intensive Care Medicine and Coronary Units. *Crit Care Med* 1999; **27**: 1447–53.
9. Pancorbo-Hidalgo PL, García-Fernandez FP, Ramírez-Pérez C. Complications associated with enteral nutrition by nasogastric tube in an internal medicine unit. *J Clin Nurs* 2001; **10**: 482–90.
10. Reese JL, Means ME, Hanrahan K, *et al.* Diarrhea associated with nasogastric feedings. *Oncol Nurs Forum* 1996; **23**: 59–66.
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 Pharm Therap* 2008; **27**: 120–45.
12. Bowling TE, Silk DBA. Colonic responses to enteral tube feeding. *Gut* 1998; **42**: 147–51.
13. Debnam ES, Grimble GK. Methods for assessing intestinal absorptive function in relation to enteral nutrition. *Curr Opin Clin Nutr Metab Care* 2001; **4**: 355–67.
14. Bliss DZ, Johnson S, Savik K, *et al.* Acquisition of *Clostridium difficile* and *Clostridium difficile*-associated diarrhea in hospitalized patients receiving tube feeding. *Ann Intern Med* 1998; **129**: 1012–9.
15. Gibson PR, Shepherd SJ. Personal view: food for thought–western lifestyle and susceptibility to Crohn's disease. The FODMAP hypothesis. *Aliment Pharm Therap* 2005; **21**: 1399–409.
16. Barrett JS, Shepherd SJ, Gibson PR. Strategies to manage gastrointestinal symptoms complicating enteral feeding. *JPEN - Parenter Enter* 2009; **33**: 21–6.
17. Muir JG, Rose R, Rosella O, *et al.* Measurement of short-chain carbohydrates in common Australian vegetables and fruits by high-performance liquid chromatography (HPLC). *J Agr Food Chem* 2009; **57**: 554–65.
18. Gibson PR, Newnham E, Barrett JS, Shepherd SJ, Muir JG. Review article: fructose malabsorption and the bigger picture. *Aliment Pharm Therap* 2007; **25**: 349–63.
19. Shepherd SJ, Parker FC, Muir JG, Gibson PR. Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. *Clin Gastroenterol Hepatol* 2008; **6**: 765–71.
20. Gearry RB, Irving PM, Barrett JS, *et al.* Reduction of dietary poorly absorbed short-chain carbohydrates (FODMAPs) improves abdominal symptoms in patients with inflammatory bowel disease – a pilot study. *J Crohns Colitis* 2009; **3**: 8–14.
21. Barrett JS, Gearry RB, Muir JG, *et al.* Dietary poorly absorbed, short-chain carbohydrates increase delivery of water and fermentable substrates to the proximal colon. *Aliment Pharm Therap* 2010; **31**: 874–82.
22. Wang YM, van Eys J. Nutritional significance of fructose and sugar alcohols. *Annu Rev Nutr* 1981; **1**: 437–75.
23. Ong DK, Mitchell SB, Smith S, *et al.* The intestinal fermentative response to dietary FODMAPs: failure to switch to methane production in patient with irritable bowel syndrome. *J Gastroenterol Hepatol* 2008; **23**: A200–21.
24. Anonymous. *A Total Commitment to Enteral Nutrition*. Botany: Abbott, 2008.
25. Anonymous. *Product Guide Australia*. 2nd ed. Mulgrave: Novartis, 2007.
26. Muir JG, Shepherd SJ, Rosella O, *et al.* Fructan and free fructose content of common Australian vegetables and fruit. *J Agr Food Chem* 2007; **55**: 6619–27.
27. Anonymous. *Nutrient Reference Values for Australia and New Zealand*. Ageing DoHa, editor. Canberra: Australian Government, 2005.
28. Lin H, Zhao X, Chu A, Lin Y, Wang L. Fiber-supplemented enteral formula slows intestinal transit by intensifying inhibitory feedback from the distal gut. *Am J Clin Nutr* 1997; **65**: 1840–4.
29. Sobotka L, Brátova M, Slemrová M, *et al.* Inulin as the soluble fiber in liquid enteral nutrition. *Nutrition* 1997; **13**: 21–5.
30. Vandewoude MF, Paridaens KM, Suy RA, Boone MA, Strobbe H. Fibre-supplemented tube feeding in the hospitalised elderly. *Age Ageing* 2005; **34**: 120–4.
31. Yang G, Wu X-T, Zhou Y, Wang Y-L. Application of dietary fiber in clinical enteral nutrition: a meta-analysis of randomized controlled trials. *World J Gastroentero* 2005; **11**: 3935–8.
32. Shepherd SJ, Gibson PR. Fructose malabsorption and symptoms of irritable bowel syndrome: guidelines for effective dietary management. *J Am Diet Assoc* 2006; **106**: 1631–9.
33. Whelan K, Judd PA, Preedy VR, Taylor MA. Covert assessment of concurrent and construct validity of a chart to characterize fecal output and diarrhea in patients receiving enteral nutrition. *JPEN-Parenter Enter* 2008; **32**: 160–8.
34. Chaudhry R, Joshy L, Kumar L, Dhawan B. Changing pattern of Clostridium difficile associated diarrhoea in a tertiary care hospital: a 5 year retrospective study. *Indian J Med Res* 2008; **127**: 377–82.
35. Schwaber MJ, Simhon A, Block C, *et al.* Factors associated with nosocomial diarrhea and Clostridium difficile-associated disease on the adult wards of an urban tertiary care hospital. *Eur J Clin Microbiol* 2000; **19**: 9–15.