Probiotics for prevention of nosocomial infections: efficacy and adverse effects

Guy J. Oudhuis[a], Dennis C.J.J. Bergmans[b] and Annelies Verbon[a,c]

[a]Department of Medical Microbiology, NUTRIM School for Nutrition, Toxicology and Metabolism, [b]Department of Intensive Care, Maastricht University Medical Centre, Maastricht and [c]Department of Internal Medicine, Erasmus Medical Centre, Rotterdam, The Netherlands

Correspondence to Dr Annelies Verbon, Department of Internal Medicine, Erasmus Medical Centre, PO box 2040, 3000 CA Rotterdam, The Netherlands
Tel: +31 10 7033510; fax: +31 10 7033510;
e-mail: a.verbon@erasmusmc.nl

Current Opinion in Critical Care 2011, 17:487–492

Purpose of review

In this era of increasing antimicrobial resistance, use of probiotics in infection prevention has brought new perspective. However, in 2008 the, until then considered, safe use of probiotics became an important topic after publication of a trial showing excess mortality in patients on probiotic prophylaxis. In this article, we review the concept of infection prevention by probiotics and the present knowledge of the efficacy of probiotics in prevention of infections among patients with abdominal diseases and in intensive care. Safety issues of probiotics will be discussed extensively.

Recent findings

Over 30 clinical trials with probiotics to prevent infections have been published, some of which were prematurely stopped recently. Studies with critically ill patients and patients with abdominal diseases showed conflicting results regarding the effects of probiotics on infection rates, as did meta-analyses. These studies are difficult to compare because different probiotics were used which all have different efficacy and safety profiles.

Summary

The efficacy of probiotics in infection prevention among critically ill patients is still not unequivocally determined. The safety profile differs per probiotic strain and should not be generalized towards other strains and patient populations. A well designed and well powered clinical trial with clear endpoints to demonstrate efficacy is warranted.

Keywords

critical care, infection prevention, lactic acid bacteria, safety

Curr Opin Crit Care 17:487–492

1070-5295

Introduction

The beneficial properties of probiotics had already been recognized by Metchnikoff at the beginning of the 1900s and were 'rediscovered' 60 years later by Lilly and Stillwell [1]. More recently, studies with critically ill patients and patients with abdominal diseases showed conflicting results regarding the effects of probiotics on infection rates, as did meta-analyses [2–4]. Furthermore, the safety of probiotics became a matter of intense debate after the publication of a clinical trial of probiotics in severe acute pancreatitis patients showing excess mortality [5]. Thereafter, only a few trials have been published in the field [6,7•–9•,10].

In this article, we will review the concept of prevention of infections by probiotics and the current knowledge of the efficacy of probiotics in abdominal diseases and intensive care-acquired infections. Moreover, safety issues regarding probiotics will be discussed.

Definitions

Probiotics, literally meaning 'for life', are live microorganisms, which confer a health benefit on the host when administered in adequate amounts [11]. A product can be called a probiotic when the following requirements are met: strains are designated individually (e.g. in case of a multispecies product); strains are speciated appropriately; strains retain a viable count at the end of their shelf life; and the designated product formulation confers a proven clinical endpoint [12].

Probiotics are often administered in conjunction with prebiotics. Prebiotics are nondigestible food ingredients consisting mainly of plant fibres that are used by gut flora as a substrate for fermentation. Prebiotics beneficially affect the host by selectively stimulating growth, activity, or both of a restricted number of bacteria in the colon [13]. Moreover, they could enhance survival of probiotic strains when administered in combination as a so-called synbiotic [14].

Numerous bacterial species can serve as probiotic. An important group is that of lactic acid bacteria (LAB), which can be divided in two subgroups: the fibre-fermenting LAB, such as the fruit/vegetable-borne LAB *Lactobacillus plantarum*, and the mainly milk-borne LAB like *L. casei*. The first occur more frequently and in larger amounts in the gut compared to the latter [15].

Possible mechanisms of action of probiotics

In order to be effective, a probiotic or synbiotic should be able to survive the hostile environment of the stomach, colonize the gut mucosa and reduce colonization and overgrowth of the intestine by potentially pathogenic microorganisms (PPMs) [16]. Many probiotics exert their action in the colon. Klarin *et al.* [17] demonstrated that *L. plantarum* 299v could survive the passage from stomach to rectum and adhere onto rectal mucosa even in critically ill patients that were treated with antibiotics. The main goal of ingestion of probiotics is to create an unfavourable local environment for pathogen colonization [18], and thereby to reduce translocation: leakage of microbes and toxins from the gut into the body [15].

Several molecular working mechanisms of probiotics have been described [15,19]. Some Lactobacilli, for example *L. plantarum*, adhere to the intestinal wall via mannose receptors and compete for these receptors with Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas* spp. [20], thereby preventing Gram-negative colonization and infection. Another way to interfere in pathogen adhesion is the production of mucins (MUC2 and MUC3). An increase in mucin messenger RNA expression was demonstrated *in vitro* when mucosal cells were incubated with *L. plantarum* 299v, which led to inhibition of adherence of *E. coli* to intestinal cells [21]. Certain *Lactobacillus* and *Bifidobacterium* strains bind and sequestrate aflatoxin B [22,23], thus decreasing sufficient amount of free toxins that can contaminate food or serve as carcinogen. Probiotics compete for nutrients with potential pathogens [24]; alter local pH [25]; produce bacteriocins to inhibit pathogens [26]; enhance intestinal barrier function [27], and scavenge superoxide radicals [28].

In addition, probiotics have been shown to be immune modulating. Defects in macrophage function (an effect of antibiotic administration) are eliminated by supply of certain low-molecular-weight peptides obtained from indigenous gut microbiota such as *Bacteroides* spp. and *Lactobacillus* [29]. Furthermore, cell-free extracts (supernatant) of *B. longum* and *L. acidophilus* significantly enhanced phagocytosis of both inert particles and viable *Salmonella* [30]. Probiotics may activate macrophages to increase antigen presentation and secretory IgA production [31,32]; modulate cytokine profiles [33]; reduce pro-inflammatory cytokines [34]; induce anti-inflammatory cytokines like IL-10 [35]; and modulate dendritic cell phenotype and function [36].

Although the exact working mechanism of probiotics is not yet clear, probiotics are increasingly being used.

Key points

- The efficacy of probiotics in infection prevention is a matter of ongoing debate.
- The safety profile differs per probiotic strain, and should not be generalized.
- A well powered clinical trial with clear endpoints to demonstrate efficacy is warranted.

Use of probiotics in humans

Due to concerns regarding development of antibiotic resistance in hospitals, rising healthcare costs and lack of new antimicrobial classes being developed, probiotics have been considered a good prophylactic or therapeutic alternative in numerous conditions. Probiotics do not have the risk of antimicrobial resistance and offer practical benefits like low-cost preparation, long shelf life, and ease of administration [18].

Most evidence is available on prevention and treatment of acute infectious diarrhoea, for instance rotavirus infection [37] or antibiotic-associated diarrhoea [38]. Also reported are prevention of lactose malabsorption or intolerance [39], the consolidation of remission of inflammatory bowel disease [40] and reduction of the incidence of atopic eczema in infants [41]. Nearly a decade ago, the first clinical studies using *L. plantarum* 299 as probiotic showed promising reductions in surgical and ICU sepsis rates [42–44]. In this review we will focus on prevention of infections in patients with abdominal diseases and ICU-acquired infections.

Prevention of infections in abdominal diseases

An important population in which probiotics are investigated is the one with patients undergoing abdominal surgery or suffering from pancreatitis.

Abdominal surgery

Rayes *et al.* [42] investigated the incidence of bacterial infections in patients after major abdominal surgery ($n = 90$) in a prospective, randomized trial. The incidence of infections was significantly lower ($P = 0.01$) in the group with enteral fibre-containing nutrition with viable *L. plantarum* 299 (10%) and heat-killed *Lactobacillus* (10%) compared with the group on parenteral nutrition or fibre-free enteral nutrition (30%) [42]. The same authors compared the incidence of postoperative infections among liver transplant recipients ($n = 95$), comparing three groups; one group using standard formula of enteral nutrition with selective bowel decontamination (SDD); one group using fibre-containing formula and viable *L. plantarum* 299 and the third group using fibre-containing formula and heat-killed *L. plantarum* 299. Patients receiving viable *L. plantarum* 299 developed significantly less bacterial infections (13%) compared with SDD (48%) and heat-killed *L. plantarum* (34%, $P = 0.02$) [43]. Two other clinical trials used Synbiotic 2000, containing four different strains: *Pediococcus pentosaceus*, *Leuconostoc mesenteroides*, *L. paracasei* and *L. plantarum* combined with fibres. Among liver transplant recipients ($n = 66$), the incidence of postoperative bacterial infections was significantly reduced when given Synbiotic 2000 (3%) compared to fibres alone (48%) [45]. Also patients undergoing pancreas resection ($n = 80$) had significantly fewer postoperative bacterial infections when given Synbiotic 2000 (12.5%) compared to fibres only (40%, $P = 0.005$) [46].

Among biliary cancer patients undergoing hepatectomy, postoperative infections were significantly reduced by a synbiotic product containing *B. breve* Yakult and *L. casei* Shirota [47]. Postoperative infectious complications were significantly reduced by a combination of *Enterococcus faecalis*, *Clostridium butyricum* and *Bacillus mesentericus* among patients undergoing pancreaticoduodenectomy [48]. By contrast, three other studies, conducted by the same research group, applying different regimens of probiotics, did not show an influence of probiotics on septic morbidity after abdominal surgery, possibly due to a relatively short period of postoperative administration [49–51].

A meta-analysis, based on the above-mentioned trials [2] and a review [52], including six additional trauma and pancreatitis trials, concluded that the use of probiotics or synbiotics reduced postoperative infections after abdominal surgery [odds ratio (OR) for any infection 0.26, 95% confidence interval (CI) 0.12–0.55, $P < 0.001$]. However, the results of the meta-analysis should be interpreted with caution due to the heterogeneity of the included studies.

Very recently, Liu *et al.* [9•] reported that patients undergoing colorectal surgery for carcinoma ($n = 100$) who received probiotics (*L. plantarum*, *L. acidophilus*, *B. longum*) experienced significantly less infectious complications compared with placebo in a trial with bacterial translocation as primary endpoint.

Pancreatitis

Patients with acute pancreatitis ($n = 45$) were randomized to either viable *L. plantarum* 299 with oat fibre substrate by nasojejunal tube, or to an identical preparation with heat-killed *Lactobacillus*. Infected pancreatic necrosis and abscesses occurred in 1 of 22 patients receiving viable *L. plantarum* 299 compared with 7 of 23 patients in the heat-killed group ($P = 0.02$) [44]. Sixty-two patients with severe acute pancreatitis were either given Synbiotic 2000 with prebiotics or prebiotics only. The total incidence of systemic inflammatory response syndrome and multiorgan failure was significantly lower in the first group ($P < 0.05$), as was the number of patients recovering with complications. A lower rate of late organ failure was detected in the synbiotic group [53]. Besselink *et al.* [5] conducted a randomized controlled trial with predicted severe acute pancreatitis patients that received a multispecies probiotic (six strains) as infection prophylaxis and compared them with placebo. In the probiotic group 16% of patients died, compared with 6% in the placebo group (relative risk 2.53). Nine patients in the probiotic group developed bowel ischemia, of which eight with fatal outcome, compared with none in the placebo group ($P = 0.004$) [5].

The conclusion of a recent meta-analysis with seven included studies on pre, pro and synbiotics for acute pancreatitis (the included studies being heterogeneous) was that no sufficient evidence to support the use of pro or synbiotics to prevent postoperative infections in pancreatitis could be demonstrated (OR 0.30, 95% CI 0.09–1.02, $P = 0.05$) [3].

Prevention of ventilator-associated pneumonia and other ICU infections

Since the prevalence of infections, for example ventilator-associated pneumonia (VAP), and subsequent mortality is high in critically ill patients, probiotics have also been applied for infection prevention in ICU.

The synbiotic formula Trevis (*L. acidophilus* La5, *B. lactis* Bb-12, *S. thermophilus*, *L. bulgaricus* with oligofructose) applied in ICU patients was not associated with measurable clinical benefit compared with placebo [54]. Another study by the same research group showed that enteral administration of *L. plantarum* 299v to critically ill patients did not significantly change septic morbidity compared with conventional ICU therapy [55]. Synbiotic2000Forte applied in critically ill, multitrauma patients significantly reduced infection and sepsis rates compared to placebo [56], as well as glutamine, fermentable fibre and peptide diet [57]. Oral administration of *L. casei rhamnosus* delayed respiratory tract colonization and infection by *P. aeruginosa* in ICU patients. There was a trend towards reduced occurrence of VAP with *P. aeruginosa* [58]. Application of *L. plantarum* 299 to critically ill patients on mechanical ventilation led to a VAP rate of 4% compared to 14% in the chlorhexidine group (not significant) [59]. Similar findings were reported for Synbiotic2000Forte [6].

A recent meta-analysis showed that use of probiotics in mechanically ventilated patients was associated with a lower incidence of VAP compared to controls [4]. However, four other recent reviews/meta-analyses [16,18,60,61], two of which with special focus on hospital-acquired pneumonia, failed to show a reduction in infections among critically ill patients or stated that there is insufficient evidence for reduction of nosocomial pneumonia by probiotics.

A possible explanation for the differences in outcome may be the inclusion of different clinical trials with low homogeneity among the populations [4], varying from patients admitted to the ICU to patients after abdominal surgery or with pancreatitis. Other factors playing a role in the variation in outcome are the application of different probiotic strains with varying properties and bioavailability, the significantly different definitions of infectious endpoints like VAP in the different trials [16], considerable variation in dose, time of onset and duration of administration of probiotics or synbiotics. All these factors are known to be crucial entities in probiotic use [62] and hamper proper comparison of trials with probiotics. Suboptimal trial design, inadequate blinding, and small study samples make it even more difficult to draw an appropriate conclusion from these data [61].

After publication of these meta-analyses, three randomized controlled trials with ICU patients have been published. In a prematurely stopped trial, 167 patients were given *Ergyphilus* (mainly *L. rhamnosus* GG, among three other strains) or placebo for the duration of mechanical ventilation. The primary endpoint 28-day mortality was not significantly different between both groups. However, among a subgroup of patients with severe sepsis, 28-day mortality was reduced in the probiotic group. By contrast, probiotics were associated with a higher mortality in patients with nonsevere sepsis, but mortality was unexpectedly low in placebo-treated patients. Additionally, no reductions in nosocomial infections (especially VAP) were demonstrated. The authors concluded that prophylactic administration of probiotics to critically ill could not be encouraged [7•].

Both oropharyngeal and gastric administration of *L. rhamnosus* GG was found to be well tolerated and efficacious in preventing (Gram-negative) VAP in a selected ICU population ($n = 146$), with high APACHE II scores and prolonged duration of mechanical ventilation, compared with placebo (incidence 19 vs. 40%, $P = 0.007$) [8•]. Mortality was not significantly different between both groups. The authors stated that results could not be generalized to a broader ICU population and should be considered as preliminary observations [8•]. A third, also prematurely stopped trial ($n = 254$) failed to demonstrate noninferiority of *L. plantarum* 299/299v and rose-hip compared with SDD in prevention of ICU-acquired infections. The results suggested that *L. plantarum* 299/299v might be inferior to SDD, although the difference in ICU mortality and mortality at day 28 was not statistically significant between both groups [10].

Adverse effects of probiotics

Until recently, the use of probiotics was generally regarded as well tolerated. Only a few case reports had been published reporting adverse effects, for example *Saccharomyces boulardii* fungaemia [63] and bacteraemia with lactobacilli [64]. These rare cases of bacteraemia or fungaemia were mostly polymicrobial [65] and occurred in patients with severe comorbidities such as immune suppression [63], short bowel syndrome [66] or in patients with indwelling central venous catheters [67]. No increase in adverse effects could be demonstrated on a population level, after a nationwide increase in probiotic consumption [68]. So, the safety issue of probiotics was not considered to be of paramount importance. However, in 2008 Besselink *et al.* [5] reported excess mortality among their group of patients with predicted severe acute pancreatitis, receiving a multispecies probiotic, compared with placebo. The authors hypothesized that the combination of severe pancreatitis, subsequent organ failure, intestinal hypoperfusion through reduction in mucosal blood flow and an increased bacterial load due to the probiotic strains could have led to increased local inflammation, further compromising mucosal blood supply resulting in bowel ischaemia [69]. They concluded that bacteraemia, infected pancreatic necrosis, organ failure and mortality were all associated with intestinal barrier dysfunction early in the course of acute pancreatitis. Prophylaxis with the specific combination of probiotic strains was associated with increased bacterial translocation and enterocyte damage in patients with organ failure specifically [69]. The authors stated that because of the results of their trial, probiotics should not be used in critically ill patients until more information became available about causes and underlying mechanism of the excess mortality.

Type and number of strains, for example single strain vs. multispecies product, may, however, influence outcome, including appearance of adverse events. Also, the investigated condition and route of administration, that is application via gastric vs. duodenal or jejunal tube may be crucial for adverse events like intestinal ischaemia. Therefore, results of one trial may not be applicable to other probiotic studies in critically ill patients, although vigilance for adverse effects is warranted, especially in this patient population.

Conclusion

Despite the vast amount of clinical trials on probiotics, no unequivocal conclusion can be drawn regarding efficacy in infection prevention. Safety of probiotic use in critically ill patients is a matter of ongoing debate. It should be emphasized that every probiotic may consist of different strains (such as lactobacilli or bifidobacteria) which exert their own specific properties, which could lead to different results with regard to efficacy or adverse effects. Results of studies with certain probiotics in specific patient populations can therefore not be readily extrapolated to other studies using different probiotics in different patient populations.

Therefore, a large, well described and well designed placebo-controlled trial with sufficient power should be initiated in a general ICU population, comparing a single strain regimen (e.g. 'experienced' strains with a good safety profile like *L. plantarum* 299 or *L. rhamnosus* GG) with a multispecies regimen (e.g. Synbiotic2000). The endpoint should be unequivocal, like 28-day mortality, in order to properly demonstrate the clinical effectiveness of probiotic intervention. Moreover, concurrent efforts must be made to identify the exact (molecular) working mechanism of each strain/mixture, to establish the right doses, schedule and timing of administration and to clarify the benefits of adding prebiotics.

Despite the ongoing debate, probiotics still seem to be a safe alternative for antibiotic prophylaxis in this era of increasing antibiotic resistance and deserve a well monitored 'second life'.

Acknowledgements

The work was supported by ZonMw (the Netherlands organization for health research and development, grant number 6100.0007).

Conflicts of interest

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 540–541).

1 Lilly DM, Stillwell RH. Probiotics: growth-promoting factors produced by microorganisms. Science 1965; 147:747–748.

2 Pitsouni E, Alexiou V, Saridakis V, *et al.* Does the use of probiotics/synbiotics prevent postoperative infections in patients undergoing abdominal surgery? A meta-analysis of randomized controlled trials. Eur J Clin Pharmacol 2009; 65:561–570.

3 Zhang MM, Cheng JQ, Lu YR, *et al.* Use of pre, pro- and synbiotics in patients with acute pancreatitis: a meta-analysis. World J Gastroenterol 2010; 16:3970–3978.

4 Siempos II, Ntaidou TK, Falagas ME. Impact of the administration of probiotics on the incidence of ventilator-associated pneumonia: a meta-analysis of randomized controlled trials. Crit Care Med 2010; 38:954–962.

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

6 Knight DJ, Gardiner D, Banks A, *et al.* Effect of synbiotic therapy on the incidence of ventilator-associated pneumonia in critically ill patients: a randomised, double-blind, placebo-controlled trial. Intensive Care Med 2009; 35:854–861.

7 • Barraud D, Blard C, Hein F, *et al.* Probiotics in the critically ill patient: a double blind, randomized, placebo-controlled trial. Intensive Care Med 2010; 36:1540–1547.
In this study, the intervention group was divided in a subgroup with severe sepsis and a subgroup with nonsevere sepsis, which yielded significantly different 28-day mortality rates.

8 • Morrow LE, Kollef MH, Casale TB. Probiotic prophylaxis of ventilator-associated pneumonia: a blinded, randomized, controlled trial. Am J Respir Crit Care Med 2010; 182:1058–1064.
This is, to the best of our knowledge, the only clinical trial in critically ill patients with both oropharyngeal and intestinal administration of probiotics.

9 • Liu Z, Qin H, Yang Z, *et al.* Randomised clinical trial: the effects of perioperative probiotic treatment on barrier function and post-operative infectious complications in colorectal cancer surgery: a double-blind study. Aliment Pharmacol Ther 2011; 33:50–63.
This study not only describes infectious complications but also ex-vivo measurements of gut mucosal barrier integrity after probiotic use.

10 Oudhuis GJ, Bergmans DC, Dormans T, *et al.* Probiotics versus antibiotic decontamination of the digestive tract: infection and mortality. Intensive Care Med 2011; 37:110–117.

11 Joint FAO/WHO expert consultation. Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. FAO/WHO; 2001. http://www.who.int/foodsafety/publications/fs_management/probiotics/en/. [Accessed 24 April 2011]

12 Joint FAO/WHO working group meeting. Guidelines for the evaluation of probiotics in food. FAO/WHO; 2002. http://www.who.int/foodsafety/publications/fs_management/probiotics2/en/. [Accessed 24 April 2011]

13 Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J Nutr 1995; 125:1401–1412.

14 Wang X, Brown IL, Evans AJ, Conway PL. The protective effects of high amylose maize (Amylomaize) starch granules on the survival of *Bifidobacterium* spp. in the mouse intestinal tract. J Appl Microbiol 1999; 87:631–639.

15 Bengmark S. Pre, pro- and synbiotics. Curr Opin Clin Nutr Metab Care 2001; 4:571–579.

16 Watkinson PJ, Barber VS, Dark P, Young JD. The use of pre pro- and synbiotics in adult intensive care unit patients: systematic review. Clin Nutr 2007; 26:182–192.

17 Klarin B, Johansson ML, Molin G, *et al.* Adhesion of the probiotic bacterium *Lactobacillus plantarum* 299v onto the gut mucosa in critically ill patients: a randomised open trial. Crit Care 2005; 9:R285–R293.

18 Isakow W, Morrow LE, Kollef MH. Probiotics for preventing and treating nosocomial infections: review of current evidence and recommendations. Chest 2007; 132:286–294.

19 Madsen K. Probiotics in critically ill patients. J Clin Gastroenterol 2008; 42 (Suppl 3 Pt 1):S116–S118.

20 Adlerberth I, Ahrne S, Johansson ML, *et al.* A mannose-specific adherence mechanism in *Lactobacillus plantarum* conferring binding to the human colonic cell line Ht-29. Appl Environ Microbiol 1996; 62:2244–2251.

21 Mack DR, Michail S, Wei S, *et al.* Probiotics inhibit enteropathogenic *E. coli* adherence in vitro by inducing intestinal mucin gene expression. Am J Physiol 1999; 276:G941–G950.

22 Haskard C, Binnion C, Ahokas J. Factors affecting the sequestration of aflatoxin by *Lactobacillus rhamnosus* strain GG. Chem Biol Interact 2000; 128:39–49.

23 Oatley JT, Rarick MD, Ji GE, Linz JE. Binding of aflatoxin B1 to bifidobacteria in vitro. J Food Prot 2000; 63:1133–1136.

24 Dai D, Walker WA. Protective nutrients and bacterial colonization in the immature human gut. Adv Pediatr 1999; 46:353–382.

25 Aiba Y, Suzuki N, Kabir AM, *et al.* Lactic acid-mediated suppression of *Helicobacter pylori* by the oral administration of *Lactobacillus salivarius* as a probiotic in a gnotobiotic murine model. Am J Gastroenterol 1998; 93:2097–2101.

26 Eckmann L. Innate immunity and mucosal bacterial interactions in the intestine. Curr Opin Gastroenterol 2004; 20:82–88.

27 Gionchetti P, Lammers KM, Rizzello F, Campieri M. Probiotics and barrier function in colitis. Gut 2005; 54:898–900.

28 Akisu M, Baka M, Yalaz M, *et al.* Supplementation with *Saccharomyces boulardii* ameliorates hypoxia/reoxygenation-induced necrotizing enterocolitis in young mice. Eur J Pediatr Surg 2003; 13:319–323.

29 Pulverer G, Ko HL, Roszkowski W, *et al.* Digestive tract microflora liberates low molecular weight peptides with immunotriggering activity. Zentralbl Bakteriol 1990; 272:318–327.

30 Hatcher GE, Lambrecht RS. Augmentation of macrophage phagocytic activity by cell-free extracts of selected lactic acid-producing bacteria. J Dairy Sci 1993; 76:2485–2492.

31 Qamar A, Aboudola S, Warny M, *et al.* *Saccharomyces boulardii* stimulates intestinal immunoglobulin A immune response to *Clostridium difficile* toxin A in mice. Infect Immun 2001; 69:2762–2765.

32 Macpherson AJ, Uhr T. Induction of protective IgA by intestinal dendritic cells carrying commensal bacteria. Science 2004; 303:1662–1665.

33 Rachmilewitz D, Katakura K, Karmeli F, *et al.* Toll-like receptor 9 signaling mediates the anti-inflammatory effects of probiotics in murine experimental colitis. Gastroenterology 2004; 126:520–528.

34 Sheih YH, Chiang BL, Wang LH, *et al.* Systemic immunity-enhancing effects in healthy subjects following dietary consumption of the lactic acid bacterium *Lactobacillus rhamnosus* Hn001. J Am Coll Nutr 2001; 20:149–156.

35 Niers LE, Timmerman HM, Rijkers GT, *et al.* Identification of strong interleukin-10 inducing lactic acid bacteria which down-regulate T helper type 2 cytokines. Clin Exp Allergy 2005; 35:1481–1489.

36 Hart AL, Lammers K, Brigidi P, *et al.* Modulation of human dendritic cell phenotype and function by probiotic bacteria. Gut 2004; 53:1602–1609.

37 Majamaa H, Isolauri E, Saxelin M, Vesikari T. Lactic acid bacteria in the treatment of acute rotavirus gastroenteritis. J Pediatr Gastroenterol Nutr 1995; 20:333–338.

38 McFarland LV. Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of *Clostridium difficile* disease. Am J Gastroenterol 2006; 101:812–822.

39 Masood MI, Qadir MI, Shirazi JH, Khan IU. Beneficial effects of lactic acid bacteria on human beings. Crit Rev Microbiol 2011; 37:91–98.

40 Kruis W. Review article: antibiotics and probiotics in inflammatory bowel disease. Aliment Pharmacol Ther 2004; 20 (Suppl 4):75–78.

41 Viljanen M, Savilahti E, Haahtela T, *et al.* Probiotics in the treatment of atopic eczema/dermatitis syndrome in infants: a double-blind placebo-controlled trial. Allergy 2005; 60:494–500.

42 Rayes N, Hansen S, Seehofer D, *et al.* Early enteral supply of fiber and *Lactobacilli* versus conventional nutrition: a controlled trial in patients with major abdominal surgery. Nutrition 2002; 18:609–615.

43 Rayes N, Seehofer D, Hansen S, *et al.* Early enteral supply of *Lactobacillus* and fiber versus selective bowel decontamination: a controlled trial in liver transplant recipients. Transplantation 2002; 74:123–127.

44 Olah A, Belagyi T, Issekutz A, *et al.* Randomized clinical trial of specific *Lactobacillus* and fibre supplement to early enteral nutrition in patients with acute pancreatitis. Br J Surg 2002; 89:1103–1107.

45 Rayes N, Seehofer D, Theruvath T, *et al.* Supply of pre and probiotics reduces bacterial infection rates after liver transplantation: a randomized, double-blind trial. Am J Transplant 2005; 5:125–130.

46 Rayes N, Seehofer D, Theruvath T, *et al.* Effect of enteral nutrition and synbiotics on bacterial infection rates after pylorus-preserving pancreatoduodenectomy: a randomized, double-blind trial. Ann Surg 2007; 246:36–41.

47 Kanazawa H, Nagino M, Kamiya S, *et al.* Synbiotics reduce postoperative infectious complications: a randomized controlled trial in biliary cancer patients undergoing hepatectomy. Langenbecks Arch Surg 2005; 390:104–113.

48 Nomura T, Tsuchiya Y, Nashimoto A, *et al.* Probiotics reduce infectious complications after pancreaticoduodenectomy. Hepatogastroenterology 2007; 54:661–663.

49 McNaught CE, Woodcock NP, MacFie J, Mitchell CJ. A prospective randomised study of the probiotic *Lactobacillus plantarum* 299v on indices of gut barrier function in elective surgical patients. Gut 2002; 51:827–831.

50 Anderson AD, McNaught CE, Jain PK, MacFie J. Randomised clinical trial of synbiotic therapy in elective surgical patients. Gut 2004; 53:241–245.

51 Reddy BS, Macfie J, Gatt M, *et al.* Randomized clinical trial of effect of synbiotics, neomycin and mechanical bowel preparation on intestinal barrier function in patients undergoing colectomy. Br J Surg 2007; 94:546–554.

52 Rayes N, Seehofer D, Neuhaus P. Prebiotics, probiotics, synbiotics in surgery: are they only trendy, truly effective or even dangerous? Langenbecks Arch Surg 2009; 394:547–555.

53 Olah A, Belagyi T, Poto L, *et al.* Synbiotic control of inflammation and infection in severe acute pancreatitis: a prospective, randomized, double blind study. Hepatogastroenterology 2007; 54:590–594.

54 Jain PK, McNaught CE, Anderson AD, *et al.* Influence of synbiotic containing *Lactobacillus acidophilus* La5, *Bifidobacterium lactis* Bb 12, *Streptococcus thermophilus*, *Lactobacillus bulgaricus* and oligofructose on gut barrier function and sepsis in critically ill patients: a randomised controlled trial. Clin Nutr 2004; 23:467–475.

55 McNaught C, Woodcock N, Anderson A, MacFie J. A prospective randomised trial of probiotics in critically ill patients. Clin Nutr 2005; 24:211–219.

56 Kotzampassi K, Giamarellos-Bourboulis EJ, Voudouris A, *et al.* Benefits of a synbiotic formula (Synbiotic 2000forte) in critically ill trauma patients: early results of a randomized controlled trial. World J Surg 2006; 30:1848–1855.

57 Spindler-Vesel A, Bengmark S, Vovk I, *et al.* Synbiotics, prebiotics, glutamine, or peptide in early enteral nutrition: a randomized study in trauma patients. JPEN J Parenter Enteral Nutr 2007; 31:119–126.

58 Forestier C, Guelon D, Cluytens V, *et al.* Oral probiotic and prevention of *Pseudomonas aeruginosa* infections: a randomized, double-blind, placebo-controlled pilot study in intensive care unit patients. Crit Care 2008; 12:R69.

59 Klarin B, Molin G, Jeppsson B, Larsson A. Use of the probiotic *Lactobacillus plantarum* 299 to reduce pathogenic bacteria in the oropharynx of intubated patients: a randomised controlled open pilot study. Crit Care 2008; 12:R136.

60 McNabb B, Isakow W. Probiotics for the prevention of nosocomial pneumonia: current evidence and opinions. Curr Opin Pulm Med 2008; 14:168–175.

61 Koretz RL. Probiotics, critical illness, and methodologic bias. Nutr Clin Pract 2009; 24:45–49.

62 Bengmark S. Synbiotics to strengthen gut barrier function and reduce morbidity in critically ill patients. Clin Nutr 2004; 23:441–445.

63 Cesaro S, Chinello P, Rossi L, Zanesco L. *Saccharomyces cerevisiae* fungemia in a neutropenic patient treated with *Saccharomyces boulardii*. Support Care Cancer 2000; 8:504–505.

64 Land MH, Rouster-Stevens K, Woods CR, *et al.* *Lactobacillus* sepsis associated with probiotic therapy. Pediatrics 2005; 115:178–181.

65 Sullivan A, Nord CE. Probiotic *Lactobacilli* and bacteraemia in Stockholm. Scand J Infect Dis 2006; 38:327–331.

66 De Groote MA, Frank DN, Dowell E, *et al.* *Lactobacillus rhamnosus* GG bacteremia associated with probiotic use in a child with short gut syndrome. Pediatr Infect Dis J 2005; 24:278–280.

67 Hennequin C, Kauffmann-Lacroix C, Jobert A, *et al.* Possible role of catheters in *Saccharomyces boulardii* fungemia. Eur J Clin Microbiol Infect Dis 2000; 19:16–20.

68 Salminen MK, Tynkkynen S, Rautelin H, *et al.* *Lactobacillus* bacteremia during a rapid increase in probiotic use of *Lactobacillus rhamnosus* GG in Finland. Clin Infect Dis 2002; 35:1155–1160.

69 Besselink MG, van Santvoort HC, Renooij W, *et al.* Intestinal barrier dysfunction in a randomized trial of a specific probiotic composition in acute pancreatitis. Ann Surg 2009; 250:712–719.