Safety of probiotics in patients receiving nutritional support: a systematic review of case reports, randomized controlled trials, and nonrandomized trials[1–3]

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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* doi: 10.3945/ajcn.2009.28759.

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 maldigestion (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

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(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 trails (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://mrw.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

TABLE 1
Detailed inclusion and exclusion criteria and data extracted[1]

PICOS	Inclusion and exclusion criteria	Data extraction
Patient	Patients of any age receiving EN and/or PN. In reports of mixed patient groups (eg, intensive care unit), 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.	Location, age when probiotic was started, diagnoses (case reports only), patient group (trials only), type of nutrition support.
Intervention	Oral and/or enteral administration of a probiotic. Reports in which this was given in addition to other compounds (eg, prebiotics) were also eligible.	Genus, species, and strain of the probiotic as given in the article. When this was not available, genus and species alone were extracted. The dose of probiotic, route of administration, and any additional compounds given were also extracted. The reason for probiotic use was extracted from case studies.
Comparators	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).	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.
Outcome	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.	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. 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.
Study design	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.	Type of study design and numbers in the intervention and comparator groups (trials only).

[1] EN, enteral nutrition; PN, parenteral nutrition; PICOS, Patient, Intervention, Comparators, Outcome, Study Design.

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), jejunostony (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 =

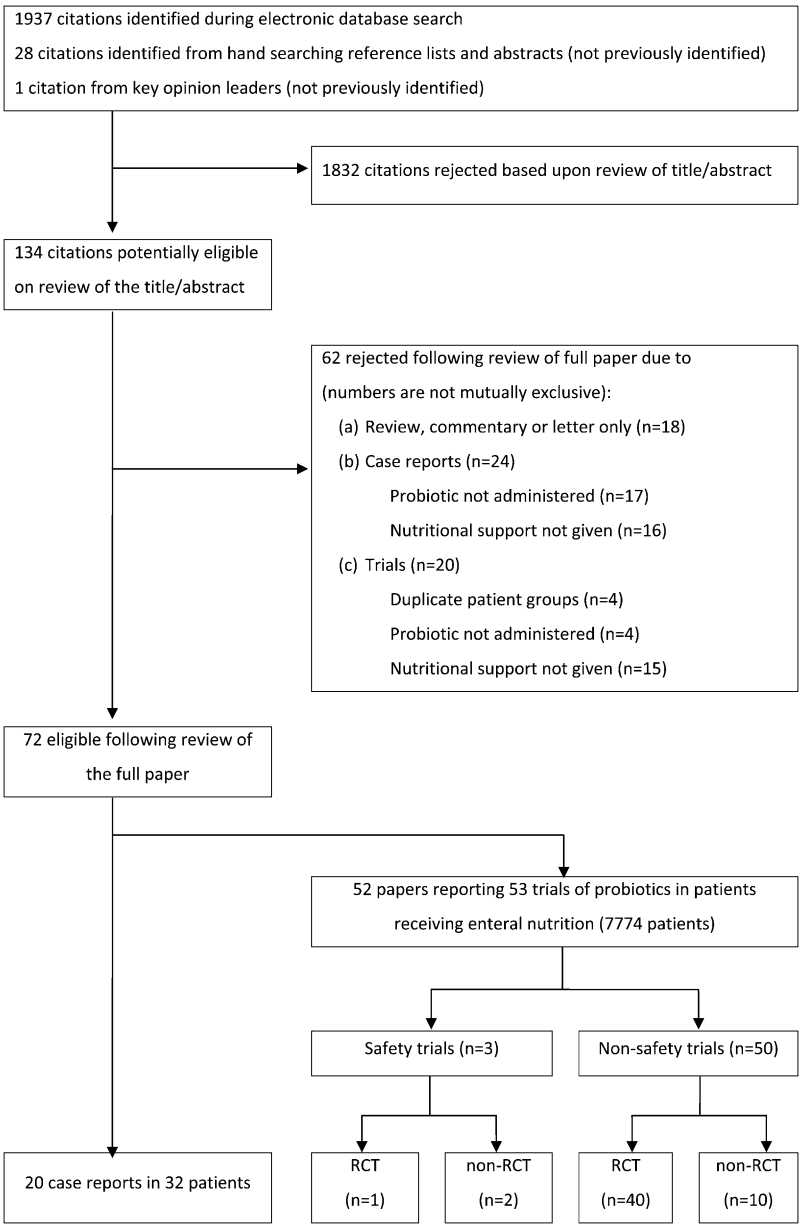

FIGURE 1. Diagram of citations included and excluded during the systematic review. RCT, randomized controlled trial.

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 caspifungin ($n = 1$). 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,

TABLE 2
Case reports of adverse events associated with the use of probiotics in patients receiving nutritional support (NS)[1]

	Patient			Intervention (probiotic)				Outcome				
Reference	Age[2]	Diagnosis[3]	NS	Species/strain	Dose	Route[4]	Purpose[5]	Adverse event	Identification[6]	Risk factor[7]	Treatment	Outcome[8]
Kunz et al, 2004 (19)	1 mo	Short bowel Cholestasis	PN	*Lactobacillus. rhamnosus* GG	1 capsule/d	Oral	Prevent SIBO	Bacteremia	Culture, RD-GE	CVC, 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	CVC, GI inflammation, short-bowel syndrome	Probiotic stopped, CVC removed, ampicillin	Recovery
Land et al, 2005 (20)	3 mo	Cardiac stenosis	EN	*L. rhamnosus* GG ATCC53103	10^{10} cells/d	PEG	Treat AAD	Bacteremia Endocarditis	Culture, PCR-GE	Antibiotics, CVC	Probiotic stopped, CVC removed, penicillin, gentamicin	Recovery
	6 y	Cerebral palsy Microcephaly	PN	*L. rhamnosus* GG ATCC53103	10^{10} cells/d	Jej	Treat AAD	Bacteremia	Culture, PCR-GE	Antibiotics, CVC	Probiotic stopped, ampicillin	Recovery
De Groote et al, 2005 (21)	10 mo	Short bowel	PN	*L. rhamnosus* GG ATCC53103	1/4 capsule/d	PEG	Treat rotavirus	Bacteremia	Culture, RNA sequencing, RD-GE	Antibiotics, *Candida. albicans,* CVC, short-bowel syndrome	CVC removed, ampicillin, gentamicin	Recovery
Lungarotti et al, 2003 (22)	1 mo	Preterm infant	PN	*Saccharomyces boulardii*	3×10^9 cells/d	—	Prevent SIBO	Fungemia	Culture	*C. albicans,* CVC	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, API strips, RD-GE	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	Antibiotics, CVC, chemotherapy	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	Antibiotics, CVC, gastroenteritis, malnutrition	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, fluconazole	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)	33 y	Colectomy Sepsis	EN	*S. boulardii*	1500 mg/d	NGT	Prevent AAD	Fungemia	Culture	Antibiotics, CVC, sepsis, H_2 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	Antibiotics, *Clostridium difficile,* CVC	Probiotic stopped	Death
Fredenucci et al, 1998 (30)	49 y	Pneumonia	EN	*S. boulardii*	4 sachets/d	NGT	Treat EN diarrhea	Fungemia	Culture, API strips, RD-GE	Antibiotics	Fluconazole	Recovery
Hennequin et al, 2000 (31)	2 y	Cystic fibrosis Ileal atresia	PN	*S. boulardii*	750 mg/d	—	Prevent diarrhea	Fungemia	Culture, API strips, RD-GE	Antibiotics, CVC	Probiotic stopped, CVC removed, amphotericin B	Recovery

(Continued)

TABLE 2 (*Continued*)

	Patient			Intervention (probiotic)				Outcome				
Reference	Age[2]	Diagnosis[3]	NS	Species/strain	Dose	Route[4]	Purpose[5]	Adverse event	Identification[6]	Risk factor[7]	Treatment	Outcome[8]
	36 y	HIV/AIDS Lymphoma	PN	*S. boulardii*	1500 mg/d	—	Treat diarrhea	Fungemia	Culture, API strips, RD-GE	Antibiotics, CVC, chemotherapy, HIV	Probiotic stopped, fluconazole	Recovery
	47 y	Esophageal cancer	EN	*S. boulardii*	2000 mg/d	—	Treat AAD	Fungemia	Culture, API strips, RD-GE	Antibiotics, CVC	Probiotic stopped, CVC removed, fluconazole	Recovery
	78 y	Pulmonary disease	EN	*S. boulardii*	1500 mg/d	—	Prevent diarrhea	Fungemia	Culture, API strips, RD-GE	Antibiotics, CVC	Probiotic stopped	Recovery
Lherm et al, 2002 (32)	50 y	Cardiac arrest	EN	*S. boulardii*	1500 mg/d	—	Prevent diarrhea	Fungemia	Culture, RD-GE, phenotypic	Antibiotics, CVC	Probiotic stopped, CVC changed	Death
	51 y	Aortic surgery	EN	*S. boulardii*	1000 mg/d	—	Prevent diarrhea	Fungemia	Culture, RD-GE, phenotypic	Antibiotics, CVC, malnutrition	Probiotic stopped, CVC changed, fluconazole	Death
	71 y	Stroke	EN	*S. boulardii*	3000 mg/d	—	Prevent diarrhea	Fungemia	Culture, RD-GE, phenotypic	Antibiotics, CVC	Probiotic stopped, CVC changed	Recovery
	75 y	Respiratory failure	EN	*S. boulardii*	2000 mg/d	—	Prevent diarrhea	Fungemia	Culture, RD-GE, phenotypic	Antibiotics, CVC	Probiotic stopped, CVC changed	Recovery
	77 y	Peritonitis	EN	*S. boulardii*	3000 mg/d	—	Prevent diarrhea	Fungemia	Culture, RD-GE, phenotypic	Antibiotics, CVC	Probiotic stopped, CVC changed, amphotericin B	Death
	82 y	Respiratory failure	EN	*S. boulardii*	1500 mg/d	—	Prevent diarrhea	Fungemia	Culture, RD-GE, phenotypic	Antibiotics, CVC	Probiotic stopped, CVC changed	Recovery
Lolis et al, 2008 (33)	56 y	Pneumonia Sepsis	PN	*S. boulardii*	2000 mg/d	NGT	Treat diarrhea	Fungemia	Culture, DNA sequencing	Antibiotics, CVC, sepsis	Probiotic stopped, CVC removed, caspofungin	Recovery
Henry et al, 2004 (34)	65 y	Oropharyngeal cancer	PN	*S. boulardii*	6 capsules/d	Oral	Treat diarrhea	Fungemia	Culture	Antibiotics, CVC, mucositis	Probiotic stopped, amphotericin B	Recovery
Munoz et al, 2005 (35)	72 y	Cardiac surgery	EN, PN	*S. boulardii*	—	NGT	Treat CDAD	Fungemia	Culture, PCR-GE	Antibiotics, *C. difficile*, CVC	—	Death
	74 y	MV replacement	EN, PN	*S. boulardii*	—	NGT	Treat CDAD	Fungemia	Culture, PCR-GE	Antibiotics, *C. difficile*, CVC, steroids	Probiotic stopped, fluconazole	Death
	76 y	MV replacement Cardiac arrest	EN, PN	*S. boulardii*	—	NGT	Treat CDAD	Fungemia Endocarditis	Culture, PCR-GE	Antibiotics, *C. difficile*, CVC, prosthetic MV	Probiotic stopped, fluconazole	Death
Rijinders et al, 2000 (36)	74 y	Neurosurgery	EN	*S. boulardii*	600 mg/d	NGT	Treat EN diarrhea	Fungemia	Culture	CVC, colitis	CVC removed, fluconazole	Death

(Continued)

TABLE 2 (*Continued*)

	Patient			Intervention (probiotic)				Outcome				
Reference	Age[2]	Diagnosis[3]	NS	Species/strain	Dose	Route[4]	Purpose[5]	Adverse event	Identification[6]	Risk factor[7]	Treatment	Outcome[8]
Niault et al, 1999 (37)	78 y	Pulmonary disease	EN	*S. boulardii*	1500 mg/d	NGT	Treat diarrhea	Fungemia	Culture	Antibiotics, CVC	Probiotic stopped, CVC removed, fluconazole	Recovery
Cherifi et al, 2004 (38)	89 y	*C. difficile* Anorexia nervosa	EN	*S. boulardii*	300 mg/d	PEG	Prevent CDAD	Fungemia	Culture	Antibiotics, *C. difficile*, malnutrition, PVC	Fluconazole	Recovery

[1] EN, enteral nutrition; PN, parenteral nutrition; MV, mitral valve; NGT, nasogastric tube; PEG, percutaneous endoscopic gastrostomy; Jej, jejunostomy; AAD, antibiotic-associated diarrhea; CDAD, *Clostridium difficile*–associated diarrhea; SIBO, small intestinal bacterial overgrowth; RD-GE, restriction digest and gel electrophoresis; PCR-GE, polymerase chain reaction and gel electrophoresis; CVC, central venous catheter; PVC, peripheral venous catheter; GI, gastrointestinal.

[2] Age is reported from the time the probiotic was started (where available). For patients >1 y, age at last birthday is reported; for those <1 y, age to the nearest month is reported.

[3] Primary diagnosis given in case report.

[4] Route of probiotic administration.

[5] Purpose of probiotic administration.

[6] Microbiological method of identification of probiotic.

[7] Risk factors for adverse event, including those suggested by report authors and those commonly found in the literature.

[8] Outcome relates to recovery or death from the adverse event. Recovery indicates that, after treatment, the patient survived the adverse event (even if they subsequently died of a seemingly unrelated event), whereas death indicates that they died of symptoms potentially linked with the adverse event.

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**).

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 $\geq$3 strains. As with the case reports, there was variation in how the doses were reported (cells/d, cells $\cdot$ kg^{-1} $\cdot$ d^{-1}, mg/d, mg $\cdot$ kg^{-1} $\cdot$ d^{-1}, mL/d, and cells $\cdot$ L^{-1} $\cdot$ d^{-1}). When it was reported as cells/d, it ranged widely from 10^7 (40) to 1.8×10^{12} cells/d (56). In a small number of trials, the probiotic was given with other supplements, including prebiotics, fiber, or glutamine. The probiotics were administered via NGT, PEG, nasojejunal tube (NJT), jejunostomy, 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 ($1–2 \times 10^{11}$ 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* (10^9 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

TABLE 3
Trials of probiotics in patients receiving nutritional support (NS)[1]

	Patient details		Study details			Intervention (probiotic)			Outcomes	
Reference	Location	Patient group	NS	Design	No. of probiotics/ comparators[2]	Species/strain[3]	Dose	Route[4]	Clinical outcomes relevant to safety[5]	Adverse events[6]
Safety trials										
Kitajima et al, 1997 (39)	Neonatal ICU	Preterm infants	EN, PN	Case series	66	*Bifidobacterium breve* YIT4010	10^9 cells/d	NGT	No relevant clinical endpoints	Functional ileus in 2 patients (cornstarch aggregates in stool), no other side effects
Srinivasan et al, 2006 (40)	Pediatric ICU	Critically ill children	EN, PN	Case series	28	*Lactobacillus casei* Shirota (Yakult)	10^7 cells/d	NGT	No relevant clinical endpoints	No lactobacillus in blood, urine, sputum, catheters, etc; no adverse events; well tolerated
Klarin et al, 2005 (41)	Adult ICU	Critically ill	EN, PN	RCT	8/7	*Lactobacillus plantarum* 299v (ProViva)	$1–2 \times 10^{11}$ cells/d	NGT	No relevant clinical endpoints compared between groups	Bowel distension in 2 patients; no probiotic in blood, urine, tracheal secretions; no adverse events
Nonsafety trials (RCTs)										
Li et al, 2004 (42)	Neonatal ICU	Preterm infants	EN, PN	RCT	20/10	*B. breve*	1.6×10^8 cells/d	NGT	NEC (NS), sepsis (NS), infections (NS)	Well tolerated, no side effects
Wang et al, 2007 (43)	Neonatal ICU	Preterm infants	EN, PN	RCT	33/33	*B. breve* M-16V	3.2×10^8 cells/d	NGT	No relevant clinical endpoints compared between groups	No adverse events
Kitajima et al, 1997 (39)	Neonatal ICU	Preterm infants	EN, PN	RCT	45/46	*B. breve* YIT4010	10^9 cells/d	NGT	No relevant clinical endpoints compared between groups	No adverse events
Mihatsch et al, 2004 (44)	Neonatal ICU	Preterm infants	EN	RCT	65/63	*Bifidobacterium lactis*	6×10^9 cells $\cdot$ $kg^{-1} \cdot d^{-1}$	NGT, OGT	Infections (NS)	No bifidobacteria bacteremia
Bin-Nun et al, 2005 (45)	Neonatal ICU	Preterm infants	EN, PN	RCT	72/30	ABC Dophilus	10^9 cells/d	NGT	Mortality (NS), NEC (reduced in probiotic)	No sepsis caused by probiotic, no adverse events
Costalos et al, 2003 (46)	Neonatal ICU	Preterm infants	EN, PN	RCT	51/36	*Saccharomyces boulardii*	50 mg $\cdot$ $kg^{-1} \cdot d^{-1}$	NGT Oral	NEC (NS), sepsis (NS)	No *S. boulardii* sepsis, well tolerated, no side effects
Dani et al, 2002 (47)	Neonatal ICU	Preterm infants	EN, PN	RCT	295/290	*Lactobacillus rhamnosus* GG (Dicoflor)	6×10^9 cells/d	NGT	NEC (NS), sepsis (NS), urinary tract infections (NSD)	No information given
Manzoni et al, 2006 (48)	Neonatal ICU	Preterm infants	EN, PN	RCT	39/41	*L. rhamnosus* GG	6×10^9 cells/d	NGT OGT	Mortality (NS), NEC (NS), sepsis (NS), fungal infections (NS)	No lactobacillus sepsis, no adverse events
Millar et al, 1993 (49)	Neonatal ICU	Preterm infants	EN, PN	RCT	10/10	*L. rhamnosus* GG	2×10^8 cells/d	NGT	Antibiotic use (NS), ICU length of stay (NS)	No lactobacillus bacteremia
Rouge et al, 2009 (50)	Neonatal ICU	Preterm infants	EN	RCT	45/49	*L. rhamnosus* GG *Bifidobacterium longum* BB536	4×10^8 cells/d	—	Mortality (NS), NEC (NS), sepsis (NS), nosocomial infections (NS)	No probiotic bacteremia, no adverse events
Samanta et al, 2009 (51)	Neonatal ICU	Preterm infants	EN	RCT	91/95	*Bifidobacterium infantis* *B. bifidum* *B. longum* *Lactobacillus acidophilus*	2×10^9 cells/d	NGT, OGT	Mortality (reduced in probiotic), sepsis (reduced in probiotic), NEC (reduced in probiotic), length of stay (reduced in probiotic)	No probiotic bacteremia

(Continued)

TABLE 3 (*Continued*)

	Patient details		Study details			Intervention (probiotic)			Outcomes	
Reference	Location	Patient group	NS	Design	No. of probiotics/ comparators[2]	Species/strain[3]	Dose	Route[4]	Clinical outcomes relevant to safety[5]	Adverse events[6]
Underwood et al, 2009 (52)	Neonatal ICU	Preterm infants	EN, PN	RCT	61/29	*L. rhamnosus* GG or *Bifidobacterium infantis* *B. bifidum* *B. longum* *L. acidophilus* (both with inulin)	10^9 cells/d	NGT, OGT, oral	Weight gain (NS)	No adverse events, well tolerated
Lin et al, 2005 (53)	Neonatal ICU	Preterm infants	EN, PN	RCT	180/187	*B. infantis* *L. acidophilus*	250 mg · $kg^{-1} \cdot d^{-1}$	OGT, oral	Mortality (reduced in probiotic), NEC (reduced in probiotic), sepsis (reduced in probiotic)	No probiotic bacteremia, no complications from probiotic
Lin et al, 2008 (54)	Neonatal ICU	Preterm infants	EN, PN	RCT	217/217	*B. bifidum* NCDO 1453 *L. acidophilus* NCDO 1748	250 mg· $kg^{-1} \cdot d^{-1}$	OGT, oral	Mortality (reduced in probiotic), NEC (reduced in probiotic), sepsis (increased in probiotic)	No probiotic bacteremia, no adverse events
Honeycutt et al, 2007 (55)	Pediatric ICU	Critically ill children	EN	RCT	31/30	*L. rhamnosus* GG	10^{10} cells/d	NGT, oral	Mortality (NS), nosocomial infections (NS)	No probiotic bacteremia, no adverse events
Alberda et al, 2007 (56)	Adult ICU	Critically ill	EN	RCT	19/9	VSL#3	1.8×10^{12} cells/d	NGT	Mortality (NS), MODS (NS)	No lactobacillus sepsis, no adverse events
Knight et al, 2009 (57)	Adult ICU	Critically ill	EN	RCT	130/129	Synbiotic 2000 Forte (20 g fiber/d)	2×10^{10} cells/d	NGT, OGT	Mortality (NS), pneumonia (NS), ICU and hospital length of stay (NS)	No complications, single *Leuconostoc* detected from a tracheal aspirate
Dadak et al, 2006 (58)	Adult ICU	Critically ill	EN, PN	RCT	6/5	Synbiotic 2000 Forte	—	NGT, NJT	Mortality (NS)	No information given
Jain et al, 2004 (59)	Adult ICU	Critically ill	EN, PN	RCT	45/45	Trevis (15 g prebiotic/d)	2×10^{10} cells/d	NGT, oral	Mortality (NS), sepsis (NS)	No information given
Forestier et al, 2008 (60)	Adult ICU	Critically ill	EN	RCT	102/106	*Lactobacillus casei rhamnosus*	2×10^9 cells/d	NGT, oral	No relevant clinical endpoints compared between groups	No lactobacillus sepsis
McNaught et al, 2005 (61)	Adult ICU	Critically ill	EN, PN	RCT	52/51	*L. plantarum* 299v (ProViva)	10^{10} cells/d	NGT, oral	Mortality (NS), sepsis (NS), ICU length of stay (NS)	No information given
Klarin et al, 2008 (62)	Adult ICU	Critically ill	EN, PN	RCT	22/22	*L. plantarum* 299v	8×10^{10} – 9.6×10^{11} cells/d	NGT, oral	Mortality (NS), ICU length of stay (NS), diarrhea (NS), bacteremia (NS), catheter tip infections (NS)	No adverse events, well tolerated
Tempé et al, 1983 (63)	Adult ICU	Critically ill	EN	RCT	20/20	*S. boulardii*	10^{10} cells · $L^{-1} \cdot d^{-1}$	NGT	Diarrhea (reduced in probiotic)	No information given
Bleichner et al, 1997 (64)	Adult ICU	Critically ill	EN	RCT	64/64	*S. boulardii*	2000 mg/d	NGT	Diarrhea (reduced in probiotic)	No adverse events, well tolerated

(*Continued*)

TABLE 3 (*Continued*)

	Patient details		Study details			Intervention (probiotic)			Outcomes	
Reference	Location	Patient group	NS	Design	No. of probiotics/ comparators[2]	Species/strain[3]	Dose	Route[4]	Clinical outcomes relevant to safety[5]	Adverse events[6]
Falcão et al, 2004 (65)	Adult ICU	Brain injury	EN	RCT	10/10	*Lactobacillus johnsonii* La1 (LC1) (glutamine)	240 mL/d	NGT	Sepsis (NS), infections (reduced in probiotic), ICU length of stay (reduced in probiotic)	No information given
Giamarellos-Bourboulis et al, 2009 (66)	Adult ICU	Trauma	EN, PN	RCT	36/36	Synbiotic 2000 Forte (10 g fiber/d)	4×10^{11} cells/d	NGT, PEG	Mortality (NS), sepsis (reduced in synbiotic)	Administration was safe, no infections caused by the probiotic
Spindler-Vesel et al, 2007 (67)	Adult ICU	Trauma	EN, PN	RCT	26/29	Synbiotic 2000 (10 g fiber/d)	8×10^{10} cells/d	NGT	Mortality (NS), infections (reduced in probiotic)	No information given
Besselink et al, 2008 (68)	Adult ICU	Severe acute pancreatitis	EN	RCT	152/144	Ecologic 641	10^{10} cells/d	NJT	Mortality (increased in probiotic), infectious complication (NS), bowel ischemia (increased in probiotic), diarrhea (NS)	No probiotic infections, bowel ischemia reported as adverse event
Heimburger et al, 1994 (69)	Adult ICU, general wards	Mixed	EN	RCT	18/23	*L. acidophilus Lactobacillus bulgaricus*	3000 mg/d	NGT	Diarrhea (NS)	No information given
Rayes et al, 2007 (70)	Adult ICU, surgical unit	Pancreato-duodenectomy	EN	RCT	40/40	Synbiotic 2000	8×10^{10} cells/d	NJT, oral	Mortality (NS), infections (reduced in probiotic), hospital length of stay (NS)	No serious side effects
Rayes et al, 2002a (71)	Adult ICU, surgical unit	Abdominal surgery	EN	RCT	30/30	*L. plantarum* 299v	2×10^{10} cells/d	NJT	Infections (NS), noninfectious complications (NS), hospital length of stay (NS)	Few side effects
Rayes et al, 2005 (72)	Adult ICU, surgical unit	Liver transplant	EN	RCT	33/33	Synbiotic 2000	8×10^{10} cells/d	NJT, oral	Infections (reduced in probiotic), noninfectious complications (increased in probiotic), hospital length of stay (NS)	Well tolerated, no serious side effects
Rayes et al, 2002b (73)	Adult ICU, surgical unit	Liver transplant	EN	RCT	31/32	*L. plantarum* 299v	2×10^{10} cells/d	NJT	Infections (reduced in probiotic), noninfectious complications (NS), ICU length of stay (NS)	Well tolerated
Olah et al, 2002 (74)	Surgical unit	Acute pancreatitis	EN	RCT	22/23	*L. plantarum* 299v	2×10^{9} cells/d	NJT	Mortality (NS), septic complications (reduced in probiotic), hospital length of stay (NS)	No information given
Qin et al, 2008 (75)	Surgical unit	Acute pancreatitis	PN	RCT	36/38	*L. plantarum* (plus EN)	10^{10} cells/d	NJT	Mortality (NS), septic complications requiring surgery (reduced in probiotic)	No adverse events

(*Continued*)

TABLE 3 (*Continued*)

	Patient details		Study details			Intervention (probiotic)			Outcomes	
Reference	Location	Patient group	NS	Design	No. of probiotics/ comparators[2]	Species/strain[3]	Dose	Route[4]	Clinical outcomes relevant to safety[5]	Adverse events[6]
Olah et al, 2007 (76)	Surgical unit	Severe acute pancreatitis	EN	RCT	33/29	Synbiotic 2000 (10 g fiber/d)	4×10^{10} cells/d	NJT	Mortality (NS), sepsis (NS), multiple organ failure (NS), hospital length of stay (NS)	No information given
Kanazawa et al, 2005 (77)	Surgical unit	Hepatectomy	EN, PN	RCT	21/23	*B. breve* Yakult *L. casei* Shirota (12 g prebiotic/d)	6×10^{8} cells/d	Jej	Mortality (NS), infections (reduced in probiotic), hospital length of stay (NS)	No information given
Sugawara et al, 2006 (78)	Surgical unit	Hepatectomy	EN	RCT	40 41	*B. breve* Yakult *L. casei* Shirota (15 g prebiotic/d)	2×10^{10} cells/d	Jej	Mortality (NS), infections (reduced in pre/postoperative synbiotic compared with postoperative synbiotic), hospital length of stay (reduced in pre/postoperative synbiotic compared with postoperative synbiotic)	No problems related to synbiotic
Schlotterer et al, 1987 (79)	Burns unit	Burns	EN, PN	RCT	9/9	*S. boulardii*	2000 mg/d	NGT	Sepsis duration (NS), diarrhea (reduced in probiotic)	No information given
Fukushima et al, 2007 (80)	General wards	Elderly	EN	RCT	12/12	*L. johnsonii* La1 (LC1)	10^{8} cells/d	NGT, PEG	Fever (NS), infection duration (NS), diarrhea duration (NS)	No adverse events
Nonsafety trials (nonrandomized trials)										
Reuman et al, 1986 (81)	Neonatal ICU	Preterm infants	EN	CT	15/15	*L. acidophilus*	2×10^{8} cells/d	NGT, oral	Mortality (NS), morbidity (NS), antibiotic duration (NSD), hospital length of stay (NS)	No information given
Satoh et al, 2007 (82)	Neonatal ICU	Preterm infants	EN	CT	338/226	*B. breve* M-16V	10^{9} cells/d	NGT	Mortality (NS), NEC (reduced in probiotic), infections (reduced in probiotic)	No information given
Hoyos et al, 1999 (83)	Neonatal ICU	Preterm infants, critically ill	EN, PN	CT	1237/1282	*L. acidophilus* *B. infantis*	2×10^{9} cells/d	OGT, oral	NEC (reduced in probiotic), NEC mortality (reduced in probiotic), sepsis (NS), hospital length of stay (NS)	No complications
Lee et al, 2007 (84)	Neonatal ICU	Preterm infants	EN, PN	Case series	73	*L. acidophilus* ATCC _ 4356	10^{8} cells/d	NGT, oral	No relevant clinical endpoints compared between groups	No information given
Laviano et al, 2004 (85)	Adult ICU	Brain injury	EN, PN	CT	12/8	VSL#3	5×10^{11} cells/d	NGT	No relevant clinical endpoints compared between groups	No information given
Shimizu et al, 2009 (86)	Adult ICU	SIRS	EN	CT	29/26	*B. breve* Yakult *L. casei* Shirota (13 g prebiotic/d)	6×10^{8} cells/d	NGT	Mortality from MODS (NS), infections (reduced in synbiotic), antibiotic duration (NS)	No adverse events, no bowel ischemia

(Continued)

TABLE 3 (*Continued*)

	Patient details		Study details			Intervention (probiotic)			Outcomes	
Reference	Location	Patient group	NS	Design	No. of probiotics/ comparators[2]	Species/strain[3]	Dose	Route[4]	Clinical outcomes relevant to safety[5]	Adverse events[6]
Candy et al, 2001 (87)	Pediatric unit	Short bowel	EN	Case report	1	*L. casei* Shirota	4.5×10^9 cells/d	PEG	No relevant clinical endpoints in the case study	No D-lactic acidosis
Del Piano et al, 2004 (88)	General wards	Permanent vegetative state	EN	Case series	7/6	B. longum W11 (2.5 g prebiotic/d)	5×10^9 cells/d	PEG	Fever (NS), antibiotic use (NS), diarrhea (NS)	No information given
Schneider et al, 2005 (89)	Community	Long-term EN	EN	CT	10	*S. boulardii*	1000 mg/d	NGT, PEG, Jej	No clinical endpoints compared between patients and healthy subjects	No saccharomyces fungemia, diarrhea in one patient
Kubota et al, 2007 (90)	Community	Hypoganglionosis	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

[1] 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.

[2] 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.

[3] Species/strain administered (as defined in the article) and the dose. Proprietary multispecies products are as follows: ABC Dophilus (Solgar, Israel) consists of *B. infantis*, *B. bifidus*, and *Streptococcus thermophilus*; Ecologic 641 (Winclove 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, Kågeröd, Des Moines, IA) consists of *Pediococcus pentosaceus, Leuconostoc mesenteroides, L. paracasei, L. plantarum,* β-glucan, inulin, pectin, and resistant starch; Trevis (Chr Hansen Biosystem, 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.*

[4] Route of probiotic administration.

[5] Clinical findings include mortality and morbidity or endpoints indicative of morbidity (eg, antibiotic use and length of stay).

[6] 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 probiotic 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 NJT (72). The intervention group (n = 33) received Synbiotic 2000 (Medipharm, Kågeröd, Sweden, and Des Moines, IA) consisting of 8×10^{10}/d of *Pediococcus pentosaceus, Leuconostoc mesenteroides, 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, lienalis-steal syndrome (none of which occurred in the control group), abdominal hemorrhage, and acute renal failure (occurred in both groups).

The second was a large multicenter RCT in 296 patients with severe acute pancreatitis who were receiving EN via an NJT (68). The intervention group (n = 152) received Ecologic 641 (Winclove 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) received 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* ($250 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$), 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 multivariate 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 relating to probiotics; 6 reported them to be well tolerated; and 14 specified that the probiotic did not cause bacteremia, fungemia, sepsis, or infections (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. boulardii*/d (89).

DISCUSSION

Probiotics have indications that support their use in patients receiving nutritional support. This systematic review has identified numerous case reports of infectious complications associated 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. boulardii*, likely reflecting their wider use in the clinical setting rather than their increased virulence. For example, in the areas of EN-associated diarrhea (10), AAD (11), CDAD (12), and necrotizing enterocolitis (13), more trial patients have been investigated by using *L. rhamnosus* GG or *S. boulardii* 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 H_2 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 $\geq$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 10^{10} 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 underreporting 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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