CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Probiotics for Antibiotic-Associated Diarrhea and *Clostridium difficile* Infection: A Review of Guidelines

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Abbreviations

AAD	Antibiotic associated diarrhea
CDI	*Clostridium difficile infection*
C. difficile	*Clostridium difficile*

Context and Policy Issues

Antibiotics are frequently prescribed for a variety of conditions worldwide.[1] Antibiotic use results in altering the gastrointestinal flora [1,2] The changes in the gastrointestinal flora allows *C. difficile* to more easily colonize and infect patients.[1] This gives rise to various symptoms, notably diarrhea which is referred to as antibiotic associated diarrhea (ADD). AAD occurs in 5% to 39% of patients treated with antibiotics.[2] AAD may result in hospitalization and increased health care costs.[3]

Probiotics are live microorganisms which, when administered in sufficient quantities, counterbalance the changes in the gastrointestinal flora resulting from antibiotic use.[3] This reduces the risk of colonization by other pathogenic bacteria and confers health benefits to the host.[3] The most commonly tested probiotic species include the *Lactobacillus* genus, *Bifidobacterium* genus and *Saccromyces* genus.[2] There is some debate surrounding the benefits of probiotics.

The purpose of this report is to review the evidence-based guidelines regarding the use of probiotics for the prevention, management, and treatment of AAD and *C. difficile* infection. A second CADTH report to be published subsequently will review the clinical effectiveness of probiotics

Research Question

What are the evidence-based guidelines regarding the use of probiotics for the prevention, management, and treatment of antibiotic-associated diarrhea and *C. difficile* infection?

Key Findings

One guideline recommended the use of probiotics for treatment of antibiotic associated diarrhea (varying strength of recommendation depending on the product).

Four guidelines did not recommend the use of probiotics for prevention of *C. difficile* infection; and two of these guidelines also did not recommend use of probiotics for treatment of *C. difficile* infection. One guideline mentioned that probiotics may be considered for prevention and treatment of *C. difficle* (weak recommendation)

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases and a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and guidelines. The search was limited to English language documents published between January 1, 2013 and August 8, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults diagnosed with or at risk for antibiotic-associated diarrhea (AAD) or *C. difficule* infection (CDI)
Intervention	Probiotics (mixed strains, individual strains [e.g., *S. boulardii, L. acidophilus, L. rhamnosus*], and Kefir)
Comparator	No comparator necessary
Outcomes	Evidence-based recommendations
Study Designs	Evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2013. Guidelines that did not appear to be evidence based were excluded.

Critical Appraisal of Individual Studies

The included guidelines were assessed with the AGREE II instrument.[4] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 346 citations were identified in the literature search. Following screening of titles and abstracts, 302 citations were excluded and 44 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search. Of these 48 potentially relevant articles, 42 publications were excluded for various reasons, while six publications met the inclusion criteria and were included in this report. These comprised six evidence-based guidelines.[3,5-9] Appendix 1 presents the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Six relevant evidence-based guidelines.[3,5-9] were identified. Study characteristics are summarized below and details are available in Appendix 2, Tables 2 and 3.

Study Design

In five guidelines[3,5-7,9] a systematic literature search was conducted, and one guideline[8] used a systematic review published by the Agency of Healthcare research and Quality. The method used for formulating the recommendations was by consensus in three guidelines,[5,6,9] and unclear in three guidelines,[3,7,8]. The recommendations were graded in five guidelines.[3,5-8] and not graded in one guideline.[9]

Country of Origin

Three guidelines were from the USA, one each published in 2018,[6] 2015,[7] and 2013.[8] Two guidelines were from the Netherlands, one each published in 2018,[3] and 2013.[5]

Patient Population

The guidelines were relevant to patients who had CDI[5-9] or AAD[3] as a result of antibiotic use.

Interventions and Comparators

Five guidelines.[5-9] mentioned probiotics in the recommendation but did not mention any specific types. One guideline[3] recommended specific probiotic products (details presented in Appendix 4 Table 5).

Outcomes

Recommendations on use of probiotics for management of CDI.[5-9] and AAD[3] were presented.

Summary of Critical Appraisal

Critical appraisal of the studies is summarized below and details are available in, Appendix 3 Table 4.

In all the included guidelines.[3,5-9] the scope, purpose, and the evidence associated with the recommendations were described. In four guidelines.[5,7-9] the guideline development group comprised experts but details were not presented, in one guideline[6] the guideline development group had multidisciplinary experts, and in one guideline[3] the composition of the guideline development group was unclear. In five guidelines.[3,5-7,9] a systematic literature search was conducted and in one guideline[8] a literature search was not undertaken but rather a previously conducted systematic review was used. In all the guidelines it was unclear if patient input or resource implications had been considered.

Recommendations were graded in five guidelines,[3,5-8] and not graded in one guideline.[9] In three guidelines[5,6,9] recommendations were formulated based on consensus, and in three guidelines[3,7,8] the method for formulating guidelines was unclear. In one guideline[5] it was mentioned that there were no conflicts of interest; in one guideline[6] conflicts of interest were declared and a process was in place to address this; in three guidelines.[3,8,9] conflicts of interest were declared and potential for bias was unclear; and in one guideline[7] conflicts of interest were not presented. Although some elements of the quality assessment tool were

not satisfied, considering that some key elements were satisfied, overall our confidence in the recommendations is not reduced.

Summary of Findings

A summary of the recommendations is presented in this section and details are available in Appendix 4, Table 5.

Guidelines

One guideline,[3] recommends the use of *Lactobacillus rhamnosus* GG for the prevention of AAD (three star rating). Other probiotic products containing one or more of the following: *Lactobacillus casei, Saccharomyces boulardii, Bifidobactirium bifidum, Bifidobacterium lactis, Enterococcus faecium,Lactobacillus acidophilus, Lactobactobacillus paracasei, Lactobacillus plantarum, Lactobacillus rhamnosus, Lactobacillus salivarous, Bifidobacterium longun*, are recommended for treatment of ADD (one star rating)

Two guidelines[6,8] do not recommend probiotic treatment for prevention of CDI, one guideline[9] does not recommend probiotics for prevention or as an adjunct treatment for CDI, and one guideline[5] does not recommend probiotics for the initial treatment of CDI. One guideline[7] mentioned that probiotics may be useful in the prevention and treatment of *C.difficile* associated diarrhea and may be considered for recurrent and recalcitrant CDI (weak recommendation based on high quality evidence).

Limitations

The AAD and CDI guidelines are based on limited available evidence on the use of probiotics for AAD or CDI. The probiotic products appear to have varied composition hence it is not clear which particular probiotic product is suitable for which category of patients or type of antibiotic used.

None of the identified guidelines were developed in Canada, hence it is possible that not all of the probiotic products mentioned in these guidelines are available in Canada.

Conclusions and Implications for Decision or Policy Making

Of the six relevant guidelines[3,5-9] reviewed, one[3] made recommendations regarding the management of AAD and five guidelines[5-9] were for the management of CDI.

Overall, the majority of the recommendations do not support the use of probiotics for the prevention or treatment of CDI. One of the five guidelines pertaining to antibiotic-induced CDI recommends that probiotics be considered for prevention and management; the guideline development group considered this a weak recommendation.

One guideline,[3] recommends the use of probiotics for treatment of AAD, with the strength of the recommendation varying depending on the specific probiotic product.

It is unclear whether all of the probiotic products recommended are available in Canada, thus it is unclear how generalizable the results are to the Canadian setting.

References

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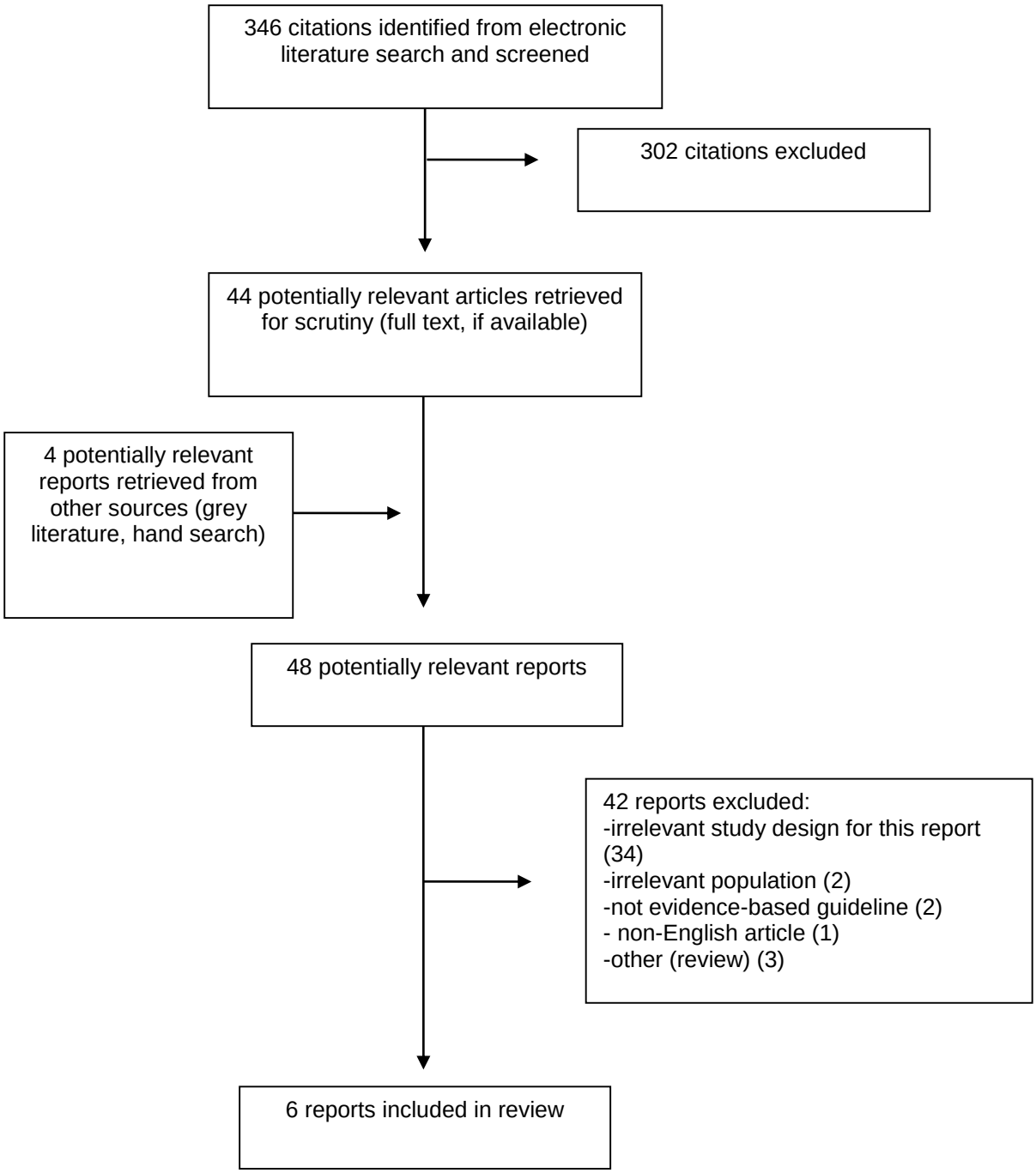
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Guidelines

Group and/or First Author, Year, Country	Objective	Guideline Development Group, Intended Users	Methodology
Agamenone,[3] 2018, The Netherlands	Aim: to provide a guide for the use of probiotics for the prevention of AAD	GDG was not specified. Intended users: healthcare professionals and patients	Systematic literature search was conducted. Multiple databases were searched. Articles were selected according to pre-defined inclusion and exclusion criteria. One person selected articles and extracted data. Unclear how the recommendations were formulated. Recommendations were graded.
ASCRS (Steele),[7] 2015, USA	Aim: to provide guidelines for the evaluation, management, and prevention of CDI	GDG comprised mainly of clinicians Intended users: practitioners, health care workers, and patients	Systematic literature search was conducted. Multiple databases were searched. Other methodological details were not presented The recommendations were formulated by the primary authors of the Guideline document and reviewed by the Clinical Practice Guidelines Committee, however the specifics of the method used was not described. Recommendations were graded using the GRADE system.
Australasian Society of Infectious Diseases (Trubiano)[9] 2016, Australia	Aim: to provided guidelines for the management of CDI in adults and children	GDG comprised experts in the area; details were not presented. Intended users: Australasian clinicians	Systematic literature search was conducted using a single database (PubMed) Recommendations were formulated based on consensus response achieved by discussion. Recommendations were not graded
ESCMID (Debast)[5], 2013, The Netherlands	Aim: to provide an overview of currently available treatment options for CDI, and to develop evidence-based update of treatment recommendations	GDG comprised experts in the area; details were not presented. Intended users: those in clinical practice	Systematic literature search was conducted using PubMed and Google Scholar Recommendations were formulated based on consensus using the method of Ullmann et al. Recommendations were graded using GRADE system

Group and/or First Author, Year, Country	Objective	Guideline Development Group, Intended Users	Methodology
IDSA & SHEA (McDonald)[6] 2018, USA	Aim: to update previous (2010) clinical practice guideline for CDI in terms of diagnosis, treatment, prevention of infection, and environmental management.	GDG comprised multidisciplinary experts (in areas of epidemiology, diagnosis, infection control, clinical management of patients Intended users: those in clinical practice	Systematic literature search was conducted using multiple databases. Recommendations were formulated based on consensus Recommendations were graded using the GRADE system.
Surawicz,[8] 2013, USA	Aim: to provide guidelines for the diagnosis, treatment, and prevention of CDI	GDG comprised experts in the area; details were not presented. Intended users: not specified	Method not described. It was mentioned however that it was based on a systematic review by AHRQ The method for formulating the recommendations was not specified Recommendations were graded using the GRADE system.

AAD = antibiotic associated diarrhea; AHRQ = Agency for Healthcare Research and Quality; ASCRS = American Society of Colon and Rectal Surgeons; CDI = *Clostridium difficile* infection; ESCMID = European Society of Clinical Microbiology and Infectious Diseases; GDG = guideline development group, GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; IDSA = Infectious Diseases Society of America; SHEA = Society for Healthcare Epidemiology of America

Table 3: Grade of Recommendations and Level of Evidence for Guidelines

Grade of Recommendations	Strength of Evidence
Agamenone,[3] 2018, The Netherlands	
Three categories of recommendations. Three star recommendation: significant effects for the reduction of AAD shown in at least three of the selected studies. Two star recommendation: significant effects for the reduction of AAD shown in at least two of the selected studies. One star recommendation: significant effects for the reduction of AAD shown in one study, a trend supported by two or more studies, or	NR
ASCRS (Steele),[7] 2015, USA	
GRADE system 1: Strong recommendation 2: weak recommendation	GRADE system A: RCTs without important limitations or overwhelming evidence from observational studies B: RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies C: Observational studies or case series

Grade of Recommendations	Strength of Evidence
Implications of the recommendation grade assigned using GRADE: 1A : Strong recommendation, can apply to most patients in most circumstances without reservation 1B: Strong recommendation, can apply to most patients in most circumstances without reservation 1C: Strong recommendation but may change when higher quality evidence becomes available 2A: Weak recommendation, best action may differ depending on circumstances or patients' or societal values 2B: Weak recommendation, best action may differ depending on circumstances or patients' or societal values 2C: Very weak recommendations; other alternatives may be equally reasonable	
Australasian Society of Infectious Diseases (Trubiano)[9] 2016, Australia	
NR	NR
ESCMID (Debast)[5], 2013, The Netherlands	
GRADE system A = strongly supports recommendation of use B = moderately supports recommendation of use C = marginally supports recommendation of use D = supports a recommendation against use	GRADE system 2a level "I Evidence from at least one properly designed randomized, controlled trial. II Evidence from at least one well-designed clinical trial, without randomization; from cohort or case–control analytic studies (preferably from more than one centre); from multiple time series; or from dramatic results of uncontrolled experiments. III Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees." Page 3
IDSA & SHEA (McDonald)[6] 2018, USA	
GRADE system Strong recommendation Weak recommendation	GRADE system Evidence level Initial confidence in estimate of effect based on study type: RCT – high confidence Observational studies – low confidence. Reasons for confidence level being lowered includes risk of bias, inconsistency, indirectness, imprecision, and publication bias. Reasons for confidence level being increased includes large effect, dose response, and all plausible confounding and bias considered
Surawicz,[8] 2013, USA	
GRADE system "The strength of a recommendation is graded as "strong", when the evidence shows the benefit of the intervention or treatment clearly outweighs any risk, and as "conditional", when uncertainty exists about the risk – benefit ratio." Page 478	GRADE system "The quality of the evidence is graded as follows: "high", if further research is unlikely to change our confidence in the estimate of the effect; "moderate", if further research is likely to have an important impact and may change the estimate; and "low", if further research is very likely to change the estimate". Page 478

AAD = antibiotic associated diarrhea; ASCRS = American Society of Colon and Rectal Surgeons; ESCMID = European Society of Clinical Microbiology and Infectious Diseases; GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; IDSA = Infectious Diseases Society of America; NR = not reported, RCT = randomized controlled trial; SHEA = Society for Healthcare Epidemiology of America;

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Guidelines using AGREE II.[4]

Strengths	Limitations
Agamennone,[3] 2018, The Netherlands	
• The scope and purpose were clearly stated. • A systematic review was conducted using standard methodology • Evidence was provided • The document was likely externally reviewed as it was published in a journal • Recommendations were not graded	• Unclear if patient preferences were considered • Unclear if resource implications were considered • Unclear if a policy was in place for updating the guideline • Conflicts of interests were declared; potential for bias seemed unlikely
ASCRS (Steele),[7] 2015, USA	
• The scope and purpose were clearly stated. • GDG comprised mainly of clinicians • A systematic review was conducted , however details of methodology were not presented • Evidence was provided • The document was likely externally reviewed as it was published in a journal • Recommendations were graded using the GRADE system	• Unclear if patient preferences were considered • Unclear if resource implications were considered • Unclear if a policy was in place for updating the guideline • Conflicts of interest of the authors were not mentioned
Australasian Society of Infectious Diseases (Trubiano)[9] 2016, Australia	
• The scope and purpose were clearly stated. • The guideline development group comprised experts in the area, details were not presented • A systematic literature search was conducted using a single database (PubMed) • Evidence was provided • As this guideline is an update of a previous guideline, it is likely that a policy for updating is in place • Conflicts of interest were declared. Some of the authors had association with industry. Potential for bias with respect to treatment with probiotics is unclear.	• Unclear if the document was externally reviewed • Unclear if patient preferences were considered • Unclear if resource implications were considered • Likely there was a policy for updating as the included guideline was an update • Recommendations were not graded
ESCMID (Debast)[5], 2013, The Netherlands	
• The scope and purpose were clearly stated. • The guideline development group comprised experts in the area, details were not presented • A systematic literature search was conducted using a single PubMed and Goggle Scholar. Method followed AGREE criteria • Evidence was provided • As this guideline is an update of a previous guideline, it is likely that a policy for updating is in place. • Recommendations were graded using GRADE • It was mentioned that the authors had no conflicts of interest.	• Unclear if the document was externally reviewed • Unclear if patient preferences were considered • Unclear if resource implications were considered • Likely there was a policy for updating as the included guideline was an update

Strengths	Limitations
IDSA & SHEA (McDonald)[6] 2018, USA	
• The scope and purpose were clearly stated. • The guideline development group comprised multidisciplinary experts • A systematic literature search was conducted between 2009 to 2016 using multiple databases • Evidence was provided • Recommendations were graded using GRADE. • As this guideline is an update of a previous guideline, it is likely that a policy for updating is in place • Conflicts of interest were declared. Some of the authors had association with industry. Potential for bias with respect to treatment with probiotics is unclear. However, there was a policy in place to handle conflicts of interest.	• Unclear if patient preferences were considered • Unclear if resource implications were considered • Unclear if the document was externally reviewed. It was reviewed by appropriate committees and Boards of IDSA and SHEA.
Surawicz,[8] 2013, USA	
• The scope and purpose were clearly stated. • The guideline development group comprised experts in the area but details were not provided • A systematic review does not appear to have been conducted however the evidence from a systematic review by AHRQ was used. • Evidence was provided • As this was published in a journal it is likely that it was externally reviewed • Conflicts of interest were declared. Some of the authors had association with industry. Potential for bias with respect to treatment with probiotics is unclear.	• Unclear if patient preferences were considered • Unclear if resource implications were considered • Unclear if there was a policy in place for updating

ASCRS = American Society of Colon and Rectal Surgeons; CDI = Clostridium *difficile* infection; ESCMID = European Society of Clinical Microbiology and Infectious Diseases; GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; IDSA = Infectious Diseases Society of America; SHEA = Society for Healthcare Epidemiology of America;

Appendix 4: Recommendations

Table 5: Recommendations and Associated Evidence

Evidence	Recommendations
Agamennone,[3] 2018, The Netherlands	
Based on systematic review and meta-analysis of the evidence identified, there was a suggestion of reduction in the incidence of AAD.	List of recommended probiotics (brand name: probiotic strains and CFU per dose) for AAD Three star recommendation: Microbial Platinum: *Lactobacillus rhamnosus* GG, 3.3×10^{10} CFU per dose Culturelle: *Lactobacillus rhamnosus* GG, 1.0×10^{10} CFU per dose One star recommendations: Actimel (dairy product): *Lactobacillus casei DN-114001*, 1.0×10^{10} CFU per dose Probioticum: *Saccharomyces boulardii*, 2.5×10^{9} CFU per dose *Winbiotic Pro-AD:* *Bifidobacterium bifidum W23*, 1.1×10^{9} CFU per dose *Bifidobacterium lactis W51*, 1.1×10^{9} CFU per dose *Enterococcus faecium W54*, 1.1×10^{9} CFU per dose *Lactobacillus acidophilus W37*, 1.1×10^{9} CFU per dose *Lactobacillus acidophilus W55*, 1.1×10^{9} CFU per dose *Lactobacillus paracasei W20*, 1.1×10^{9} CFU per dose *Lactobacillus plantarum W62*, 1.1×10^{9} CFU per dose *Lactobacillus rhamnosus W71*, 1.1×10^{9} CFU per dose *Lactobacillus salivarius W24*, 1.1×10^{9} CFU per dose Probactial Duo: *Saccharomyces boulardii*, 6.0×10^{9} CFU per dose *Lactobacillus acidophilus NCFM*, 2.1×10^{9} CFU per dose *Lactobacillus paracasei Lpc-37*, 2.1×10^{9} CFU per dose *Bifidobacterium lactis* Bi-04, 2.1×10^{9} CFU per dose *Bifidobacterium lactis* Bi-07, 2.1×10^{9} CFU per dose Imutis: *Saccharomyces boulardi*i 6.0×10^{9} CFU per dose *Lactobacillus acidophilus* 2.0×10^{9} CFU per dose *Lactobacillus rhamnosus* 3.0×10^{9} CFU per dose *Bifidobacterium longum*, 2.0×10^{9} CFU per dose Advanced Multi-Billion Dophilus: *Lactobacillus acidophilu, LA-5*, 1.3×10^{9} CFU per dose *Lactobacillus paracasei L CASEI 431*, 1.3×10^{9} CFU per dose *Lactobacillus rhamnosus GG*, 1.3×10^{9} CFU per dose *Bifidobacterium lactis BB-12*, 1.3×10^{9} CFU per dose
ASCRS (Steele),[7] 2015, USA	
Two systematic reviews suggested reduced incidence of *C. difficile* associated diarrhea with the	Recommendation: "Probiotics may be useful in the prevention and treatment

Evidence	Recommendations
use of probiotics. Two systematic reviews suggested that only specific probiotic strains such as *Lactobacillus acidophilus* CL1285, *Lactobacillus casei* LBC80R, and *Saccharomyces boulardii* are effective in the prevention of *C. difficile* infection. The authors further mentioned that that there was still uncertainty regarding the optimal agent, the length of therapy, and the dose.	of *C difficile*-associated diarrhea." Page 15 Recommendation grade: 2A (weak recommendation based on high quality evidence)
Australasian Society of Infectious Diseases (Trubiano)[9] 2016, Australia	
The authors mentioned that a previous Australian guideline did not recommend probiotic therapy for prevention or adjunctive treatment option for CDI. A Cochrane review and some reports did not support probiotic therapy. Further a revised Cochrane systematic review and two recent RCTs were reviewed. One large RCT did not show any benefit in preventing CDI with a probiotic mixture of lactobacilli and bifidobacteria.	Recommendation: "While probiotics may be of some value in limited studies, we do not recommend probiotic therapy use in prevention or adjunctive treatment in CDI." Page 483
ESCMID (Debast)[5], 2013, The Netherlands	
Findings for probiotic treatment for CDI appear to be conflicting. One meta-analysis concluded that moderate quality evidence suggested benefit with probiotic prophylaxis for CDI. Whereas a Cochrane systematic review concluded that evidence was insufficient to recommend use of probiotics, in general, as an adjunct to antibiotic treatment for CD diarrhea One RCT and one evidence-based review based on subgroup analysis showed efficacy with adjunct probiotic for recurrent CDI but not for initial CDI, on comparing relapse rates.	Recommendation: 'There is insufficient evidence to support administration of probiotics, toxin-binding resins and polymers, or monoclonal antibodies." Page 10 For the recommendation on the adjunct therapy for initial CDI, the quality of evidence is level 1, and the strength of probiotic recommendation is level D, Page 14, 18
IDSA & SHEA (McDonald)[6] 2018, USA	
Several meta-analyses suggested that probiotics may prevent CDI when given to patients on antibiotics, who do not have a history of CDI. However, in the studies with the greatest influence on the meta-analyses results, the placebo arm had CDI rates much higher than that would be expected for the patient population studied, potentially biasing the results towards benefit with probiotics. Furthermore, the organisms present in the probiotic formulations have the potential of causing infections in hospitalized patients (from three publications).	Recommendation: "There are insufficient data at this time to recommend administration of probiotics for primary prevention of CDI outside of clinical trials *(no recommendation)*." Page e30
Surawicz,[8] 2013, USA	
One meta-analysis concluded that *S. boulardii* was effective for C. *difficile* disease, however a Cochrane systematic review concluded that there was insufficient evidence to recommend probiotics, in general as an adjunct to antibiotics in the treatment of CDI.	Recommendation: "There is limited evidence for the use of adjunct probiotics to decrease recurrences in patients with RCDI. (Moderate recommendation, moderate-quality evidence)" Page 487 "Although there is moderate evidence that two probiotics (*L. rhamnosus*

Evidence	Recommendations
There is no strong evidence to support use of probiotics for the treatment of RCDI, and only weak evidence regarding the efficacy of *S. bourlardi*. Evidence on decrease in CDI with probiotics is limited One RCT showed that a probiotic yoghurt drink (containing *Lactobacillus casei*, *Lactobacillus bulgaricus*, and *Streptococcus thermophiles*) decreased the risk of CDI, however this RCT had with a small number of patients and also the placebo arm patients experienced greater rate of CDI than normally expected, potentially the results towards benefit with probiotics. Another study found capsules containing *Lactobacillus acidiphilus* and *Lactobacillus casei* were effective in preventing both AAD and CDI in hospitalized patients.	GG and *S. boulardii*) decrease the incidence of antibiotic associated diarrhea, there is insufficient evidence that probiotics prevent CDI. (Strong recommendation, low-quality evidence)" Page 491

AAD = antibiotic associated diarrhea, ASCRS = American Society of Colon and Rectal Surgeons; CDI = *Clostridium difficile* infection; ESCMID = European Society of Clinical Microbiology and Infectious Diseases; IDSA = Infectious Diseases Society of America; RCDI = recurrent CDI; RCT = randomized controlled trial; SHEA = Society for Healthcare Epidemiology of America;