

Practical Reference Guide

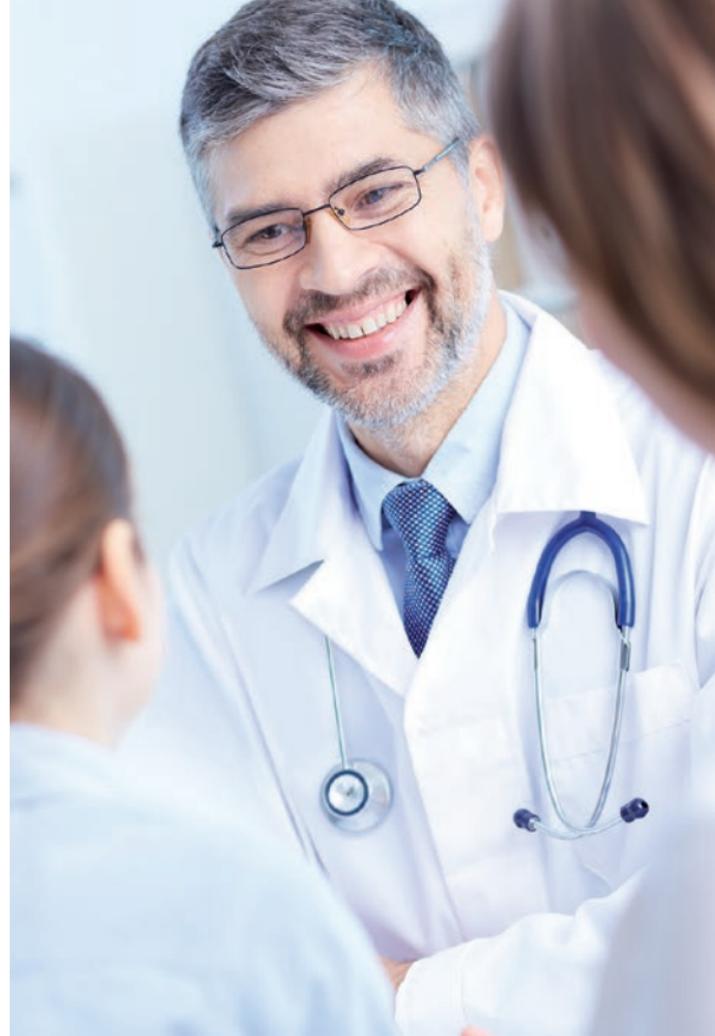
Probiotics in the management
of lower GI symptoms in clinical practice

Based on the full open access publication:

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**Systematic review: probiotics in the management
of lower gastrointestinal symptoms in clinical practice –
an evidence-based international guide.**

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Acronyms

IBS, irritable bowel syndrome

IBS-C, constipation-predominant IBS

IBS-D, diarrhoea-predominant IBS

NA: not available

References: 1. Thompson M. Considering the implication of variations within Delphi research. *Fam Pract* 2009;26: 420-4. 2. Linstone HA, Turoff M. *The Delphi method: techniques and applications*, 2002. Available at: <http://is.njit.edu/pubs/delphibook/>. Accessed December 2012. 3. Dalkey N. An experimental study of group opinion: the Delphi method. *Futures* 1969;1:408-26. 4. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328: 1490.

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The aim of this document is to provide clinicians with a practical reference guide on the role of specified available probiotics in the treatment of particular lower GI symptoms/problems in adults in clinical practice



Methods:

Systematic literature searching identified 37 randomized, placebo-controlled trials in adults; evidence for each symptom/problem was graded and statements were developed (modified Delphi*¹⁻³ consensus process; 10-member Consensus Group panel).

The term “**probiotics**” has been used to refer to products that contain probiotics, regardless of whether the product contains a single strain or multiple strains. As results cannot be generalized between different probiotics, individual probiotics were identified per each statement.

* The Delphi process is an increasingly widely used technique for reaching expert consensus. It uses a process of anonymous and iterative feedback and voting to achieve consensus among a panel of independent experts by means of stepwise refinement of responses.

Level of supporting evidence and strength of each statement (rated by GRADE^{#4}):



HIGH

Further research is unlikely to change our confidence in the estimate of effect

LOW

Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

MODERATE

Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

VERY LOW

Any estimate of effect is very uncertain

Practical implications of consensus statements for physicians



Grade of evidence for effect	Symptoms/indications	Meaning for physicians
High	Overall symptoms and abdominal pain in IBS Prevention or reduction of diarrhoea in patients receiving antibiotics, including <i>Helicobacter pylori</i> eradication therapy	Probiotics with supportive evidence for benefit should be tried
Moderate	Overall symptoms in IBS-D Bowel movements and bloating / distension in IBS	Probiotics with supportive evidence for benefit could be tried
Low	Overall symptoms in IBS-C	Probiotics with supportive evidence for benefit could be considered
Very low	Flatus in IBS [†] Diarrhoea in IBS	Currently no evidence to support use of probiotic

Constipation in IBS is not addressed in this table because consensus was not achieved for this statement.

[†] The grade of evidence was initially deemed to be low (rather than very low) for flatus in IBS, but the statement was revised to be negative in response to voter feedback during the Delphi process.

Overview of statements, grading and probiotics (marketed products and investigative strains) with supportive evidence[‡]

Statement	Grade of evidence for effect	Level of agreement (%)	Probiotics for which studies show supportive evidence of benefit (bold font indicates primary end point data)
IBS & global symptom assessment			
Specific probiotics help relieve overall symptom burden in some patients with IBS	High	100	<i>Bifidobacterium bifidum</i> MIMBb75 , <i>B. longum</i> subsp. <i>infantis</i> 35624 (Bifantis® / Align®) <i>Escherichia coli</i> DSM17252 (Symbioflor®-2) Investigative combinations: BIFIDO / Valio Bb99 Marketed combinations (Gefilus MAX® / LAB4®)
Specific probiotics may help relieve overall symptom burden in some patients with IBS-C	Low	80	<i>B. animalis</i> subsp. <i>lactis</i> DN-173 010 (Activia®)
Specific probiotics help relieve overall symptom burden in some patients with IBS-D	Moderate	100	<i>B. longum</i> subsp. <i>infantis</i> 35624 (Bifantis® / Align®) Marketed combinations (AB100 Jianneng / Duolac7)



Statement	Grade of evidence for effect	Level of agreement (%)	Probiotics for which studies show supportive evidence of benefit (bold font indicates primary end point data)
IBS & Abdominal pain			
Specific probiotics help to reduce abdominal pain in some patients with IBS	High	100	[<i>Bacillus coagulans</i> GBI-30, 6086 (Digestive Advantage Gas Defense Formula)], <i>B. animalis</i> subsp. <i>lactis</i> DN-173 010 (Activia®) <i>[B. animalis</i> subsp. <i>lactis</i> HN019 (HOWARU Bifido / DR10)], <i>B. bifidum</i> MIMBb75 <i>B. longum</i> subsp. <i>infantis</i> 35624 (Bifantis® / Align®) <i>Escherichia coli</i> DSM17252 (Symbioflor®-2) Investigative combinations: (BIFIDO / SDC / Valio Bb99) <i>[L. reuteri</i> DSM17938 (Reuterin®)] Marketed combinations (AB100 Jianneng, Lactibiane®)

‡ For simplicity, single-strain probiotics are identified by the name of the strain, and multi-strain products are identified as ‘combination (X)’ and listed on page 13.

Overview of statements, grading and probiotics (marketed products and investigative strains) with supportive evidence[‡]

Statement	Grade of evidence for effect	Level of agreement (%)	Probiotics for which studies show supportive evidence of benefit (bold font indicates primary end point data)
IBS & Boating/distensión			
Specific probiotics help to reduce bloating / distension in some patients	Moderate	70	<i>B. animalis</i> subsp. <i>lactis</i> DN-173 010 (Activia®) <i>B. animalis</i> subsp. <i>lactis</i> DN-173 010 (Activia®) <i>B. bifidum</i> MIMBb75 <i>B. longum</i> subsp. <i>infantis</i> 35624 (Bifantis® / Align®) <i>Escherichia coli</i> DSM17252 (Symbioflor®-2) <i>L. reuteri</i> DSM17938 (Reuterin®) Marketed combinations (Gefilus MAX® / LAB4®)
IBS & Flatus			
Probiotics tested to date do not reduce flatus in patients with IBS	Low	90	<i>B. animalis</i> subsp. <i>lactis</i> DN-173 010 (Activia®) <i>B. animalis</i> subsp. <i>lactis</i> HN019 (HOWARU® Bifido / DR10™) <i>B. longum</i> subsp. <i>infantis</i> 35624 (Bifantis® / Align®) <i>L. reuteri</i> DSM17938 (Reuterin®) Marketed combinations (AB100 Jianneng / VSL#3)



Statement	Grade of evidence for effect	Level of agreement (%)	Probiotics for which studies show supportive evidence of benefit (bold font indicates primary end point data)
IBS & Constipation			
Specific probiotics may help reduce constipation in some patients with IBS	Low	60 (no consensus)	<i>B. animalis</i> subsp. <i>lactis</i> DN-173 010 (Activia®) <i>B. animalis</i> subsp. <i>lactis</i> HN019 (HOWARU® Bifido / DR10™)
IBS & Bowel habit			
Specific probiotics help to improve frequency and/or consistency of bowel movements in some patients with IBS	Moderate	70	<i>B. animalis</i> subsp. <i>lactis</i> Bb12 (Yosa) <i>B. animalis</i> subsp. <i>lactis</i> DN-173 010 (Activia®) <i>B. animalis</i> subsp. <i>lactis</i> HN019 (HOWARU® Bifido / DR10™) <i>B. bifidum</i> MIMBb75,56 <i>B. longum</i> subsp. <i>infantis</i> 35624 (Bifantis® / Align®) <i>Escherichia coli</i> DSM17252 (Symbioflor®-2) Investigative combinations: Bioferme / CH / SDC / Valio Bb99 Marketed combinations (Duolac7/ LAB4 / Lactibiane®)

Overview of statements, grading and probiotics (marketed products and investigative strains) with supportive evidence[‡]

Statement	Grade of evidence for effect	Level of agreement (%)	Probiotics for which studies show supportive evidence of benefit (bold font indicates primary end point data)
Diarrhoea			
Probiotics tested to date do not reduce diarrhoea in patients with IBS	Very low	80	<i>L. reuteri</i> DSM17938 (Reuterin®)
In patients receiving antibiotic therapy, specific probiotics are helpful as adjuvant therapy to prevent or reduce the duration of associated diarrhoea	High	100	<i>L. paracasei</i> subsp. <i>paracasei</i> DN-114 001 (Actimel®) Marketed combination (Bio-K+CL1285)
In patients receiving <i>H. pylori</i> eradication therapy, specific probiotics are helpful as adjuvant therapy to prevent or reduce the duration/intensity of associated diarrhoea	High	100	<i>L. rhamnosus</i> GG (Giflorex®) Marketed combinations (ABT-21 culture® / Enterogermina®) <i>Saccharomyces boulardii</i> (Codex® / Reflor®)



Statement	Grade of evidence for effect	Level of agreement (%)	Probiotics for which studies show supportive evidence of benefit (bold font indicates primary end point data)
Health-related quality of life			
With specific probiotics, improvement of symptoms has been shown to lead to improvement in some aspects of health-related	Moderate	80	<i>B. animalis</i> subsp. <i>lactis</i> DN-173 010 (Activia®), <i>B. animalis</i> subsp. <i>lactis</i> DN-173 010 (Activia®), <i>B. bifidum</i> MIMBb <i>Escherichia coli</i> DSM17252 (Symbioflor®-2) Investigative combination (GoL12) Marketed combinations (Duolac7 / LAB4® / Lactibiane®)
Adverse events			
Probiotics have a favourable safety profile in patients with a range of lower GI symptoms typically managed in primary care or general practice	High	100	<i>B. animalis</i> subsp. <i>lactis</i> DN-173 010 (Activia®) <i>B. animalis</i> subsp. <i>lactis</i> (HOWARU® Bifido / DR10™) <i>B. bifidum</i> MIMBb <i>B. longum</i> subsp. <i>infantis</i> 35624 (Bifantis® / Align®) Investigative combinations (BIFIDO / CH / GoL6 / GoL12 / SDC / Valio Bb99) <i>L. paracasei</i> subsp. <i>paracasei</i> DN-114 001 (Actimel®) <i>L. rhamnosus</i> GG (Giflorex®) Marketed combinations (AB100 Jianneng / ABT-21 culture / Bio-K+CL1285 / Cultura / Duolac7, GEFILUS MAX / LAB4 / Lacidofil cap / VSL#3) <i>Saccharomyces boulardii</i> (Codex® / Reflor®)

Overview of statements, grading and probiotics (marketed products and investigative strains) with supportive evidence[‡]



Statement	Grade of evidence / Agreement
General statements	
Specific probiotics have a role in the management of some IBS symptoms and can also be used as an adjunct to conventional treatment	NA / 90% Derived from the evidence collated during this international consensus and from the clinical experience of the Consensus Group
Probiotic strains should be selected based on the patient's symptoms, the clinical indication and the available evidence; no probiotic alleviates the full range of symptoms in IBS	NA / 80% Some studies in patients with IBS showed a beneficial effect of a given probiotic on some symptoms but not others
When trying a probiotic therapy for a chronic GI problem, the product should be taken for 1 month; dose selection should be based on available evidence and manufacturers' recommendations	NA / 80% The treatment duration was for at least 4 weeks in most studies that examined probiotics for the treatment of chronic GI problems

‡ Investigative combinations:

Valio Bb99: *Lactobacillus rhamnosus* GG, *L. rhamnosus* Lc705,

Propionibacterium freudenreichii subsp. *shermanii* JS and *Bifidobacterium breve* Bb99 (Valio Ltd, Helsinki, Finland).

BIFIDO: *Bifidobacterium bifidum* BGN4, *B. animalis* subsp. *lactis* AD011, *Lactobacillus acidophilus* AD031

and *L. paracasei* subsp. *paracasei* BS041 (BIFIDO Co. Ltd, Hongchun, Korea).

Bioferme: *Bifidobacterium longum* subsp. *longum* 46 and *B. longum* subsp. *longum* 2C (Bioferme Ltd, Kaarina, Finland).

CH: *Bifidobacterium animalis* subsp. *lactis* Bb12 and *Lactobacillus paracasei* subsp. *paracasei* CRL-431 (Chr. Hansen A/S, Hoersholm, Denmark).

GoL6 contains non specified strains from the species: *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Bacillus subtilis*, *L. delbrueckii* subsp. *bulgaricus*,

L. delbrueckii subsp. *lactis* and *Bacillus licheniformis* (Garden of Life, West Palm, FL, USA).

GoL12 contains non specified strains from the species: *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *L. delbrueckii* subsp. *bulgaricus*,

L. delbrueckii subsp. *lactis*, *L. brevis*, *L. caucasicus* (nomina rejicienda; now *L. delbrueckii* subsp. *delbrueckii*), *L. fermentum*, *L. leichmanii*,

L. paracasei subsp. *paracasei*, *L. plantarum*, *L. helveticus* and *Saccharomyces boulardii* (Garden of Life, West Palm, FL, USA).

SDC: *Lactobacillus acidophilus* SDC 2012 and *L. acidophilus* SDC 2013 (Seoul Dairy Cooperative, Seoul, Korea).

‡ Marketed combinations:

AB100 Jianneng: *Streptococcus salivarius* subsp. *thermophilus*, *Lactobacillus delbrueckii* subsp. *bulgaricus*,

L. acidophilus and *Bifidobacterium longum* subsp. *longum* (Bright Dairy, Shanghai, China).

ABT-21 culture: *Lactobacillus acidophilus* LA+5, *Bifidobacterium animalis* subsp. *lactis* Bb12 and *Streptococcus salivarius* subsp. *thermophilus*

(Christian Hansen, Nienburg, Germany).

Bio-K+CL1285: *Lactobacillus acidophilus* CL1285 and *L. paracasei* subsp. *paracasei* LBC80R (Bio-K+International Inc., Quebec, QC, Canada).

Cultura: *Lactobacillus paracasei* subsp. *paracasei* F19, *L. acidophilus* La5 and *Bifidobacterium animalis* subsp. *lactis* Bb12 (Arla Foods Innovation, Stockholm, Sweden).

Duolac7: *Lactobacillus acidophilus* LH5, *L. plantarum* LP1, *L. rhamnosus* LR3, *Bifidobacterium breve* BR2, *B. animalis* subsp. *lactis* BL2, *B. longum* subsp. *longum* BG3

and *Streptococcus salivarius* subsp. *thermophilus* ST3 (Cell Biotech, Co. Ltd, Seoul, Korea).

Enterogermina: *Bacillus clausii* strains O/C, N/R, T and SIN (Sanofi Synthelabo OTC, Milan, Italy).

Gefilus MAX: *Lactobacillus rhamnosus* GG, *L. rhamnosus* Lc705, *Propionibacterium freudenreichii* subsp. *shermanii* JS

and *Bifidobacterium animalis* subsp. *lactis* Bb12 (Valio Ltd, Helsinki, Finland).

LAB4: *Lactobacillus acidophilus* (CUL60 and CUL21), *Bifidobacterium animalis* subsp. *lactis* CUL34 and *B. bifidum* CUL20 (Cultech, Port Talbot, UK).

Lacidofil cap: *Lactobacillus rhamnosus* R0011 and *L. acidophilus* R0052 (Lallemand Inc., Montreal, QC, Canada).

Lactibiane: *Bifidobacterium longum* subsp. *longum* LA 101, *Lactobacillus acidophilus* LA 102, *L. delbrueckii* subsp. *lactis* LA 103

and *Streptococcus salivarius* subsp. *thermophilus* LA 104 (PiLeJe, Paris, France).

VSL#3: *Bifidobacterium longum* subsp. *longum*, *B. infantis* subsp. *infantis*, *B. breve*, *Lactobacillus acidophilus*, *L. paracasei* subsp. *paracasei*,

L. delbrueckii subsp. *bulgaricus*, *L. plantarum* and *Streptococcus salivarius* subsp. *thermophilus* (VSL Pharmaceuticals Inc., Gaithersburg, MD, USA)

Probiotic availability by country in Europe, the USA and China

Product	Company	Food form	AT	BE	BG	CN	CZ	DK	FI	FR	DE	GR	HU	IE	IT	NL	NO	PL	PT	RU	SK	SI	ES	SE	TN	TR	UK	UA	US	
ABT-21 culture®	Hansen	Fermented milk									•																		•	
AB100 Jianneng	Bright Dairy	Fermented milk																												
Actimel®	Danone	Fermented milk	•	•			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•			•	•	•	•	•	•	•
Activia®	Danone	Fermented milk	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Align®	Procter & Gamble	Capsules																											•	
Bio-K + CL1285	Bio-K + international Inc.	Fermented milk																											•	
Bifantis®	Procter & Gamble	Capsules																											•	
Bifido Co	Hongchum	Sachets																												
Codex®	Smithkline Beecham / Zambon-Italia / Laboratoires Biocodex	Sachets and capsules													•														•	
Cultura®	Arla	Fermented milk						•									•													
Duolac7	Cell Biotech	Capsules			•					•	•					•		•					•				•			
Digestive Advantage Gas Defense Formula	Ganeden Biotech	Capsules																												
Enterogermina®	Sanofi	Vials								•				•	•												•			
Giflorex®	Errekappa	Sachets																												



Product	Company	Food form	AT	BE	BG	CN	CZ	DK	FI	FR	DE	GR	HU	IE	IT	NL	NO	PL	PT	RU	SK	SI	ES	SE	TN	TR	UK	UA	US
HOWARU®	Woolworths	Capsules				●																							●
LAB4®	Cultech, Port Talbot	Capsules														●											●		●
Lacidofil®	Lallemand	Capsules								●	●				●								●				●		
Lactibiane®	PILeJe	Sachets		●				●	●	●	●			●	●			●	●				●		●	●	●		
ProViva	Skänemejeirer Malmö	Fermented oatmeal gruel																●						●					●
ProBioPCC	Probiomics	Capsules																											●
Reflor®	Sanofi Synthelabo	Sachets																											●
Reuterin®	Noos	2 pills																●											
Symbioflor®	Symbiopharm GmbH	Oral liquid		●				●	●	●	●			●													●		
Gefilus®	Valio Ltd	Milk-based drink							●																				
VSL#3	Pharmaceuticals Inc.	Sachets		●						●				●													●		●
Yosa®	Bioferme	Fermented oat drink							●															●					

AT, Austria; BE, Belgium; BG, Bulgaria; CN, China; CZ, Czech Republic; DK, Denmark; FI, Finland; FR, France; DE, Germany; GR, Greece; HU, Hungary; IE, Ireland; IT, Italy; NL, Netherlands; NO, Norway; PL, Poland; PT, Portugal; RU, Russia; SK, Slovakia; SI, Slovenia; ES, Spain; SE, Sweden; TN, Tunisia; TR, Turkey; UK, United Kingdom; UA, Ukraine; US, United States of America



The European Society for
Primary Care Gastroenterology



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