REVIEW

Probiotics and diarrhoea management in enterally tube fed critically ill patients—What is the evidence?

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KEYWORDS
Enteral nutrition; Diarrhoea; Critical illness; Probiotics; Probiotic species; Randomised control trial

Summary

Objective: The aim of this literature review is to identify the role of probiotics in the management of enteral tube feeding (ETF) diarrhoea in critically ill patients.

Background: Diarrhoea is a common gastrointestinal problem seen in ETF patients. The incidence of diarrhoea in tube fed patients varies from 2% to 68% across all patients. Despite extensive investigation, the pathogenesis surrounding ETF diarrhoea remains unclear. Evidence to support probiotics to manage ETF diarrhoea in critically ill patients remains sparse.

Method: Literature on ETF diarrhoea and probiotics in critically ill, adult patients was reviewed from 1980 to 2010. The Cochrane Library, Pubmed, Science Direct, Medline and the Cumulative Index of Nursing and Allied Health Literature (CINAHL) electronic databases were searched using specific inclusion/exclusion criteria. Key search terms used were: enteral nutrition, diarrhoea, critical illness, probiotics, probiotic species and randomised clinical control trial (RCT).

Results: Four RCT papers were identified with two reporting full studies, one reporting a pilot RCT and one conference abstract reporting an RCT pilot study. A trend towards a reduction in diarrhoea incidence was observed in the probiotic groups. However, mortality associated with probiotic use in some severely and critically ill patients must caution the clinician against its use.

Conclusion: Evidence to support probiotic use in the management of ETF diarrhoea in critically ill patients remains unclear. This paper argues that probiotics should not be administered to critically ill patients until further research has been conducted to examine the causal relationship between probiotics and mortality, irrespective of the patient’s disease state or projected prophylactic benefit of probiotic administration.

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Introduction

Nutritional support is widely accepted as standard care for critically ill patients (Cassee et al., 2000; Heyland, 2000; Jollies et al., 1999). Approximately 60% of critically ill patients receive enteral nutrition during their intensive care unit (ICU) stay (Lee and Auyeung, 2003). A common gastrointestinal problem in enterally tube fed (ETF) patients is diarrhoea (Whelan et al., 2001). Electrolyte imbalance, dehydration, perianal skin breakdown, wound contamination, alterations in intestinal microflora, psychological embarrassment, sleep disturbances and increased health care costs may be complications associated with ETF diarrhoea. Diarrhoea management strategies and ETF practices vary widely between ICUs. This is evidenced by the disagreement seen in diarrhoea management strategies including the administration of probiotics in some critical care environments (Barbut and Meynard, 2000; Cole et al., 1998; Weisen et al., 2006; Whelan et al., 2001; Whelan et al., 2003).

Background

Enteral tube feeding

The optimal time to start nutritional support in critical illness remains unclear. It is widely accepted to commence ETF in the ICU as early as possible as ETF is purported to preserve the gut’s immunological barrier, reduce bacterial translocation, reduce rates of sepsis and multi-organ failure and improve wound healing (Davies and Bellomo, 2004; Kennedy, 1997; Lopez-Herce et al., 2008; Marshall and West, 2004). However, ETF is not without complications including diarrhoea, abdominal distension, pulmonary aspiration, hyperglycaemia, electrolyte derangement, dehydration and secondary infections (Lopez-Herce et al., 2008; Pancorbo-Hidalgo et al., 2001; Williams and Leslie, 2004). It is not uncommon for ETF to be delayed or ceased for these reasons (Adam and Batson, 1997; Heyland et al., 2003).

Diarrhoea epidemiology

The incidence of diarrhoea in ETF patients is suggested to vary between 2% and 68% (Bengmark, 2002; Bowling, 1995; Bowling and Silk, 1998; Cole et al., 1998; McNaught et al., 2005; Weisen et al., 2006; Whelan et al., 2001). However, the incidence of diarrhoea is argued to vary more widely between 2% and 95% in critically ill patients (Cataldi-Betcher et al., 1983). The variability of diarrhoea incidence reported in different subsets of hospitalised patients may be related to the inconsistencies in diarrhoea definitions and the clinical application of these definitions (Weisen et al., 2006; Whelan et al., 2003). Therefore, the prevalence of diarrhoea may depend on the definition used (Lebak et al., 2003; Weisen et al., 2006).

Diarrhoea pathogenesis

The pathogenesis of diarrhoea in critical illness remains unclear; however, diarrhoea is thought to be caused by infectious and non-infectious aetiologies (Weisen et al., 2006). The higher incidence of ETF diarrhoea in critical illness may be related to (i) microbial contamination of the ETF formula; (ii) altered colonic responses to intra gastric feeding; (iii) hypoalbuminaemia; (iv) increased use of antibiotic therapy; and (v) medications such as stool softeners, prokinetics and histamine-2 agents (Bowling, 1995; Cassee et al., 2000; Cole et al., 1998; Heyland, 2000).

Diarrhoea management strategies

Diarrhoea management remains inconsistent between ICUs. The management of diarrhoea includes diarrhoea management algorithms, rehydration, electrolyte replacement, anti-diarrhoeal medications, continuation of ETF and the administration of metronidazole or glycopeptides for Clostridium difficile (Bowling, 1995). A new addition to this debate is probiotics. In non-critically ill situations, probiotics have been shown to exert a beneficial effect on the incidence and severity of diarrhoea (Barbut and Meynard, 2000; Lee and Auyeung, 2003; Whelan et al., 2001). The place for regular probiotic administration in diarrhoea management in critical illness is not yet fully explored or understood.

Probiotics

Probiotics are defined as viable non-pathogenic microorganisms which when ingested, exert a beneficial effect and positive influence on the health and well being of the host (Fioramonti et al., 2003; Marteau and Seksik, 2002; Fioramonti et al., 2003). Current evidence suggests that probiotic effects are strain specific and the effects seen in one probiotic strain may not be seen in a different probiotic strain (Cataldi-Betcher et al., 1983). Furthermore, probiotic effects may be enhanced when prebiotic, probiotic or symbiotic preparations are administered (defined in Table 1) (Bengmark, 2005; Guarner et al., 2008; Watkinson et al., 2007). The most frequently administered probiotics include Lactobacilli, Bifidobacilli and Saccharomyces (Hamilton-Miller, 2004; Thomas et al., 2003). Probiotics are commercially available in the form of capsules, enriched yoghurts, powders and fermented milk and cheese products (Whelan et al., 2001).

Table 1

| Definitions |
|-----------------|----------------------------------|
| Prebiotic | Non-digestible substances that beneficially effect the host through selectively stimulating the growth and/or activity of indigenous bacteria. |
| Probiotic | Viable, non-pathogenic microorganisms which when ingested exert a beneficial effect and positive influence on the health and well being of the host. |
| Symbiotic | Products combining both prebiotics and probiotics. Symbiotics provide a beneficial synergistic effect to the host. |

(Cataldi-Betcher et al., 1983; Marteau and Seksik, 2002; Fioramonti et al., 2003).
For reasons of safety and efficacy, a probiotic should fulfill strict selection criteria (Whelan et al., 2001). A probiotic must have the ability to resist gastric juices and exposure to bile, be able to multiply and colonise the digestive tract and maintain safety, effectiveness and potency for the duration of its shelf life (FAO/WHO, 2001, 2002; Senok et al., 2005).

Mechanisms of action of probiotics

Although the role and beneficial effects of probiotic ingestion remains uncertain, recent studies suggest that some probiotics have been used as an adjuvant in the treatment and prevention of many diseases including diarrhoea, immunostimulation, urogenital health and cancer prevention (Bengmark, 2002; Broekaert and Walker, 2006; Gorbach, 2000; Hammitton-Miller, 2004; Klaenhammer, 2000; Manzoni, 2007; Thomas et al., 2003). Several probiotic mechanisms of action have been suggested including: (1) antagonistic activity; (2) stimulation of mucosal defence; and (3) nutrient production in the intestine (Erickson and Hubbard, 2000; Fooks and Gibson, 2002; Isolauri and Salminen, 2004; Sullivan and Nord, 2005). Recent studies suggest that probiotics exert their mechanism of action through chemical inhibition and stimulation, nutrient competition, immune clearance and competition for adhesion receptors (Bengmark, 2002). It must be emphasised that the exact mechanisms by which probiotics achieve their physiological effect(s) remain unclear (Baker and Day, 2008; Bengmark, 2002; Quigley, 2008).

The aims of this review

The aim of this literature review is to identify the role of probiotics in the management of enteral tube feeding (ETF) diarrhoea in critically ill, adult patients.

Search strategy

The studies included in this review were identified through the Cochrane Library, Pubmed, Science Direct, Medline and the CINAHL databases for English language sources published from 1980 to 2010. Key search terms used were: enteral nutrition, diarrhoea, critical illness, probiotics, probiotic species and randomised clinical control trials. Studies were included if they used a RCT design examining probiotics and ETF in critically ill, hospitalised patients experiencing diarrhoea. Combinations of critically ill and general ward patient studies were included. Studies were excluded if they: (i) did not employ an RCT design; (ii) patients were not hospitalised; and (iii) patients were not receiving ETF and probiotics. Reference lists of retrieved papers were manually checked and abstracts were reviewed by one reviewer. Papers were selected with reference to the aims of this review paper.

Results

The limited availability of research examining probiotic efficacy in the management of ETF diarrhoea in critically ill adult patients was demonstrated with only four RCT papers, two reporting full studies (Bleichner et al., 1997; Heimburger et al., 1994), one reporting a pilot RCT (Alberda et al., 2007) and one conference abstract reporting an RCT pilot study (Chaboyer et al., 2007) (see Table 2). The design and methodologies of these studies are presented in Table 2.

Discussion

This review has highlighted inconclusive evidence to support probiotic administration in critically ill, ETF patients who experience diarrhoea. The larger, multi-centre study by Bleichner et al. (1997) demonstrated a significant reduction in the percentage of diarrhoea days in patients receiving Saccharomyces boulardii (S. boulardii) from 18.9% to 14.2%.

However, the three smaller studies (Alberda et al., 2007; Chaboyer et al., 2007; Heimburger et al., 1994) showed only a trend towards less diarrhoea in the probiotic groups. The absence of a statistically significant difference might be related to a lack of power in the studies reviewed. Although statistical significance was not found in the smaller studies, a small treatment effect was observed (Alberda et al., 2007; Chaboyer et al., 2007; Heimburger et al., 1994). This suggests that probiotics may be beneficial in the treatment of ETF diarrhoea; however, larger, adequately powered studies are required to support this trend.

There are a number of other identified issues arising from the studies which were not reported (Alberda et al., 2007; Bleichner et al., 1997; Chaboyer et al., 2007; Heimburger et al., 1994). The infrequent resiting of feeding tubes may directly influence bacterial colonisation and potential development of infectious diarrhoea. Although stool cultures were reported as a non-significant cause of diarrhoea in two RCTs (Bleichner et al., 1997; Heimburger et al., 1994) it was not reported on in the two pilot studies (Alberda et al., 2007; Chaboyer et al., 2007).

The ETF preparation and administration techniques and infection control practices were inadequately reported on (Alberda et al., 2007; Bleichner et al., 1997; Chaboyer et al., 2007; Heimburger et al., 1994). Only one study reported ETF administration methods. It is known that infection control practices may vary between research sites (Alberda et al., 2007). Contamination of ETF is a known cause of diarrhoea. Although stool cultures were reported as a non-significant cause of diarrhoea in two RCTs (Bleichner et al., 1997; Heimburger et al., 1994) it was reported only in the two pilot studies (Alberda et al., 2007; Chaboyer et al., 2007).

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### Table 2 Probiotic and diarrhoea studies published between 1980 and 2010.

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<th>Intervention</th>
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<tr>
<td>Heimburger et al.</td>
<td>Prospective, randomised, double-blind, placebo-controlled trial</td>
<td>Multi-centre: ICUs and general wards, teaching and general hospitals between September 1988 and February 1991 Participants: ETF critically ill adult patients</td>
<td>Assess whether (1) antibiotics, hypoalbuminaemia or hypertonic ETF is associated with diarrhoea; (2) determine the frequency of ETF related diarrhoea; (3) does <em>Lactobacillus</em> reduce the incidence of ETF diarrhoea</td>
<td><em>L. acidophilus &amp; L. bulgaricus</em> 1 g (<em>n</em> = 18) vs. placebo (<em>n</em> = 23) TDS. Study duration not identified ETF: Osmolite HN, isocal or sustacal to maximum 10 days ICU patients (<em>N</em> = 25): Probiotic group (<em>n</em> = 13) vs. placebo group (<em>n</em> = 12) Randomisation: Stratified random assignment with regard to three putative risk factors: 1. Antibiotics; 2. Serum albumin ≤25 or ≥25 g/l; 3. ETF osmolality ≤350 or ≥350 mosmol/kg Three diarrhoea risk factors: 1. Antibiotics; 2. Hypoalbuminaemia; 3. ETF osmolality</td>
<td>1. Diarrhoea defined as the excretion of &gt;200 g of stool in 24 hours; 2. 34 patients completed 5 days of ETF without diarrhoea; 3. Diarrhoea developed in 17% (<em>n</em> = 7) of patients; 4. <em>Lactobacillus</em> did not alter risk of diarrhoea; 5. No statistical significance identified in the incidence of diarrhoea between the two groups</td>
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<td>Bleichner et al.</td>
<td>Prospective, randomised, double-blind, placebo-controlled trial</td>
<td>Multi-centre (11) ICUs in teaching and general hospitals between April 1992 and June 1993 Participants: Adult ICU patients expecting ETF &gt;6 days</td>
<td>Assess prophylactic effect of <em>S. boulardii</em> on diarrhoea in ETF critically ill patients</td>
<td><em>S. boulardii</em> 500 mg (<em>n</em> = 64) vs. placebo (<em>n</em> = 64) QID for 21 days or withdrawal of ETF ETF: Intact protein diet without fibre of lactose for minimum 6 days Randomisation: Stratified blocks of four random assignment with regard to hospital 1. 15 risk factors studied 2. Five independent risk factors: Previous TPN; Malnutrition; Hypoalbuminaemia &lt;26 g/l; Infection site; Hyper/hypothermia</td>
<td>1. Diarrhoea measured as number of days a patient experienced diarrhoea and volume and consistency of stool; 2. Frequency of diarrhoea days 18.9% (placebo) vs. 14.2% (<em>S. boulardii</em>) (<em>p</em> = 0.0069); 3. Diarrhoea days reduced by 25%; 4. Risk factor adjustment showed diarrhoea days reduced 42% vs. 25% =52% reduction</td>
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were reported as a non-significant mortality risk factor in only one study (Alberda et al., 2007). Mortality was not associated with probiotics in the studies reviewed (Alberda et al., 2007; Bleichner et al., 1997; Chaboyer et al., 2007; Heimburger et al., 1994). It may be concluded that the scientific weaknesses of probiotics such as their mechanisms of action have not been fully understood when exploring diarrhoea, ETF and mortality in critically ill patients.

**Diarrhoea and enteral formulae**

Diarrhoea is frequently defined by the number of loose stools passed each day (Elia et al., 2008; Lebak et al., 2003; Pancorbo-Hidalgo et al., 2001; Thomas et al., 2003; Whelan et al., 2003). Definitions of diarrhoea that rely on a subjective assessment of stool consistency and frequency or by the summed daily score of stool frequency, consistency and volume unreliably measure diarrhoea in the critical care environment (Duncan et al., 1997; Elia et al., 2008; Hart and Dobb, 1988; Manley et al., 2007; Pancorbo-Hidalgo et al., 2001; Thomas et al., 2003). Disparity of diarrhoea definitions was noted in all studies. Diarrhoea was identified by the duration of diarrhoea monitoring. Percentages of diarrhoea days or proportions of diarrhoea free days were inconsistently reported (Alberda et al., 2007; Bleichner et al., 1997; Chaboyer et al., 2007; Heimburger et al., 1994). The absence of a single agreed diarrhoea definition will continue to influence research outcomes and generalisation of study results in the critical care environment.

Enteral tube feeding is often cited as a diarrhoea risk factor. Putative factors associated with diarrhoea and ETF include fibre-enriched ETF, hyper-osmolality and contamination of the ETF (Lebak et al., 2003; Pancorbo-Hidalgo et al., 2001; Weisen et al., 2006; Whelan et al., 2001; Whelan et al., 2003). Clinical trials examining the effects of fibre containing ETF formulae on gastro-intestinal (GIT) function show variable results (Thomas et al., 2003).

The various ETF formulae used in the studies reviewed were inconsistently reported (Alberda et al., 2007; Bleichner et al., 1997; Chaboyer et al., 2007; Heimburger et al., 1994) (see Table 2). Diarrhoea was found to be inconsistently associated with the type of ETF formulae administered. The unpredictability of these results might be associated with the ETF formulae, duration of ETF, probiotic species administered, inadequately powered sample sizes or other confounding physiological or pharmacological reasons not reported. Interestingly, a trend to continue ETF in the presence of diarrhoea was observed in the studies reviewed (Alberda et al., 2007; Bleichner et al., 1997; Chaboyer et al., 2007; Heimburger et al., 1994).

It is important to note that the faecal intestinal flora of study participants was not examined for changes to normal GIT microbiota in the four RCTs (Alberda et al., 2007; Bleichner et al., 1997; Chaboyer et al., 2007; Heimburger et al., 1994). It would be beneficial to explore microbial changes at an individual patient level prior to administering probiotics. Should alterations to the individual’s intestinal flora occur, then it might be appropriate to consider probiotics as an adjuvant to diarrhoea management.
Probiotics and diarrhoea

Dissimilarity between probiotic species, dose and frequency of administration was evident between the studies (refer to Table 2) (Alberda et al., 2007; Bleichner et al., 1997; Chaboyer et al., 2007; Heimburger et al., 1994). Although little is understood regarding the therapeutic dose(s) of probiotic species, a minimum of $5 \times 10^6$ colony forming units (cfu) is suggested to guide the clinical benefits in most diarrhoeal and disease states (Sartor, 2004). The disparity between probiotic species and concentrations of the studies reviewed (100,000,000$^7$, 500 mg$^8$, 9 $\times 10^{11}$ bacteria$^9$, 450 billion$^{10}$ cfu) may attribute to the inconclusive findings.

The principle of using harmless bacteria to overcome pathological intestinal pathogens has been acknowledged for many years (Montrose and Floch, 2005). Probiotic ingestion by definition infers that the host will receive a physiological and therapeutic benefit (Chaboyer et al., 2007; Isolauri and Salminen, 2004). The risk of morbidity must be balanced against the sparse evidence supporting probiotic efficacy in the management of ETF related diarrhoea in critically ill patients.

*S. boulardii* is a yeast used to treat antibiotic and ETF diarrhoea in critically ill adults at a dose of 1–2 g/day. Seven cases of fungaemia were observed in critically ill, mechanically ventilated patients who were treated with broad-spectrum antibiotics and had central venous catheter access between June 1996 and October 1998 (Lherm et al., 2002). Six of these patients were treated with *S. boulardii*. Complications associated with fungaemia in critically ill and immunocompromised patients have been increasingly reported since the 1990s. Lherm et al. (2002) argue that *S. boulardii* should not be administered to critically ill or immunocompromised patients. Surprisingly, the largest study by Bleichner et al. (1997) did not report any cases of fungaemia in the *S. boulardii* treated group.

Most research to date has focused on the mechanisms by which pathogenic bacteria exert their effect (Fedorak and Madsen, 2004; Fioramonti et al., 2003; Rolfe, 2000). A better understanding of probiotics mechanism of action will result in more efficacious application to the symbiotic relationship between the host and gut barrier function.

The scientific weaknesses of probiotics have been inadequately examined and cautious use is recommended in critically ill patients. Commonly noted scientific weaknesses of probiotics which may explain the absence of a significant reduction in diarrhoea includes:

- Numerous and often inadequately described probiotic genera, species and strains with varying effects at varying endpoints in the gastrointestinal tract;
- Inadequate understanding of probiotic species and strain dosages and the efficacious window of opportunity of administration; and
- Inconsistent or inadequately stored probiotic cultures may result in reduced bacterial viability (Guarnier et al., 2008).

Why might probiotics be harmful?

Alterations to intestinal microflora during critical illness lend the intestine vulnerable to pathogenic microorganisms. Factors influencing this pathogenic environment include gut dysmotility, changes in nutrient availability, pH balance, oxygen supply/demand, increased release of stress hormones such as catecholamine, osmolality of ETF, medications and antibiotics (Singhi and Baranwal, 2008).

Theoretically, probiotics are responsible for four types of side effects including (1) systemic infections; (2) injurious metabolic activities; (3) undue or excessive immune stimulation; and (4) gene transfer (Elia et al., 2008; Hamilton-Miller, 2004; Yan and Polk, 2006).

Several studies did not meet the inclusion criteria of this review paper as diarrhoea was not identified as an outcome measure (Besselink et al., 2008; Falcao de Arruda and de Aguilar-Nascimento, 2004; Forestier et al., 2008; Kotzampassi et al., 2006; Rayes et al., 2002; Spindler-Vesel et al., 2007) (see Table 3). However, it is important to discuss the efficacy of probiotics in relation to critical illness. A number of clinical trials have reported significant reduction in infection acquisition rates, systemic inflammatory response, sepsis, ICU and hospital lengths of stay, early return of bowel function, reduced mechanical ventilation days, decreased intestinal permeability and mortality rates in the probiotic groups (Alberda et al., 2007; Forestier et al., 2008; Klarin et al., 2008; Kotzampassi et al., 2006; Rayes et al., 2002; Spindler-Vesel et al., 2007). Conversely, some studies found no increase in infection acquisition rates or mortality (Besselink et al., 2008) in the probiotic treated patients. These findings may be because of the small sample sizes, incongruence’s between severity of illness scores, heterogeneity of participant populations, variations between probiotic/synbiotic species and doses and inadequate pretrial testing of probiotic combinations.

Mortality and probiotic trials have been infrequently reported on for reasons including inadequate sample sizes and mortality not cited as a study endpoint. Besselink et al. (2008) demonstrated a significant mortality rate which is in contrast to many other study findings (Alberda et al., 2007; Bleichner et al., 1997; Chaboyer et al., 2007; Falcao de Arruda and de Aguilar-Nascimento, 2004; Heimburger et al., 1994; Kotzampassi et al., 2006).

In the Besselink et al. (2008) study, a six species, powder probiotic preparation was administered enterally or orally, twice daily for 28 days. Baseline group characteristics were similar. Infectious complications occurred in 30% (n = 46) of the probiotics and 28% (n = 41) of the placebo patients. Probiotic group mortality was 16% (n = 24) compared to placebo group mortality of 6% (n = 9). Bowel ischaemia was diagnosed at autopsy in nine probiotic group patients (eight fatal) and no placebo group patients (p = 0.004).

Of particular note in the Besselink et al. (2008) study was the significant bowel ischaemia and mortality findings in the probiotic group. These findings may be potentially related to the following study limitations:
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<th>Results/limitations</th>
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<tr>
<td>Rayes et al. (2002)</td>
<td>Prospective, randomised, double-blinded, placebo-controlled trial</td>
<td>Single centre ICU</td>
<td>To examine three different treatment strategies on the incidence of early post-operative infection following liver transplantation Group 1: early enteral nutrition (fibre-free) with selective bowel decontamination (SBD); Group 2: fibre-enriched formula plus live Lactobacillus plantarum 299 (L. plantarum); Group 3: heat inactivated (placebo) L. plantarum 299</td>
<td>EEN started within 24 hour of operation and continued until day 12 post-operatively Group 1: SBD of 80 mg Tobramycin, 500 mg Amphotericin B, 100 mg colistin sulphate QID for 6 weeks post-operatively (n=32); Group 2: Nutrison fibre plus L. plantarum 10^9 cfu BD for 12 post-operative days (n=31); Group 3: heat-killed L. plantarum plus oat fibre BD for 12 post-operative days (n=32) Randomisation: Stratified randomisation by sealed envelope</td>
<td>1. Serum albumin higher, shorter ICU and hospital LOS and earlier return of bowel function (not significant) in group 2; 2. Significantly less infections in group 2 (p = 0.017) Limitations: 1. Statistical significance poorly identified and discussed; 2. Small sample size; 3. Extrapolation of results to include probiotic administration to the donor is unsubstantiated</td>
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<td>Falcao de Arruda and de Aguilar-Nascimento (2004)</td>
<td>Prospective RCT Blinding of participants not identified</td>
<td>Single centre ICU</td>
<td>Evaluate the effects of EEN with glutamine against infectious complications, LOS ICU, time spent mechanical ventilation</td>
<td>Intervention: Glutamine 30 g (administered as a bolus), 240 ml fermented milk with probiotic Lactobacillus johnsonii (La 1) (n=11); Control: Standard polymeric diet (n=12) Randomisation: Method not identified</td>
<td>1. No mortality observed; 2. Higher infection rate in control group (p = 0.03); 3. Infections per patient higher (p &lt; 0.01), ICU LOS (p &lt; 0.01) and days mechanically ventilated (p = 0.04) higher in control group</td>
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<td>Study</td>
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<td>Kotzampassi et al. (2006)</td>
<td>Prospective, randomised, double-blind, placebo-controlled, pilot trial</td>
<td>Multi-centre (5) ICU</td>
<td>Participants: Mechanically ventilated, severe poly-trauma, adult ICU patients with expected ICU LOS &gt; 15 days</td>
<td>Intervention: synbiotic formulae consisted of (1) four probiotics ($10^{11}$ cfu each) <em>Pediococcus pentosaceus</em>, <em>Leuconostoc mesenteroides</em>, <em>Lactobacillus plantarum</em>, <em>Lactobacillus spp. paracasei</em>; and (2) prebiotics of insulin, oat bran, pectin, resistant starch. Dose of 12g daily for 15 days ($n = 35$); Control: placebo ($n = 30$)</td>
<td>1. Significant less combinations of infections in Group D ($p = 0.003$); 2. Intestinal permeability decreased only in Group D from 0.148 (0.056–0.240) on day 4 to 0.061 (0.040–0.099) on day 7 ($p &lt; 0.05$); Total gastric retention volume higher in Group D ($p &lt; 0.02$)</td>
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<tr>
<td>Spindler-Vesel et al. (2007)</td>
<td>Prospective, randomised, controlled trial</td>
<td>Single centre ICU</td>
<td>Participants: Multiple trauma, adult, patients</td>
<td>Group 1: Alitraq EN plus 1.55 g glutamine, 446 mg arginine, 154 mg α-linoleic acid per 100 ml; Group 2: Nova Source EN; Group 3: Nutricomp peptide EN; Group D: Nutricomp standard plus synbiotic (<em>Pediococcus pentosaceus</em> $10^{10}$, <em>Lactococcus raffinolactis</em> $10^{10}$, <em>L. paracasei</em> sub species <em>paracasei</em> $10^{10}$, <em>L. plantarum</em> $10^{10}$) and four fibres (β-glucan, insulin, pectin, resistant starch)</td>
<td>1. Significant less combinations of infections in Group D ($p = 0.001$); 2. Trend toward normalisation of upper GIT motility in synbiotic group</td>
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<td>1. EN started within 24 hours of ICU admission; 2. EN stopped × 6 hour over night; 3. Total patient sample: $N = 113$</td>
<td>Randomisation: Random allocation</td>
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<tr>
<td>Author</td>
<td>Methodology</td>
<td>Setting participants</td>
<td>Aim</td>
<td>Intervention</td>
<td>Results/limitations</td>
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<td>Forestier et al. (2008)</td>
<td>Prospective, randomised, double-blind, placebo-controlled pilot RCT</td>
<td>Single centre ICU Participants: ICU patients with LOS &gt; 48 hours and NGT</td>
<td>Investigate the effectiveness of an oral probiotic on gastric and respiratory colonisation/infection with <em>Pseudomonas aeruginosa</em> (<em>P. aeruginosa</em>)</td>
<td>Intervention: <em>Lactobacillus casei rhamnosus</em> 10⁹ cfu BD from day 3 of ICU admission to discharge (<em>n</em> = 102); Control: placebo (not identified) BD from day 3 ICU admission to discharge (<em>n</em> = 106) Randomisation: Computer generated, equal random allocation through sealed envelopes</td>
<td>Delayed (11 vs. 50 days) respiratory colonisation of <em>P. aeruginosa</em> (<em>p</em> = 0.01) in probiotic group; Reduced <em>P. aeruginosa</em> VAP in probiotic group (not significant)</td>
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<tr>
<td>Klarin et al. (2008)</td>
<td>Prospective, randomised, double-blind, placebo-controlled RCT</td>
<td>Single centre ICU Participants: ICU patients with LOS &gt; 3 days, &gt;18 years of age, no previous positive <em>C. difficile</em> infection, commence ETF within 24 hours of ICU admission, no allergy to study protocol probiotics, not moribund</td>
<td>Investigate the effectiveness of enteral administration of <em>Lactobacillus plantarum</em> 299v on the prevalence of <em>Clostridium difficile</em> (<em>C. difficile</em>) infection in critically ill patients treated with antibiotics</td>
<td>Intervention: fermented oatmeal gruel with 8 × 10⁸ cfu/ml of <em>Lactobacillus plantarum</em> 299v 100 ml bolus doses BD by 6 days, followed by 50 ml bolus doses BD ICU discharge; Control: Same gruel as the intervention group, less the <em>Lactobacillus plantarum</em> 299v. Lactic acid added to achieve same pH Randomisation: Method not identified</td>
<td>No <em>C. difficile</em> colonisation in intervention group; <em>C. difficile</em> in 19% of control group; No differences in frequency or consistency of bowel movements; Statistics not reported</td>
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<tr>
<td>Besselink et al. (2008)</td>
<td>Prospective, randomised, double-blinded, placebo-controlled trial</td>
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<tr>
<td><strong>Participants</strong></td>
<td>First episode of severe, acute, pancreatitis in adult patients</td>
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<tr>
<td><strong>Assess</strong></td>
<td>the effects of probiotic prophylaxis on infectious complications in patients with severe, acute pancreatitis</td>
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<td><strong>Intervention</strong></td>
<td>6 strains of freeze-dried viable bacteria: <em>L. acidophilus</em>, <em>L. casei</em>, <em>L. salivarius</em>, <em>Lactococcus lactis</em>, <em>Bifidobacterium bifidum</em>, <em>Bifidobacterium lactis</em> to total of $10^{10}$ bacteria plus cornstarch and maltodextrins ($n=152$); Placebo: cornstarch and maltodextrins only ($n=144$); Probiotic or placebo administered BD and added to continuously infused fibre-enriched ETF (Nutrison Multi-fibre) or until oral intake resumed for 28 days</td>
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<tr>
<td><strong>Randomisation</strong></td>
<td>Computer generated permuted blocks of 4, balanced by admitting hospital and presumed cause of pancreatitis</td>
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</table>

1. Significantly higher mortality in probiotic group ($p=0.01$); 2. Bowel ischaemia higher in probiotic group 9 vs. 0 ($p=0.004$); 3. Early onset MOF in all probiotic patients who died

**Limitations:**
- Inadequate pre-trial testing of probiotic combination (Ecological 641);
- MOF rate on day of randomisation was significantly higher ($p<0.02$) in the probiotic ($n=20$) vs. placebo ($n=7$) groups;
- Pre-treatment MOF events closely correlate mortality rates (24 vs. 9) and incidence of bowel ischaemia (9 vs. 0);
- Haemodynamic instability is a pre-cursor to MOF and non-occlusive bowel ischaemia in acute pancreatitis;
- Hyper-caloric ETF and inadequate gut function may explain bowel ischaemia;
- High doses of probiotics ($5 \times 10^9$ cfu BD) untested;
- Probiotic bypassing of gastric acid may have led to higher bacterial colonisation in the jejunum;
- Infectious complications (the aim of this study) poorly discussed
Many patients had previous exposure to alcohol misuse, delayed upper GIT peristalsis seen in pancreatitis may have increased exposure to the probiotic; higher probiotic bacterial loads may have increased oxy-
cise commensal bacteria? Does the site of probiotic admin-
istration such as intra gastric or jejunal, affect splanchnic
physiological questions require further research.

The study by Besselink et al. (2008) raises many ques-
tions. Does probiotic therapy require additional oxygen
requirements that cannot be met in a critically ill patient
with reduced splanchnic blood flow? Is it possible that mul-
tiple organ failure associated with sepsis or infection affects
the intestine’s (1) epithelial lining; (2) homeostatic environ-
ment; (3) regulation of microbial environment; and (4) mod-
ifies commensal bacteria? Does the site of probiotic admin-
istration such as intra gastric or jejunal, affect splanchnic
oxygen consumption and GIT permeability in critical illness?
Are the results of the Besselink et al. (2008) study only evi-
dent in acute pancreatitis patients who are at an increased
risk of intestinal permeability or are these results similar in
other subsets of critically ill patients? The answers to these
physiological questions require further research.

A recent systematic review (Whelan and Myers, 2010)
identified 72 articles examining probiotic safety in ETF
patients. Of these articles, 20 were case reports of adverse
events in 32 patients and 52 were articles that reported 53
trials in which 4131 patients received probiotics. Notably,
the majority of trials reported either no effect or a positive
effect related to the outcome measure of safety (mortal-
ity and infection). An increase in patient complications
was reported in only three trials. These complications were
predominantly non-infectious and in specific cohorts of patients
including transplant and pancreatitis patients. Probiotics
were administered via a post-pyloric tube in two of these
three trials. Whelan and Myers (2010) recommend that (1)
safety trials be conducted when a probiotic or combination
of probiotics is administered in a disease state for the first
time; (2) efficacy trials should include a data monitoring
committee to monitor adverse events; (3) probiotics asso-
ciated with an increased risk of adverse events in specific
disease states should not be administered to those particular
patients; and (4) administer probiotics cautiously in high-
risk patients such as critically ill patients and patients with
a central venous line in situ. A notable recommendation by
Whelan and Myers (2010) is that probiotics should not be
withheld in high-risk patients or research as the potential
benefits outweigh the potential risks. In this situation, a risk-
benefit analysis and surveillance monitoring is required for
individual patients to detect early adverse events.

Recommendations

This literature review has identified a number of areas that
require further attention. The definition and efficacy of
probiotics in severely and critically ill patients requires cau-
tious application. Clearly, probiotics are not beneficial to
the host when mortality is observed in severely ill pancre-
atitis patients. Mechanisms of actions of probiotics may be
linearly affected by the probiotic species, dose, frequency
and method of administration in specific disease states such as
diarrhoea, constipation and infections. Future research
must examine morbidity and mortality causes in critically
ill patients who receive probiotics. Intestinal flora changes
must be examined at an individual patient level prior to the
addition of probiotics as adjuvant treatment in critical illness.

Conclusion

From the evidence reviewed, it would appear that probi-
otics do not conclusively reduce the incidence of ETF related
diarrhoea in critically ill patients. An increased incidence of
mortality in probiotic patients, on the basis of one study
must lend caution to their use in critically ill patients. Fur-
ther in vivo and animal studies are required to confirm the
mortality findings in severely and critically ill patients. Only
then, can probiotics be safely administered to critically ill
patients to manage enteral tube feeding diarrhoea. In con-
clusion, as clinicians, we need to challenge the theoretical
approach that probiotics are beneficial to the critically ill patient.

References

Adam S, Batson S. A study of problems associated with the delivery
of enteral feed in critically ill patients in five ICUs in the UK.
therapy in critically ill patients: a randomized, double-blind,
placebo controlled trial. American Journal of Clinical Nutrition
2007;85:816—23.
Baker H, Day B. Probiotics: where are they going next? New and
emerging areas of research. British Nutrition Foundation Nutri-
Barbut F, Meynard JL. Managing antibiotic associated diarrhoea:
role for prebiotics, probiotics, and synbiotics? Current Opinion
Bengmark S. Gut microbial ecology in critical illness: is there a
role for probiotics, prebiotics, and synbiotics? Current Opinion
in Critical Care 2002;8:145—51.
Bengmark S. Bioecological control of the gastrointestinal tract: the
role of flora and supplemented probiotics and synbiotics. Gas-
Besselink MGH, van Santvoort HC, Buskens E, Boeumeester MA, et
al. Probiotic prophylaxis in predicted severe acute pancreati-
tis: a randomised, double-blind, placebo-controlled trial. Lancet
Bjarnason A, Adler SN, Bjarnason I. Letter to the Editor: probi-
otic prophylaxis in predicted severe acute pancreatitis. Lancet
2008;372:114—5.


Duncan HD, Cole SJ, Bowling TE, Silk DBA. Does the mode of feeding play a role in the pathogenesis of enteral feeding related diarrhoea. Proceedings of the Nutrition Society 1997;56:216A.


Pancorbo-Hidalgo PL, Garcia-Fernandez FP, Ramirez-Perez C. Complications associated with enteral nutrition by nasogastric...


