Safety of probiotics in patients receiving nutritional support: a systematic review of case reports, randomized controlled trials, and nonrandomized trials

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ABSTRACT

Background: Probiotics are increasingly used in patients receiving nutritional support; however, some case reports and trials have questioned their safety in such patients.

Objective: The objective was to investigate the safety of probiotics in patients receiving nutritional support through a systematic review of case reports, randomized controlled trials (RCTs), and nonrandomized trials.

Design: The systematic review followed Cochrane and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations. Six electronic databases were searched, a hand search of conference proceedings and reference lists was performed, and experts were contacted. Case reports, RCTs, and nonrandomized trials of probiotic use in patients also receiving enteral or parenteral nutrition were included in the review. Two reviewers independently screened the relevant articles and extracted the data.

Results: In total, 1966 articles were identified, of which 72 fulfilled the inclusion criteria. There were 20 case reports of adverse events in 32 patients, all of which were infections due to Lactobacillus rhamnosus GG or Saccharomyces boulardii; the risk factors included central venous catheters and disorders associated with increased bacterial translocation. There were 52 articles reporting 53 trials in which 4131 patients received probiotics. Most trials showed either no effect or a positive effect on outcomes related to safety (eg, mortality and infections). Only 3 trials showed increased complications, which were largely noninfectious in nature and in specific patient groups (eg, transplant and pancreatitis). In 2 of these trials, the probiotic was administered through a postpyloric tube.

Conclusion: Many probiotics have been used safely in patients receiving nutritional support, although some probiotic products (strains or combinations) have been shown to increase the risk of complications in specific patient groups. Am J Clin Nutr 2010;91:687–703.

INTRODUCTION

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (1). The most common probiotics are the bacteria lactobacilli and bifidobacteria and the yeast Saccharomyces boulardii. The health benefits of specific strains involve effects on infections, immune function, inflammation, and gastrointestinal transit, which result from microbial competition, bacteriocin production, and specific and nonspecific immune stimulation (2, 3). In view of their functional characteristics and apparent safety profile in healthy persons, probiotics have been investigated for their role in disease management. This includes the treatment of eczema (4), lactose malabsorption (5), irritable bowel syndrome (6), and inflammatory bowel disease (7).

The safety of probiotics is supported by the fact that many strains are of human origin and have a long history of safe use. Despite their widespread use, the incidence of bacteremia attributable to probiotic strains remains extremely low (8). However, the safety of probiotics in patient groups has been questioned because of the potential for bacterial translocation across the gastrointestinal epithelium, the potential for transfer of antibiotic resistance to other microorganisms, and the risks of infection in otherwise immunocompromised patients (9). Many case reports have described infections resulting from probiotic use; however, a systematic review of these reports has not been conducted.

Of particular relevance to clinical nutrition is the use of probiotics in patients receiving nutritional support, such as enteral nutrition (EN) or parenteral nutrition (PN). Probiotics have been used in such patients for the prevention of EN-associated diarrhea (10), antibiotic-associated diarrhea (AAD) (11), Clostridium difficile–associated diarrhea (CDAD) (12), the prevention of necrotizing enterocolitis in preterm neonates (13), and the prevention of infections and sepsis in the critically ill (14).

The use of probiotics in patients receiving nutritional support presents specific safety issues. Interventions that increase gastric pH (eg, gastric acid–suppressing drugs) or administration that bypasses gastric acid completely (eg, postpyloric EN) will result in increased probiotic survival in the small intestine. In addition, central venous catheters (CVCs) used in the delivery of PN have been identified as a potential risk factor for probiotic infection
(15). Finally, patients receiving nutritional support may have risk factors for bacterial translocation (eg, critical illness) or be immunocompromised and therefore harbor other risk factors for infection.

The convincing safety profile of probiotics in healthy persons cannot be assumed to translate to patients receiving nutritional support who may have increased probiotic survival in conjunction with additional risk factors for probiotic infection. The aim of this study was to investigate the safety of probiotics in patients receiving nutritional support through a systematic review of case reports, randomized controlled trials (RCTs), and nonrandomized trials.

METHODS

When possible, the systematic review was undertaken in line with the recommendations of the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions and with particular reference to adverse events (16). This systematic review adhered to the relevant criteria of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (17). The following methods used in the systematic review, including identification, screening, eligibility, and inclusion, were agreed between the authors in advance.

References were identified by searching an electronic database, hand-searching conference abstracts and key reference lists, and contacting experts in the area. The search strategy was developed by the authors in conjunction with a senior information specialist. An electronic search of the following 6 electronic databases was undertaken: MEDLINE (US National Library of Medicine, Bethesda, MD; Ovid interface: http://ovidsp.ovid.com) from 1950 to July 2009, EMBASE (Elsevier BV, Netherlands; Ovid interface: http://ovidsp.ovid.com) from 1980 to July 2009; CINAHL (CINAHL Information Systems, USA; EBSCO host interface: http://search.ebscohost.com) from 1982 to 2009, CENTRAL (The Cochrane Library, Chichester, United Kingdom; Wiley InterScience: http://www.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.html) for all years, Nutrition and Food Sciences (CAB International, United Kingdom; CAB Direct interface: http://www.cabi.org/nutrition/) for all years, and Web of Science (ISI Thomson Scientific, United Kingdom; Web of Knowledge portal: http://isiknowledge.com) from 1900 to July 2009. The final search date was 30 July 2009. The search used combinations of the terms probiotics, safety, and nutritional support as both MeSH headings and key or free text words and included a wide range of derivations to ensure as wide a search strategy as possible. A list of the search strategy used is available online as supplemental material (see “Supplemental data” in the online issue).

Hand searching of abstracts from the 2000 to 2009 annual conferences of the following organizations was undertaken to obtain conference reports that would not be identifiable through electronic searching: the American Society for Parenteral and Enteral Nutrition (J Parent Enteral Nutr), the European Society for Clinical Nutrition and Metabolism (Clin Nutr, Clin Nutr Suppl, and e-SPEN), and the British Association for Parenteral and Enteral Nutrition (Proc Nutr Soc). In addition, hand-searching of the reference lists of relevant reviews and studies fulfilling the inclusion criteria was undertaken to identify further relevant references.

Experts in probiotics or nutritional support were contacted to obtain published or unpublished references not identified during electronic or hand-searching. Information was requested from experts in probiotics, including authors of reviews or trials on probiotic safety (n = 37), authors of case reports of probiotic adverse events (n = 11), and the scientific departments of manufacturers of probiotics (n = 14) or nutritional support products (n = 6).

The research question and inclusion and exclusion criteria were developed by using a PICOS structure (Patient, Intervention, Comparators, Outcome, Study Design) (18). The inclusion criteria were any articles reporting the administration of a probiotic to patients who were also receiving nutritional support. Details of the inclusion and exclusion criteria are described in Table 1.

The references were imported into a bibliographic database to automatically exclude duplicates (Reference Manager, version 12). Then, 2 researchers independently reviewed the title and abstract of each reference to assess its eligibility. The full article was obtained for all potentially eligible references, and the inclusion criteria were applied to each. When articles contained insufficient information to assess their eligibility or to extract relevant data, the corresponding author was contacted for further information and this occurred for 31 such articles. When disagreements regarding eligibility and data extraction occurred (11 articles), they were resolved through further contact with report authors, discussion, and consensus.

The 2 researchers independently extracted the data from eligible articles. Data relating to the patient or group, the intervention, the comparator group (where relevant), the outcomes measured (adverse events, mortality, and morbidity), and the study design were extracted as detailed in Table 1.

The studies were then categorized into 1) case reports of adverse events, 2) safety trials (trials of any design whose major aim was to investigate adverse events or safety and that undertook routine sampling/screening for these), which were divided into RCTs and nonrandomized trials; and 3) nonsafety trials (trials that did not qualify as safety trials but that reported clinical outcomes relevant to safety, eg, mortality, morbidity, and adverse events), which were also divided into RCTs and nonrandomized trials. A meta-analysis was not conducted because of the necessarily wide eligibility of patient groups, probiotic strains and doses, type and method of monitoring of adverse events and clinical outcomes, and study designs. Assimilating clinical outcome data (eg, mortality and morbidity) into a meta-analysis may actually negate safety issues in specific patient groups and therefore was not undertaken.

RESULTS

A total of 1966 nonduplicated articles were identified in the search. The titles and abstracts were reviewed, and only 134 were deemed potentially eligible. After a review of the full article, 72 fulfilled the inclusion criteria: 20 case reports and 52 papers relating to trials of probiotics (Figure 1).

Case reports

Of the 134 full articles obtained, 44 were case reports of adverse events, of which 24 were excluded because a probiotic was not administered or the patient was not receiving nutritional support. Therefore, 20 case reports of adverse events of probiotic
administration in 32 patients receiving nutritional support were included (19–38) (Figure 1).

The patients ranged from 1 mo to 89 y of age, had diagnoses of various major organ disorders, and were receiving EN (n = 17), PN (n = 12), or both (n = 3) (Table 2). The adverse events occurred after the administration of the probiotic bacteria *Lactobacillus rhamnosus* GG (n = 5) or the yeast *S. boulardii* (n = 27). There was variation in how the doses were reported (cells/d, mg/d, capsules/d, and sachets/d), and no dose was obtainable for 4 patients. Doses for *S. boulardii* were frequently reported in mg/d and ranged widely from 150 (27) to 3000 mg/d (32). When information was obtainable, the probiotics were administered via nasogastric tube (NGT; n = 9), percutaneous endoscopic gastrostomy (PEG; n = 6), jejunostomy (n = 1), or orally (n = 4). Probiotics were used for the prevention or treatment of AAD (n = 5), *C. difficile* (n = 5), small intestinal bacterial overgrowth (SIBO; n = 3), EN (n = 2), rotavirus (n = 1), or of unspecified origin (n = 16).

Depending on the organism, the adverse events that occurred were bacteremia (n = 5) or fungemia (n = 27), which were diagnosed based on clinical signs and confirmation of the probiotic as the source of the infection using culture analysis (n =

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**TABLE 1**
Detailed inclusion and exclusion criteria and data extracted

<table>
<thead>
<tr>
<th>PICOS</th>
<th>Inclusion and exclusion criteria</th>
<th>Data extraction</th>
</tr>
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<tbody>
<tr>
<td>Patient</td>
<td>Patients of any age receiving EN and/or PN. In reports of mixed patient groups, only those in whom more than half were receiving EN and/or PN were eligible. When there were 2 reports related to the same patient group (eg, a conference abstract subsequently published in full), the most complete was eligible to avoid duplication of patient numbers.</td>
<td>Location, age when probiotic was started, diagnoses (case reports only), patient group (trials only), type of nutrition support.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Oral and/or enteral administration of a probiotic. Reports in which this was given in addition to other compounds (eg, prebiotics) were also eligible.</td>
<td>Genus, species, and strain of the probiotic as given in the article. When this was not available, genus and species alone were extracted.</td>
</tr>
<tr>
<td>Comparators</td>
<td>Reports with or without a comparator group. Reports without a control group were included because the aim was to investigate potentially rare adverse events (16).</td>
<td>The dose of probiotic, route of administration, and any additional compounds given were also extracted.</td>
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<td>Outcome</td>
<td>Reports of presence or absence of adverse events. Reports of the clinical endpoints of mortality and morbidity (eg, infections) were included to offer insights into safety, as were clinical endpoints indicative of morbidity (eg, length of stay). Reports not recording adverse events or relevant clinical endpoints, but that were otherwise eligible, were also included.</td>
<td>The reason for probiotic use was extracted from case studies. Numbers in the intervention and comparator group, when relevant (trials only). In studies with multiple comparator groups (eg, EN and live probiotics compared with EN and heat-killed probiotics compared with PN), the most similar group to a control group was used (ie, EN and heat-killed probiotics) where possible.</td>
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<tr>
<td>Study design</td>
<td>Randomized controlled trials, controlled trials (eg, nonrandomized, historical controls), case series, and case reports were eligible, all of which were all relevant to the measurement of adverse events and safety (16). Although the search was undertaken in English, foreign language reports that were identified were translated when possible.</td>
<td>Details of an adverse event, microbiological method of identification, risk factors (as suggested by authors and literature), treatment, and outcome (case reports only). Presence or absence of adverse events or safety issues (as reported by the reference). When no information on safety, adverse events, side effects, or tolerance was given, this is reported.</td>
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</table>

The effect of the intervention on clinical endpoints (trials only).

For duplicate reports (eg, an abstract followed by subsequent full paper) only the most complete population was included; however, if relevant data (eg, adverse events) were in the brief report but not in the complete report, they were extracted and reported within the complete report. In studies with multiple comparator groups, the clinical endpoints between the intervention group with the most similar comparator group were compared.

Data relating to clinical (eg, stool frequency) and physiologic (eg, stool microbiology) outcomes not indicative of disease endpoints were not extracted.

Type of study design and numbers in the intervention and comparator groups (trials only).
32), sometimes in conjunction with other phenotypic analyses (eg, API strips, morphology; n = 14), or genotypic analyses such as restriction digest and gel electrophoresis (RD-GE; n = 14), polymerase chain reaction and gel electrophoresis (PCR-GE; n = 5), or DNA/RNA sequencing (n = 2). In 12 patients, phenotypic analyses alone were used to confirm the probiotic as the infective organism. Two patients also developed endocarditis, one after *L. rhamnosus* GG (20) and one after *S. boulardii* (35). In one patient, the vegetation was attached to a prosthetic mitral valve (35) and in the other between a CVC tip and the right atrium (20).

The risk factors for these adverse events, as identified by the authors and from the literature, were varied. A majority of patients had received antibiotics (n = 27) or had intravenous access (n = 30) via a CVC or a peripheral venous catheter. Other less frequently cited were those risk factors associated with bacterial translocation (eg, *C. difficile* colitis, sepsis, and mucositis) or immune suppression (eg, preterm birth, sepsis, and HIV).

Treatment of the adverse event frequently included stopping the probiotic (n = 25) and removing or changing the CVC when present (n = 17). The antibiotics prescribed in the 5 cases of bacteremia included ampicillin (n = 4), ceftriaxone, penicillin, and gentamicin (all n = 1), whereas the antifungals prescribed in 20 (74%) of the incidents of fungemia included fluconazole (n = 13), amphotericin B (n = 8), voriconazole (n = 1), and caspofungin (n = 1). In 8 (25%) patients, the adverse event reportedly resulted in death.

**Trials**

Of the 134 full articles obtained, 72 reported trials. Of these, 20 were excluded because they reported duplicate patient groups,
| Reference          | Age | Diagnosis            | NS   | Species/strain                      | Dose          | Route   | Purpose                       | Adverse event       | Identification | Risk factor               | Treatment                  | Outcome         |
|-------------------|-----|----------------------|------|-----------------------------------|---------------|---------|--------------------------------|---------------------|---------------|----------------------------|-----------------------------|----------------|----------------|
| Kunz et al., 2004 (19) | 1 mo | Short bowel Cholestasis | PN   | Lactobacillus rhamnosus GG        | 1 capsule/d   | Oral    | Prevent SIBO                  | Bacteremia          | Culture     | GI inflammation, short-bowel syndrome | Probiotic stopped, CVC removed, ceftriaxone, ampicillin | Recovery       |
|                   | 3 mo | Short bowel Cholestasis | PN   | L. rhamnosus GG                  | 1 capsule/d   | PEG     | Prevent SIBO                  | Bacteremia          | Culture     | GI inflammation, short-bowel syndrome | Probiotic stopped, CVC removed, ampicillin | Recovery       |
| Land et al., 2005 (20) | 3 mo | Cardiac stenosis      | EN   | L. rhamnosus GG ATCC5103         | $10^{10}$ cells/d | PEG     | Treat AAD                      | Bacteremia Endocarditis | Culture     | Antibiotics, CVC                | Probiotic stopped, CVC removed, penicillin, gentamicin | Recovery       |
|                   | 6 y  | Cerebral palsy Microcephaly | PN   | L. rhamnosus GG ATCC5103         | $10^{10}$ cells/d | Jej     | Treat AAD                      | Bacteremia          | Culture     | Antibiotics, CVC                | Probiotic stopped, ampicillin, gentamicin | Recovery       |
| De Groote et al, 2005 (21) | 10 mo | Short bowel           | PN   | L. rhamnosus GG ATCC5103         | 1/4 capsule/d | PEG     | Treat rotavirus                | Bacteremia          | Culture     | RNA sequencing, RD-GE            | Probiotic stopped, ampicillin, gentamicin | Recovery       |
| Langarotti et al, 2003 (22) | 1 mo | Preterm infant        | PN   | Saccharomyces boulardii          | $3 \times 10^6$ cells/d | —       | Prevent SIBO                  | Fungemia            | Culture     | C. albicans                     | Probiotic stopped, CVC removed, amphotericin B | Recovery       |
| Perapoch et al, 2000 (23) | 3 mo | Cardiopathy           | PN   | S. boulardii                     | 2 sachets/d   | —       | Treat diarrhea                 | Fungemia            | Culture     | Antibiotics, CVC                | CVC removed, amphotericin B | Recovery       |
| Cesaro et al, 2000 (24) | 8 mo | Leukemia              | PN   | S. boulardii                     | —             | Oral    | Prevent AAD                    | Fungemia            | Culture     | API strips, RD-GE               | Probiotic stopped, amphotericin B | Recovery       |
| Pletincx et al, 1995 (25) | 1 y  | Pneumonia Enteritis   | PN   | S. boulardii                     | 600 mg/d      | Oral    | Treat diarrhea                 | Fungemia            | Culture     | API strips, CVC                  | Probiotic stopped, fluconazole | Recovery       |
| Viggiano et al, 1995 (26) | 14 y | Burns                 | EN   | S. boulardii                     | 4 sachets/d   | PEG     | Prevent diarrhea               | Fungemia            | Culture     | Antibiotics, CVC                | Probiotic stopped, amphotericin B | Recovery       |
| Burkhardt et al, 2005 (27) | 19 y | Tetraparesis          | EN   | S. boulardii                     | 150 mg/d      | PEG     | Prevent diarrhea               | Fungemia            | Culture     | Proton pump inhibitor, prokinetic | Fluconazole, voriconazole | Recovery       |
| Zunic et al, 1991 (28) | 53 y | Colectomy Sepsis      | EN   | S. boulardii                     | 1500 mg/d     | NGT     | Prevent AAD                    | Fungemia            | Culture     | Antibiotics, CVC, sepsis, H2 antagonists | Probiotic stopped, amphotericin B, fluconazole | Recovery       |
| Lestin et al, 2003 (29) | 48 y | Diabetes Foot necrosis | EN   | S. boulardii                     | 150 mg/d      | NGT     | Treat CDAD                     | Fungemia            | Culture     | API strips, CVC                  | Probiotic stopped, Clostridium difficile, CVC | Recovery       |
| Fredenucci et al, 1998 (30) | 49 y | Pneumonia             | EN   | S. boulardii                     | 4 sachets/d   | NGT     | Treat EN diarrhoea             | Fungemia            | Culture     | API strips, RD-GE               | Fluconazole | Recovery       |
| Hmoquivi et al, 2000 (31) | 2 y  | Cystic fibrosis ileal atresia | PN   | S. boulardii                     | 750 mg/d      | —       | Prevent diarrhea               | Fungemia            | Culture     | Antibiotics, CVC                | Probiotic stopped, CVC removed, amphotericin B | Recovery       |

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<thead>
<tr>
<th>Reference</th>
<th>Patient</th>
<th>Diagnosis</th>
<th>NS</th>
<th>Age</th>
<th>Intervention (probiotic)</th>
<th>Outcome</th>
<th>Adverse event</th>
<th>Identification</th>
<th>Risk factor</th>
<th>Treatment</th>
<th>Outcome</th>
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<tr>
<td>Lherm et al, 2002 [32]</td>
<td>36 y</td>
<td>HIV/AIDS Lymphoma</td>
<td>EN</td>
<td>50</td>
<td>S. boulardii 1500 mg/d — Treat diarrhea</td>
<td>Fungemia</td>
<td>Culture, API strips</td>
<td>Antibiotics, CVC, chemotherapy, HIV</td>
<td>Probiotic stopped, fluconazole</td>
<td>Recovery</td>
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<tr>
<td></td>
<td>47 y</td>
<td>Esophageal cancer</td>
<td>EN</td>
<td>57</td>
<td>S. boulardii 2000 mg/d — Treat AAD</td>
<td>Fungemia</td>
<td>Culture, API strips, RD-GE</td>
<td>Antibiotics, CVC</td>
<td>Probiotic stopped, CVC removed, fluconazole</td>
<td>Recovery</td>
<td></td>
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<tr>
<td></td>
<td>78 y</td>
<td>Pulmonary disease</td>
<td>EN</td>
<td>56</td>
<td>S. boulardii 1500 mg/d — Prevent diarrhea</td>
<td>Fungemia</td>
<td>Culture, API strips, RD-GE</td>
<td>Antibiotics, CVC</td>
<td>Probiotic stopped</td>
<td>Recovery</td>
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<tr>
<td>Liols et al. 2008 [33]</td>
<td>50 y</td>
<td>Cardiac arrest</td>
<td>EN</td>
<td>51</td>
<td>S. boulardii 1500 mg/d — Prevent diarrhea</td>
<td>Fungemia</td>
<td>Culture, RD-GE, phenotypic</td>
<td>Antibiotics, CVC, malnutrition</td>
<td>Probiotic stopped, CVC changed</td>
<td>Death</td>
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<td>Henry et al., 2004 [34]</td>
<td>57 y</td>
<td>Oropharyngeal cancer</td>
<td>PN</td>
<td>56</td>
<td>S. boulardii 1000 mg/d — Prevent diarrhea</td>
<td>Fungemia</td>
<td>Culture, RD-GE, phenotypic</td>
<td>Antibiotics, CVC</td>
<td>Probiotic stopped, CVC changed, fluconazole</td>
<td>Recovery</td>
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<td>Munoz et al., 2005 [35]</td>
<td>59 y</td>
<td>Cardiac surgery</td>
<td>EN, PN</td>
<td>65</td>
<td>S. boulardii 6 capsules/d Oral</td>
<td>Treat diarrhea</td>
<td>Fungemia</td>
<td>Culture, PCR-GE</td>
<td>Antibiotics, CVC, mucositis, C. difficile, CVC</td>
<td>—</td>
<td>Death</td>
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<tr>
<td></td>
<td>74 y</td>
<td>MV replacement</td>
<td>EN, PN</td>
<td>54</td>
<td>S. boulardii — NGT</td>
<td>Treat CDAD</td>
<td>Fungemia</td>
<td>Culture, PCR-GE</td>
<td>Antibiotics, C. difficile, CVC, steroids</td>
<td>Probiotic stopped, fluconazole</td>
<td>Death</td>
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<tr>
<td></td>
<td>76 y</td>
<td>MV replacement</td>
<td>EN, PN</td>
<td>53</td>
<td>S. boulardii — NGT</td>
<td>Treat CDAD</td>
<td>Fungemia</td>
<td>Culture, PCR-GE</td>
<td>Antibiotics, C. difficile, CVC, prosthetic MV</td>
<td>Probiotic stopped, fluconazole</td>
<td>Death</td>
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<td>Rijinders et al., 2000 [36]</td>
<td>74 y</td>
<td>Neurosurgery</td>
<td>EN</td>
<td>73</td>
<td>S. boulardii 600 mg/d NGT</td>
<td>Treat EN diarrhea</td>
<td>Fungemia</td>
<td>Culture</td>
<td>—</td>
<td>CVC removed, fluconazole</td>
<td>Death</td>
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<td>Diagnosis</td>
<td>Outcome</td>
<td>Treatment</td>
<td>Recovery</td>
<td>Adverse event Identification</td>
<td>Purpose</td>
<td>Risk factors</td>
<td>Reference</td>
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<tr>
<td>Pulmonary disease</td>
<td>EN</td>
<td>S. boulardii</td>
<td>1500 mg/d</td>
<td>NGT</td>
<td>1 y</td>
<td>AE, antibiotic-associated diarrhea, CVC</td>
<td>Niault et al, 1999 (37)</td>
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<td></td>
<td>C. difficile, malnutrition, PVC</td>
<td>Cherifi et al, 2004 (38)</td>
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Table 3: Continued

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<thead>
<tr>
<th>Reference</th>
<th>Patient</th>
<th>Diagnosis</th>
<th>Outcome</th>
<th>Intervention (probiotics)</th>
<th>Dose Route</th>
<th>Screw insemination</th>
<th>Adverse event</th>
<th>Purpose of probiotic administration</th>
<th>Primary diagnosis given in case report</th>
<th>Age</th>
<th>Age reported from the time the probiotic was started (where available)</th>
<th>Risk factors for adverse event, including those suggested by report authors and those commonly found in the literature</th>
<th>Age at last birthday</th>
<th>Outcome relates to recovery or death from the adverse event</th>
<th>CVC, central venous catheter; PVC, peripheral venous catheter; GL, gastrointestinal.</th>
</tr>
</thead>
</table>

The trials were classified as safety trials (1 RCT and 2 nonrandomized trials) (39–41), and 50 were nonsafety trials (40 RCTs and 10 nonrandomized trials) (39, 42–90) (Table 3). The trials were based in a variety of locations including neonatal, pediatric, or adult ICUs; surgical units; burns units; general wards; or in the community, and the disorders reflected these locations, including preterm infants, critical illness, postoperative, trauma, pancreatitis, and burns (Table 3). The inclusion and exclusion criteria therefore varied widely depending on the patient group under investigation. The probiotics included single strains of lactobacilli, bifidobacteria, or S. boulardii, the combined use of single strains or proprietary mixtures of ≥3 strains. As with the case reports, there was variation in how the doses were reported (cells/d, cells kg⁻¹ d⁻¹, mg/d, mg kg⁻¹ d⁻¹, mL/d, and cells L⁻¹·d⁻¹). When it was reported as cells/d, it ranged widely from 10⁷ (40) to 1.8 × 10¹⁴ cells/d (56). In a small number of trials, the probiotic was given with other supplements, including probiotics, fiber, or glutamine. The probiotics were administered via NGT, PEG, nasojejunal tube (NJT), jejunoscopy, orogastric tube (OGT), or orally; within some trials, a range of methods was often used depending on the access routes available.

The 3 safety trials were classified as such because a stated aim was to investigate the safety of probiotic administration and because they undertook routine screening for adverse events or complications (39–41). The only safety RCT was an open-label trial in 15 critically ill adults receiving EN in addition to PN in some cases (41). Eight patients received L. plantarum 299v (1–2 × 10⁹ cells/d in fermented oatmeal formula) via an NGT for the duration of their ICU stay and 7 patients acted as a control (no placebo given). Safety was investigated through weekly microbiological screening of samples (eg, blood, urine, tracheal secretions, and wounds), whereas CVC tips were screened on removal or as clinically indicated. All samples were analyzed for the presence of the probiotic or other organisms, and none were found to contain any lactobacillus. Two patients developed bowel distension at the higher probiotic dose, but there were no other adverse events (41).

One safety trial was a case series of 66 preterm infants on neonatal ICU who were receiving EN of expressed breast milk or formula (in addition to PN until EN was sufficient) (39). Patients received B. breve (10⁹ cells/d) via an NGT per an “early and short-term” protocol (before 7 d of age and continued for 7 d) or a “delayed and longer-term” protocol (after 7 d of age and continued for between 7 and 48 d). Adverse events were monitored throughout. Two infants who received “delayed and longer-term” administration had mild functional ileus and aggregates of cornstarch from the probiotic product were a probiotic was not administered, or an insufficient number of patients were receiving nutritional support. For the 4 duplicate patient groups, no relevant information (eg, adverse events) was contained within the earlier abstract/article that was not contained within the complete article. In total, 52 citations were included reporting 53 trials [one article reported a case series and an RCT (39)], in which 4131 patients received probiotics and 3643 patients were in a relevant comparator group (Figure 1). One trial in patients undergoing hepatectomy compared probiotics given pre- and postoperatively with those given postoperatively only; therefore, both groups contributed to the overall patient numbers receiving probiotics (78). Of the 53 trials, only 3 were classified as safety trials (1 RCT and 2 nonrandomized trials) (39–41), and 50 were nonsafety trials (40 RCTs and 10 nonrandomized trials) (39, 42–90) (Table 3).
<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Patient group</th>
<th>NS</th>
<th>Design</th>
<th>No. of probiotics/comparators</th>
<th>Species/strain</th>
<th>Dose</th>
<th>Route</th>
<th>Adverse events</th>
<th>Clinical outcomes relevant to safety</th>
<th>Outcomes</th>
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<td></td>
<td></td>
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<tr>
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<td>Neonatal ICU</td>
<td>Preterm infants</td>
<td>EN, PN</td>
<td>Case series</td>
<td>66</td>
<td><em>Bifidobacterium breve</em> YIT4010</td>
<td>10^7 cells/d</td>
<td>NGT</td>
<td>No relevant clinical endpoints</td>
<td>Functional ileus in 2 patients (cornstarch aggregates in stool), no other side effects</td>
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<tr>
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<td>Critically ill children</td>
<td>EN, PN</td>
<td>Case series</td>
<td>28</td>
<td><em>Lactobacillus casei</em> Shirotah (Yakult)</td>
<td>10^7 cells/d</td>
<td>NGT</td>
<td>No relevant clinical endpoints</td>
<td>No lactobacillus in blood, urine, sputum, catheters, etc; no adverse events; well tolerated</td>
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<tr>
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<td>Adult ICU</td>
<td>Critically ill</td>
<td>EN, PN</td>
<td>RCT</td>
<td>87</td>
<td><em>Lactobacillus plantarum</em> 299v (ProViva)</td>
<td>1–2 × 10^11 cells/d</td>
<td>NGT</td>
<td>No relevant clinical endpoints compared between groups</td>
<td>Bowel distension in 2 patients; no probiotic in blood, urine, tracheal secretions; no adverse events</td>
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<tr>
<td>Nonsafety trials (RCTs)</td>
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<td>Li et al, 2004 (42)</td>
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<td>Preterm infants</td>
<td>EN, PN</td>
<td>RCT</td>
<td>20/10</td>
<td><em>B. breve</em></td>
<td>1.6 × 10^8 cells/d</td>
<td>NGT</td>
<td>NEC (NS), sepsis (NS), infections (NS)</td>
<td>Well tolerated, no side effects</td>
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<td>Wang et al, 2007 (43)</td>
<td>Neonatal ICU</td>
<td>Preterm infants</td>
<td>EN, PN</td>
<td>RCT</td>
<td>33/33</td>
<td><em>B. breve M-16V</em></td>
<td>3.2 × 10^8 cells/d</td>
<td>NGT</td>
<td>No relevant clinical endpoints compared between groups</td>
<td>No adverse events</td>
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<td>Neonatal ICU</td>
<td>Preterm infants</td>
<td>EN, PN</td>
<td>RCT</td>
<td>45/46</td>
<td><em>B. breve</em> YIT4010</td>
<td>10^8 cells/d</td>
<td>NGT</td>
<td>No relevant clinical endpoints compared between groups</td>
<td>No adverse events</td>
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<td>EN, PN</td>
<td>RCT</td>
<td>65/63</td>
<td><em>Bifidobacterium lactis</em></td>
<td>6 × 10^9 cells kg^-1 d^-1</td>
<td>NGT, OGT</td>
<td>Infections (NS)</td>
<td>No <em>Bifidobacteria</em> bacteremia</td>
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<td>Bin-Nun et al, 2005 (45)</td>
<td>Neonatal ICU</td>
<td>Preterm infants</td>
<td>EN, PN</td>
<td>RCT</td>
<td>72/30</td>
<td>ABC Dophilus</td>
<td>10^9 cells/d</td>
<td>NGT</td>
<td>Mortality (NS), NEC (reduced in probiotic)</td>
<td>No sepsis caused by probiotic, no adverse events</td>
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<tr>
<td>Costalos et al, 2003 (46)</td>
<td>Neonatal ICU</td>
<td>Preterm infants</td>
<td>EN, PN</td>
<td>RCT</td>
<td>51/36</td>
<td><em>Saccharomyces boulardii</em></td>
<td>50 mg · kg^-1 · d^-1</td>
<td>Oral</td>
<td>NEC (NS), sepsis (NS)</td>
<td>No <em>S. boulardii</em> sepsis, well tolerated, no side effects</td>
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<td>Dani et al, 2002 (47)</td>
<td>Neonatal ICU</td>
<td>Preterm infants</td>
<td>EN, PN</td>
<td>RCT</td>
<td>295/290</td>
<td><em>Lactobacillus rhamnosus</em> (Dicolitis)</td>
<td>6 × 10^9 cells/d</td>
<td>NGT</td>
<td>NEC (NS), sepsis (NS), urinary tract infections (NSD)</td>
<td>No information given</td>
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<td>Manzoni et al, 2006 (48)</td>
<td>Neonatal ICU</td>
<td>Preterm infants</td>
<td>EN, PN</td>
<td>RCT</td>
<td>39/41</td>
<td><em>L. rhamnosus</em> GG</td>
<td>6 × 10^9 cells/d</td>
<td>OGT</td>
<td>Mortality (NS), NEC (NS), sepsis (NS), fungal infections (NS)</td>
<td>No lactobacillus sepsis, no adverse events</td>
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<tr>
<td>Millar et al, 1993 (49)</td>
<td>Neonatal ICU</td>
<td>Preterm infants</td>
<td>EN, PN</td>
<td>RCT</td>
<td>10/10</td>
<td><em>L. rhamnosus</em> GG</td>
<td>2 × 10^8 cells/d</td>
<td>NGT</td>
<td>Antibiotic use (NS), ICU length of stay (NS)</td>
<td>No lactobacillus bacteremia</td>
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<tr>
<td>Rouge et al, 2009 (50)</td>
<td>Neonatal ICU</td>
<td>Preterm infants</td>
<td>EN, PN</td>
<td>RCT</td>
<td>45/49</td>
<td><em>L. rhamnosus</em> GG <em>Bifidobacterium longum</em> BB536</td>
<td>2 × 10^8 cells/d</td>
<td>—</td>
<td>Mortality (NS), NEC (NS), sepsis (NS), nosocomial infections (NS)</td>
<td>No probiotic bacteremia, no adverse events</td>
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<tr>
<td>Samanta et al, 2009 (51)</td>
<td>Neonatal ICU</td>
<td>Preterm infants</td>
<td>EN, PN</td>
<td>RCT</td>
<td>91/95</td>
<td><em>Bifidobacterium infantis</em> <em>B. bifidum</em> <em>B. longum</em> <em>Lactobacillus acidophilus</em></td>
<td>2 × 10^9 cells/d</td>
<td>NGT, OGT</td>
<td>Mortality (reduced in probiotic), sepsis (reduced in probiotic), NEC (reduced in probiotic), length of stay (reduced in probiotic)</td>
<td>No probiotic bacteremia</td>
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<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Patient group</th>
<th>NS Design</th>
<th>No. of probiotics/comparators</th>
<th>Intervention (probiotic)</th>
<th>Outcomes</th>
<th>Adverse events</th>
</tr>
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<tbody>
<tr>
<td>Underwood et al., 2009 (52)</td>
<td>Neonatal ICU</td>
<td>Preterm infants</td>
<td>EN, PN</td>
<td>RCT 61/29</td>
<td>L. rhamnosus GG or Bifidobacterium infantis B. bifidum B. longum L. acidophilus (both with inulin)</td>
<td>10^9 cells/d NGT, OGT, oral Weight gain (NS)</td>
<td>No adverse events, well tolerated</td>
</tr>
<tr>
<td>Lin et al., 2005 (53)</td>
<td>Neonatal ICU</td>
<td>Preterm infants</td>
<td>EN, PN</td>
<td>RCT 180/187</td>
<td>B. infantis L. acidophilus</td>
<td>250 mg · kg^-1 · d^-1 OGT, oral Mortality (reduced in probiotic), NEC (reduced in probiotic), sepsis (reduced in probiotic)</td>
<td>No probiotic bacteremia, no complications from probiotic</td>
</tr>
<tr>
<td>Lin et al., 2008 (54)</td>
<td>Neonatal ICU</td>
<td>Preterm infants</td>
<td>EN, PN</td>
<td>RCT 217/217</td>
<td>B. bifidum NCDO 1453 L. acidophilus NCDO 1748</td>
<td>250 mg · kg^-1 · d^-1 OGT, oral Mortality (reduced in probiotic), NEC (reduced in probiotic), sepsis (increased in probiotic)</td>
<td>No probiotic bacteremia, no adverse events</td>
</tr>
<tr>
<td>Honeycutt et al., 2007 (55)</td>
<td>Pediatric ICU</td>
<td>Critically ill children</td>
<td>EN</td>
<td>RCT 31/30</td>
<td>L. rhamnosus GG</td>
<td>10^10 cells/d NGT, oral Mortality (NS), nosocomial infections (NS)</td>
<td>No probiotic bacteremia, no adverse events</td>
</tr>
<tr>
<td>Alberda et al., 2007 (56)</td>
<td>Adult ICU</td>
<td>Critically ill</td>
<td>EN</td>
<td>RCT 19/9</td>
<td>VSL#3</td>
<td>1.8 · 10^12 cells/d NGT</td>
<td>Mortality (NS), MODS (NS)</td>
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<tr>
<td>Knight et al., 2009 (57)</td>
<td>Adult ICU</td>
<td>Critically ill</td>
<td>EN</td>
<td>RCT 130/129</td>
<td>Synbiotic 2000 Forte (20 g fiber/d)</td>
<td>2 · 10^10 cells/d NGT, OGT, oral Mortality (NS), pneumonia (NS), ICU and hospital length of stay (NS)</td>
<td>No complications, single Lesacncoccic detected from a tracheal aspirate</td>
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<tr>
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<td>Adult ICU</td>
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<td>EN, PN</td>
<td>RCT 6/5</td>
<td>Synbiotic 2000 Forte</td>
<td>— NGT, NJT</td>
<td>Mortality (NS)</td>
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<tr>
<td>Jain et al., 2004 (59)</td>
<td>Adult ICU</td>
<td>Critically ill</td>
<td>EN, PN</td>
<td>RCT 45/45</td>
<td>Trevis (15 g prebiotic/d)</td>
<td>2 · 10^10 cells/d NGT, OGT, oral Mortality (NS), sepsis (NS)</td>
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<td>Forestier et al., 2008 (60)</td>
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<td>EN</td>
<td>RCT 102/106</td>
<td>Lactobacillus casei rhamnosus</td>
<td>2 · 10^9 cells/d NGT, oral No relevant clinical endpoints compared between groups</td>
<td>No lactobacillus sepsis</td>
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<td>McNaught et al., 2005 (61)</td>
<td>Adult ICU</td>
<td>Critically ill</td>
<td>EN, PN</td>
<td>RCT 52/51</td>
<td>L. plantarum 299v (ProViva)</td>
<td>10^10 cells/d NGT, oral Mortality (NS), sepsis (NS), ICU length of stay (NS)</td>
<td>No information given</td>
</tr>
<tr>
<td>Klarin et al., 2008 (62)</td>
<td>Adult ICU</td>
<td>Critically ill</td>
<td>EN, PN</td>
<td>RCT 22/22</td>
<td>L. plantarum 299v</td>
<td>8 · 10^10 −9.6 · 10^11 cells/d NGT, OGT, oral Mortality (NS), ICU length of stay (NS), sepsis (NS), bacteremia (NS), catheter tip infections (NS)</td>
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<td>Tempé et al., 1983 (63)</td>
<td>Adult ICU</td>
<td>Critically ill</td>
<td>EN</td>
<td>RCT 20/20</td>
<td>S. boullardii</td>
<td>10^10 cells · L^-1 · d^-1 NGT</td>
<td>Diarrhea (reduced in probiotic)</td>
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<td>Bleicher et al., 1997 (64)</td>
<td>Adult ICU</td>
<td>Critically ill</td>
<td>EN</td>
<td>RCT 64/64</td>
<td>S. boullardii</td>
<td>2000 mg/d NGT</td>
<td>Diarrhea (reduced in probiotic)</td>
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<td>Reference</td>
<td>Location</td>
<td>Patient group</td>
<td>NS</td>
<td>Design</td>
<td>No. of probiotics/comparators</td>
<td>Intervention (probiotic)</td>
<td>Outcomes</td>
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<td>Adult ICU</td>
<td>Brain injury</td>
<td>EN</td>
<td>RCT</td>
<td>10/10</td>
<td><em>Lactobacillus johnsonii</em> Lat (LC1) (glutamine)</td>
<td>Sepsis (NS), infections reduced in probiotic, ICU length of stay reduced in probiotic</td>
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<td>Giamarellos-Bourboulis et al, 2009 (66)</td>
<td>Adult ICU</td>
<td>Trauma</td>
<td>EN, PN</td>
<td>RCT</td>
<td>36/36</td>
<td><em>Synbiotic 2000 Forte</em> (10 g fiber/d)</td>
<td>Mortality (NS), sepsis reduced in synbiotic</td>
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<tr>
<td>Spindler-Vesel et al, 2007 (67)</td>
<td>Adult ICU</td>
<td>Trauma</td>
<td>EN, PN</td>
<td>RCT</td>
<td>26/29</td>
<td><em>Synbiotic 2000</em> (10 g fiber/d)</td>
<td>Mortality (NS), infections reduced in probiotic</td>
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<td>Adult ICU</td>
<td>Severe acute pancreatitis</td>
<td>EN</td>
<td>RCT</td>
<td>152/144</td>
<td>Ecologic 641</td>
<td>Mortality (increased in probiotic), infectious complication (NS), bowel ischemia (increased in probiotic), diarrhea (NS)</td>
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<td>Heimburger et al, 1994 (69)</td>
<td>Adult ICU, general wards</td>
<td>Mixed</td>
<td>EN</td>
<td>RCT</td>
<td>18/23</td>
<td><em>L. acidophilus</em></td>
<td>Diarrhea (NS)</td>
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<td>Adult ICU, surgical unit</td>
<td>Pancreato-duodenectomy</td>
<td>EN</td>
<td>RCT</td>
<td>40/40</td>
<td><em>Synbiotic 2000</em></td>
<td>Mortality (NS), infections reduced in probiotic, hospital length of stay (NS)</td>
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<td>Adult ICU, surgical unit</td>
<td>Abdominal surgery</td>
<td>EN</td>
<td>RCT</td>
<td>30/30</td>
<td><em>L. plantarum 299v</em></td>
<td>Infections (NS), noninfectious complications (NS), hospital length of stay (NS)</td>
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<td>Rayes et al, 2005 (72)</td>
<td>Adult ICU, surgical unit</td>
<td>Liver transplant</td>
<td>EN</td>
<td>RCT</td>
<td>33/33</td>
<td><em>Synbiotic 2000</em></td>
<td>Infections (reduced in probiotic), noninfectious complications (increased in probiotic), hospital length of stay (NS)</td>
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<td>Rayes et al, 2002b (73)</td>
<td>Adult ICU, surgical unit</td>
<td>Liver transplant</td>
<td>EN</td>
<td>RCT</td>
<td>31/32</td>
<td><em>L. plantarum 299v</em></td>
<td>Infections (reduced in probiotic), noninfectious complications (NS), ICU length of stay (NS)</td>
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<td>Olah et al, 2002 (74)</td>
<td>Surgical unit</td>
<td>Acute pancreatitis</td>
<td>EN</td>
<td>RCT</td>
<td>22/23</td>
<td><em>L. plantarum 299v</em></td>
<td>Mortality (NS), septic complications (reduced in probiotic), hospital length of stay (NS)</td>
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<tr>
<td>Qin et al, 2008 (75)</td>
<td>Surgical unit</td>
<td>Acute pancreatitis</td>
<td>EN</td>
<td>RCT</td>
<td>36/38</td>
<td><em>L. plantarum</em> (plus EN)</td>
<td>Mortality (NS), septic complications requiring surgery (reduced in probiotic)</td>
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<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Patient group</th>
<th>Study details</th>
<th>Intervention (probiotic)</th>
<th>Outcomes</th>
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<td>Surgical unit</td>
<td>Severe acute pancreatitis</td>
<td>EN RCT 33/29</td>
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<td>4 × 10^{10} cells/d</td>
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<td>Kanazawa et al, 2005 (77)</td>
<td>Surgical unit</td>
<td>Hepatectomy</td>
<td>EN, PN RCT 21/23</td>
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<td>EN RCT 40/41</td>
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<td>2 × 10^{10} cells/d</td>
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<td>Schlotterer et al, 1987 (79)</td>
<td>Burns unit</td>
<td>Burns</td>
<td>EN, PN RCT 9/9</td>
<td><em>S. boulandii</em></td>
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<td>Fukushima et al, 2007 (80)</td>
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<td>Elderly</td>
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<td>Reuman et al, 1986 (81)</td>
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<td><em>L. acidophilus</em></td>
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<td>Saoh et al, 2007 (82)</td>
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<td>EN CT 338/226</td>
<td><em>B. breve</em> M-16V</td>
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<td>Preterm infants, critically ill</td>
<td>EN, CN CT 1237/1282</td>
<td><em>L. acidophilus</em> B. infantis</td>
<td>2 × 10^{9} cells/d</td>
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<td>Lee et al, 2007 (84)</td>
<td>Neonatal ICU</td>
<td>Preterm infants</td>
<td>EN, PN Case series 73</td>
<td><em>L. acidophilis</em> ATCC _ 4356</td>
<td>10^{8} cells/d</td>
</tr>
<tr>
<td>Laviano et al, 2004 (85)</td>
<td>Adult ICU</td>
<td>Brain injury</td>
<td>EN, PN CT 12/8</td>
<td>VSL#3</td>
<td>5 × 10^{11} cells/d</td>
</tr>
<tr>
<td>Shimizu et al, 2009 (86)</td>
<td>Adult ICU</td>
<td>SIRS</td>
<td>EN CT 20/26</td>
<td><em>B. breve</em> Yakult <em>L. casei</em> Shirota (13 g prebiotic/d)</td>
<td>6 × 10^{8} cells/d</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Patient group</th>
<th>NS</th>
<th>Design</th>
<th>No. of probiotics/comparators</th>
<th>Species/strain&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Dose</th>
<th>Route&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Clinical outcomes relevant to safety&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Adverse events&lt;sup&gt;6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candy et al, 2001 (87)</td>
<td>Pediatric unit</td>
<td>Short bowel</td>
<td>EN</td>
<td>Case report</td>
<td>1</td>
<td><em>L. casei</em> Shirota</td>
<td>$4.5 \times 10^9$ cells/d</td>
<td>PEG</td>
<td>No relevant clinical endpoints in the case study</td>
<td>No d-lactic acidosis</td>
</tr>
<tr>
<td>Del Piano et al, 2004 (88)</td>
<td>General wards</td>
<td>Permanent vegetative state</td>
<td>EN</td>
<td>Case series</td>
<td>7/6</td>
<td><em>B. longum W11</em> (2.5 g prebiotic/d)</td>
<td>$5 \times 10^9$ cells/d</td>
<td>PEG</td>
<td>Fever (NS), antibiotic use (NS), diarrhea (NS)</td>
<td>No information given</td>
</tr>
<tr>
<td>Schneider et al, 2005 (89)</td>
<td>Community</td>
<td>Long-term EN</td>
<td>EN</td>
<td>CT</td>
<td>10</td>
<td><em>S. boulardii</em></td>
<td>1000 mg/d</td>
<td>NGF, PEG, Jef</td>
<td>No clinical endpoints compared between patients and healthy subjects</td>
<td>No saccharomyces fungemia, diarrhea in one patient</td>
</tr>
</tbody>
</table>
| Kubota et al, 2007 (90) | Community | Hypopaganglionosis | PN   | Case reports | 2                           | *B. breve* Yakult  
*L. casei* Shirota  
(3 g prebiotic/d) | 6000 mg/d | Oral     | Catheter related sepsis (reduced in both cases) | No information given  |

<sup>1</sup> ICU, intensive care unit; SIRS, systemic inflammatory response syndrome; EN, enteral nutrition; PN, parenteral nutrition; RCT, randomized controlled trial; CT, controlled trial; NGT, nasogastric tube; PEG, percutaneous endoscopic gastrostomy; Jej, jejunostomy; OGT, orogastric tube; NEC, necrotizing enterocolitis; NJT, nasojejunal tube; MODS, Multiple Organ Dysfunction Syndrome.

<sup>2</sup> In studies with numerous comparator groups, the most similar group to a control group for the probiotic intervention was used. The numbers are reported as in the article and relate to how the clinical outcome data were compared and therefore may be intention to treat or per protocol.

<sup>3</sup> Species/strain administered (as defined in the article) and the dose. Proprietary multispecies products are as follows: ABC Dophilus (Solgar, Natanya, Israel) consists of *B. infantis*, *B. bifidus*, and *Streptococcus thermophilus*; Ecologic 641 (Windlove Bio Industries, Amsterdam, Netherlands) consists of *L. acidophilus*, *L. casei*, *L. salivarius*, *L. lactis*, *B. bifidum*, and *B. lactis*; Synbiotic 2000/Synbiotic 2000 Forte (Medipharm, Kägeröd, Sweden, and Des Moines, IA) consists of *Pediococcus pentosaceus*, *Leuconostoc mesenteroides*, *L. paracasei*, *L. plantarum*, β-glucan, inulin, pectin, and resistant starch; Trevis (Chr Hansen Biosystem, Horsholm, Denmark) consists of *L. acidophilus* La5, *L. bulgaricus*, *B. lactis* Bb-12, and *S. thermophilus*; VSL#3 (VSL Pharmaceuticals, Ft Lauderdale, FL) consists of *L. casei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii subsp. bulgaricus*, *B. longum*, *B. breve*, *B. infantis*, and *S. thermophilus*.

<sup>4</sup> Route of probiotic administration.

<sup>5</sup> Clinical findings include mortality and morbidity or endpoints indicative of morbidity (eg, antibiotic use and length of stay).

<sup>6</sup> Relates to the presence or absence of adverse events, safety issues, side effects, or tolerance and is reported as detailed in the article. When an article did not report such information, it was reported.
identified in stools. In the subsequent RCT conducted by the
group, only the probiotic supernatant fluid was administered,
to remove the cornstarch particles, without any adverse effects
reported (39).

The remaining safety trial was a case series of 28 critically ill
children on pediatric ICU, all who were receiving EN, in addition
to PN in 3 cases (40). Patients received L. casei Shirota (10^7
cells/d) via an NGT for up to 5 d, and safety was investigated
through microbiological screening for the presence of the pro-
biotic in compartments in which it should not be detected (eg,
blood, catheters). There were no adverse events attributable to
the probiotic, and L. casei Shirota was not detected in any
normally sterile body fluid or surface (40).

In total, 40 trials were classified as nonsafety RCTs (39, 42–
80). In these trials, clinical outcomes relevant to safety (eg,
mortality and infections) were measured to test the hypothesis
that probiotics reduced their incidence, and microbiological
sampling was undertaken often only when a patient’s clinical
signs dictated it.

These nonsafety RCTs reported a range of clinical endpoints
measured at a variety of time points, only a selection of which are
reported here. Mortality was reported as an endpoint in 22 trials
(probiotics lowered mortality in 3 trials, made no significant
difference in 18 trials, and increased mortality in 1 trial).
Interestingly, all 3 trials in which mortality was reduced were
undertaken in the neonatal ICU (51, 53, 54). The incidence or
duration of sepsis or septic complications was reported in 16 trials
(probiotics lowered it in 5 trials, made no significant difference in
10 trials, and increased it in 1 trial). The incidence or duration of
infections was reported in 17 trials (probiotics lowered it in 7
trials and made no significant difference in the remaining 10 trials).
The effects of probiotics on the other clinical endpoints
indicative of safety are shown in Table 3.

In total, 3 RCTs reported a statistically significantly greater
incidence of negative clinical endpoints in patients receiving
probiotics (54, 68, 72). One was in 66 patients after liver
transplant who were receiving postoperative EN via an NGT (72).
The intervention group (n = 33) received Symbiotic 2000
(Medipharm, Kägeröd, Sweden, and Des Moines, IA) consisting
of 8 × 10^10/d of Pediococcus pentosaceus, Leuconostoc mes-
enteroides, L. paracasei, and L. plantarum and 20 g/d of
β-glucan, inulin, pectin, and resistant starch, whereas the control
group (n = 33) received only the fiber component for 14 d. There
was a significant reduction in infections and antibiotic duration
and no significant difference in hospital length of stay in the
intervention group. However, there was a significant increase
in noninfectious complications in the probiotic group (n = 12;
36%) compared with the control group (n = 4; 12%; P = 0.022).
These complications were biliary tract stenoses, fistulas, lienal-
steal syndrome (none of which occurred in the control group),
abdominal hemorrhage, and acute renal failure (occurred in both
groups).

The second was a multicenter RCT in 296 patients with
severe acute pancreatitis who were receiving EN via an NGT (68).
The intervention group (n = 152) received Ecologic 641 (Win-
clove Bio Industries, Amsterdam, Netherlands) consisting of
8 × 10^10 of L. acidophilus, L. casei, L. salivarius, L. lactis, B.
bifidum, and B. lactis), whereas the control group (n = 144) re-
ceived an identically packaged placebo for up to 28 d. There was
significantly higher mortality in the probiotic group (n = 24,
16%) than in the control group (n = 9; 6%; P = 0.01). Bowel
ischemia, detected during surgery or autopsy, occurred in 9 (6%)
patients in the probiotic group, but did not occur in any patients
in the control group (P = 0.004). There were no differences in
the incidence of infectious complications between groups (30% 
probiotic compared with 28% control; P = 0.80), and none of
the infections were caused by the probiotic strains.

The third study was a multicenter open-label RCT in 434 very-
low-birth-weight preterm infants on the neonatal ICU who were
receiving EN and/or PN (54). The intervention group (n = 217)
received B. bifidum and L. acidophilus (250 mg · kg^-1 · d^-1),
whereas the control group (n = 217) received no additional
supplement. There was a significantly higher incidence of sepsis
in the probiotic (n = 40; 18.4%) group than in the control group
(n = 24; 11.1%; P = 0.03). However, after univariate and mul-
tivariate analysis accounting for confounding variables, the
significance of this increased incidence did not persist.

Of the nonsafety RCTs, 21 reported that there were no adverse
events, side effects, or complications related to probiotics; 6
reported them to be well tolerated; and 14 specified that the
probiotic did not cause bacteremia, fungemia, sepsis, or infec-
tions (numbers are not mutually exclusive). Twelve of the trials
did not comment on adverse events or tolerance.

Ten studies were classified as nonsafety, nonrandomized trials,
including 6 controlled trials (CTs), 2 case series, and 2 case
reports (of 3 patients) (81–90). Most CTs used historic controls,
and one of these contributed 2519 patients to this systematic
review (83). One of the CTs used a control group of healthy
subjects not receiving EN or PN; therefore, comparative data
were not extracted (89). None of the CTs reported an increase in
mortality or morbidity in the probiotic groups compared with
the control groups. No adverse events were reported in any of
these trials, except for the development of diarrhea in one patient
who was receiving long-term EN with 1000 mg S. bouardiili (89).

DISCUSSION

Probiotics have indications that support their use in patients
receiving nutritional support. This systematic review has iden-
tified numerous case reports of infectious complications asso-
ciated with probiotics in this setting. However, many trials have
been undertaken over a wide range of patient ages (including
preterm infants) and locations (including ICUs), which have
largely shown either no effect or a positive effect of probiotics
on the outcomes measured. Only 3 trials showed increased
complications that were largely noninfectious in nature and in
specific situations (patient groups, probiotics, dose, and route of
administration).

All case reports detailed infections caused by L. rhamnosus
GG or S. bouardiili, likely reflecting their wider use in the
clinical setting rather than their increased virulence. For exam-
ple, in the areas of EN-associated diarrhea (10), AAD (11),
CDAD (12), and necrotizing enterocolitis (13), more trial pa-
tients have been investigated by using L. rhamnosus GG or S.
bouardiili than any other probiotic. Therefore, their use in
practice is likely to be greater.

The presence of a CVC was a frequently reported risk factor
for probiotic infections. However, many patients were on the ICU
and therefore would inevitably have a CVC in situ, and CVC tips
were investigated for contamination in very few cases. The risk
likely relates to environmental contamination with the probiotic that gains access to the systemic circulation when the CVC is handled. Opening a sachet of *S. boulardii* can result in hand contamination, which does not completely resolve even after hand-washing (31). This may explain the case reports of *S. boulardii* fungemia in patients who were not receiving the probiotic, but who neighbored those who were (91, 92). Some meta-analyses have shown that PN may itself increase the risk of infectious complications when compared with no nutritional support (93) or with EN (94). In the current systematic review, when possible, data were extracted from probiotic groups and control groups receiving similar nutritional support (eg, both PN, both EN, or both mixed); in only one trial was this not possible (PN compared with PN/EN/probiotics) (75). Therefore the effect of PN, as opposed to the effect of a combination of the probiotic and the CVC, on infectious complications and therefore the findings of this systematic review are likely to be minimal.

Most case reports of probiotic infections were in patients who were also receiving antibiotics. Antibiotics alter the gastrointestinal microbiota (95), which potentially enables proliferation of the probiotic in the gastrointestinal tract. However, antibiotics are frequently used in patients requiring nutritional support, and the prevention of AAD is a proven indication for probiotics (11). Antibiotic use in those who developed probiotic infections may be a marker of other risk factors, such as the presence of CVC or critical illness. In critical illness, bacterial translocation across the gastrointestinal epithelium can occur, which in combination with impaired immune function can result in infection. However, studies in animals (96, 97) and humans (98) indicate that translocation can occur from any component of the host’s microbiota, rather than specifically the probiotic. In addition, some probiotics may actually improve intestinal barrier function (99), although this has yet to be convincingly shown in the critically ill (56, 59, 61).

Other risk factors for adverse events were those that increased probiotic survival to the small intestine (eg, increasing gastric pH and postpyloric administration). Intragastric EN may itself increase gastric pH (100). Meanwhile, although infrequently reported in the clinical trials, gastric acid–suppressing drugs (eg, proton pump inhibitors and H2 antagonists) are likely to have been frequently used in the ICU (101). Some studies have reported that oral consumption of probiotics by healthy subjects results in 0.5–10% survival of the bacteria into the small intestine (102–104), depending on the resistance of the strains to gastric acid and biliary and pancreatic secretions (104). In contrast, postpyloric EN allows complete survival of the probiotic into the small intestine, thereby increasing the dose reaching the small intestine by ≥10-fold. Of the case reports, only one patient was receiving probiotics via a jejunostomy (20); however, of the 3 RCTs reporting increased negative clinical outcomes, 2 were in patients in whom the probiotic was administered via an NJT (68, 72).

In the postoperative liver transplant trial, the complications consisted of biliary tract stenoses, fistulas, and lienalis-steal syndrome (72). Lienalis-steal syndrome is the hypoperfusion of the hepatic artery after liver transplantation because of a diversion of blood flow into a different arterial branch (105). The prevalence of lienalis-steal syndrome was 4/33 (12%), compared with a previously reported prevalence of 4–6% (105); however, in view of the low actual numbers, this could have been a type 1 statistical error. In the severe acute pancreatitis trial (68), the authors speculated that the increased mortality due to bowel ischemia might also have involved hypoperfusion, but in this case intestinal hypoperfusion, due to acute pancreatitis, mucosal inflammation, and increased oxygen demand due to both EN and probiotics (68). A recent subgroup analysis has since shown increased urinary concentrations of intestinal fatty acid binding protein, a marker of enterocyte damage, in those patients receiving the probiotic, particularly in those who developed bowel ischemia (106), the exact mechanisms of which effect require investigation. Importantly, this trial used a novel probiotic that lacked extensive animal and human safety testing (107). Other, albeit smaller, trials have been conducted in which probiotics were given via a postpyloric feeding tube (58, 70, 71, 73–78) or to patients with liver transplant (73) or pancreatitis (74–76), and such adverse events were either not recorded or were not statistically significantly increased.

Many issues regarding the design or reporting of case reports and trials limited their interpretation. Many did not characterize the probiotic to the strain level, despite potentially different phenotypic characteristics within a species. Inconsistent methods were used to report the dose (eg, cells/d and mg/d), and, where consistent methods were used, the actual doses varied widely. Interestingly, probiotic infections occurred across various doses. Toxicity studies have shown that some probiotics can be safely tolerated at doses in excess of 1010 cells/d by mice, corresponding to much higher safe doses in humans (96, 97). Taken together, these observations imply that the risk of probiotic infections may result from patient-related factors or the strain used, rather than merely its dose.

There were very few safety trials of probiotics in patients receiving nutritional support. Only one of these trials was an RCT (41), albeit in a small group of patients, whereas another gave the probiotic for only a short time (40). Some of the nonsafety, nonrandomized trials used historic controls, and one contributed a large number of patients (*n* = 2519) (83). Although trials have been conducted in a wide range of patient groups, only one has been conducted in patients receiving nutritional support in the community (89).

Studies have shown that many clinical trials do not report adverse events, and those that do lack information on how the adverse events were monitored, which leads to their under-reporting in the literature (108). Similar issues were faced here, with many trials reporting that probiotics were “well tolerated”; however, few of these trials provided details about the criteria used to judge this. Three trials were published in abstract form only and therefore lacked detail (44, 58, 85). In cases in which patients died, it was sometimes difficult to directly attribute the patients’ death to the probiotic infection. In addition, many identified the probiotic as the infective agent using only phenotypic analysis (eg, culture and morphology). Limitations in classification criteria and the phenotypic similarity between some probiotics make it difficult to distinguish between strains in this way (109). When probiotic infection is suspected, it is recommended that genotypic analysis complement phenotypic techniques.

In summary, to date, probiotic infections have been reported in 32 patients receiving probiotics in conjunction with nutritional support (EN and/or PN). This is in context of their widespread
use, as evidenced by 53 clinical trials in which probiotics were given to 4131 patients. Although many trials showed reductions in mortality, sepsis, or infections, only 3 found significant increases in negative clinical sequelae, which were largely noninfectious in nature.

In the future, when a probiotic is to be investigated for the first time in a specific patient group receiving nutritional support, it is recommended that preliminary safety trials should be undertaken that include routine monitoring for adverse events. In addition, efficacy trials should define, monitor, and report adverse events and consider the use of a data monitoring committee. When data show that a specific probiotic in a specific patient group has resulted in an increase in adverse events, its use should clearly be contraindicated. Elsewhere, caution should be taken in patients with risk factors for adverse events (eg, patients with CVC and increased bacterial translocation). However, the use of probiotics should not necessarily be contraindicated in such patients, either as part of clinical practice or research, because they may have the potential to benefit from their use. Rather, a risk-benefit analysis should be undertaken in each patient, and routine surveillance for adverse events should be undertaken when probiotics are used.

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