CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF INCREASED INTESTINAL PERMEABILITY: IP GUIDELINE

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1. EXECUTIVE SUMMARY

Increased intestinal permeability (IP), also known as 'leaky gut', has gained researchers attention in recent years, with research linking the integrity of the intestine to health and disease.[1] IP can be defined as the loss of integrity between the cells of the small intestine caused by the disassembling of the proteins holding the cells together. The idea of IP was first mentioned in the literature during the 1960s[2] however, it was not until the 2000s where evidence emerged describing the potential mechanism of action.[3] Although the consequence of IP remains unclear, preliminary evidence suggest Australian adults with suspected IP experience disease burden.[4] This disease burden includes increased healthcare costs associated with the management of IP, lower subjective wellbeing compared to the Australian population and poor health related quality of life.[4]

The need to develop a clinical practice guideline for the management of increased intestinal permeability (IP Guideline) was identified after health services research revealed gaps in both the published literature and clinical practice[5,6] with discrepancy between what practitioners are using and what patients desire.[4-7] This clinical practice guideline serves as the first guideline for IP as no guideline surrounding any part of the management of IP has been developed in Australia or internationally.

The Working Group undertook a structured and evidence-based approach based on the NHMRC Guidelines for Guidelines Handbook to meet the 2016 NHMRC Standards for Guidelines in the development of the IP Guideline.[8] A total of 16 clinical questions were addressed, producing 38 recommendations: 27 evidence based recommendations, seven practice points and four consensus based recommendations. Each recommendation was reviewed and assessed by key stakeholders.

2. GUIDELINE PURPOSE AND AIM

The purpose of the IP Guideline is to utilise the best available evidence while considering the views and preferences from a multidisciplinary group of stakeholders and consumers. The IP Guideline aims to provide practitioners and consumers with a transparent evidence-based guidance for the management of altered IP to optimise patient care, improve health outcomes and reduce variation in care for Australian practitioners in private practice.

The IP Guideline aims to ensure Australian adults with IP receive, optimal evidence-based care by:

1. identifying any dietary choices available for the management of altered IP in Australian adults;
2. identifying any probiotic, prebiotic and syn biotic supplementation available for the the management of altered IP in Australian adults;
3. identifying any amino acid supplementation available for the management of altered IP in Australian adults;
4. identifying any plant-based medicine sup plementation available for the management of altered IP in Australian adults;
5. identifying any essential fatty acid supple mentation available for the management of altered IP in Australian adults;
6. identifying any mineral supplementation available for the management of altered IP in Australian adults;
7. identifying any vitamin supplementation available for the management of altered IP in Australian adults;
8. identifying any colostrum supplementation available for the management of altered IP in Australian adults.

3. SETTING AND AUDIENCE

The IP Guideline and developed recommendations are designed to support Australian adults with suspected or confirmed IP by clinicians in private clinical practice. Confirmed IP is classified as an elevation in the commercially available lactulose/mannitol ratio urine test or elevation of stool zonulin.

4. GUIDELINE DEVELOPMENT GROUP

The Guideline Development Group was comprised of two sub-groups: the Working Group and Stakeholder Group. These groups were formed from a multidisciplinary background of health professionals representing all potential clinicians which may see patients with IP, content experts, consumers and other major stakeholders. The Working was involved in the development of the IP Guideline. Whereas the Stakeholder Group provided their views and preferences on the drafted recommendations. A detailed description of the recruitment strategy, responsibilities of each member, and the method used to assess the conflict of interest of each member are in the Guideline Development Process.

5. GUIDELINE DEVELOPMENT METHODS

The IP Guideline was based on the NHMRC Guidelines for Guidelines Handbook to meet the 2016 NHMRC Standards for Guidelines.[8] The level of evidence for each recommendation was determined based on both the NHMRC grades for recommendations and NHMRC Evaluation of Evidence process.[9] The reporting of the IP Guideline followed the RIGHT statement.[10] A total of 12 steps were undertaken to develop the IP Guideline:

1. Create multidisciplinary guideline development group;
2. Identify scope and topics for guideline;
3. Develop a structured clinical question;
4. Perform a systematic review;
5. Summarise the relevant data;
6. Risk of bias assessment;
7. Assess the body of evidence and formulate recommendations;
8. Grade recommendation according to NHMRC;
9. Write the content narrative;
10. Stakeholders review recommendations;
11. Finalise guideline content;
12. Disseminate and implement IP Guideline.

6. CONSUMER INVOLVEMENT

The views and preferences of consumers were continuously integrated into the development of the IP Guideline from the initial scoping and planning through to the implementation of the IP Guideline according to the NHMRC requirement A.4. A survey study design was used to involve the consumers (target population) in the development of the IP Guideline. This method ensured the views and preference of the target population were incorporated in the IP Guideline, ensuring it is both relevant and appropriate.

A cross-sectional survey (The Leaky Gut Survey) of 589 Australian adults with suspected IP was undertaken during the initial stages of the IP Guideline development process.[4,7] The Leaky Gut Survey was designed to capture the health-seeking behaviours, views and preference of Australian adults identifying as having suspected or confirmed IP concerning the management and assessment of IP. Although the Stakeholder Group did not include a representative from Aboriginal and Torres Strait Islander Peoples, the views and preferences of the community were incorporated during The Leaky Gut Survey as participants included in this study identified as Aboriginal and Torres Strait Islander.

7. FUNDING

The development of the IP Guideline was funded by the Australian Research Centre in Complementary and Integrative Medicine (ARCCIM), providing a total of $4470 in support of guideline development, publication and dissemination. The Australian Government Research Training Program Scholarship provided Bradley Leech with a scholarship. The scholarship funding had no influence on the development or content of the guidelines.

8. INTEROPERATING THE RECOMMENDATIONS

A detailed method of guideline development including the process used to evaluate and form the recommendations can be found in the Guideline Development Process. To assist in interpreting the IP Guideline each recommendation has been categorised according to the type of available evidence (Table 1) and classified according to the strength of the recommendation (Table 2).

8.1 RECOMMENDATION WORDING ACCORDING TO STRENGTH OF EVIDENCE

The IP Guideline utilises the National Institute for Health and Care Excellence methodology for the wording of the recommendations.[11] Wording for a strong recommendation uses terms such as “offer”, “advise”, “do NOT offer”, or “do NOT advise”, while the wording for a recommendation contains “consider” or “consider NOT”. For options, consensus-based recommendations and practice points, the key terminology contains “may consider” to reflect the strength of the recommendation and evidence.

Table 1 Categories of the IP Guideline recommendations

EBR	Evidence-based recommendations: A recommendation formulated after a systematic review of the evidence, with supporting references.
CBR	Consensus-based recommendations: A recommendation formulated in the absence of quality evidence, with the guideline development group forming a consensus.
PP	Practice points: A recommendation on a subject that is outside the scope of the search strategy for the systematic review, based on expert opinion and formulated by a consensus process

Table 2 Strength of recommendations

Strong recommendation	⊕⊕⊕⊕	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Recommendation	⊕⊕⊕	Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Option	⊕⊕	Clinicians should be flexible in their decision making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.
Consensus-based recommendation	⊕⊕	
Practice point	⊕	
No recommendation	∅	Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.

9. RECOMMENDATION SUMMARY

Table 3 Recommendation Summary

No.	Category	Recommendation	Strength
Dietary based recommendations			
Alcohol recommendations			
1.1	EBR	People with intestinal permeability should consider consuming no more than 10 standard alcoholic drinks a week and no more than 4 standard alcoholic drinks on any one day in accordance with the Australian Dietary Guidelines during the treatment of intestinal permeability.	⊕⊕⊕⊕
1.2	CBR	People with intestinal permeability may consider limiting or avoiding alcohol consumption during the short-term treatment of intestinal permeability.	⊕⊕
Dietary fibre recommendations			
1.3	EBR	People with intestinal permeability should consider trialling and if tolerated, consume a diet high in dietary fibre from a diverse range of sources.	⊕⊕⊕⊕
1.4	CBR	Clinicians are advised to trial and if tolerated, recommend patients to consume 38g for men and 28g for female of dietary fibre daily while treating patients with intestinal permeability.	⊕⊕
1.5	CBR	Clinicians are encouraged to recommend gluten-free sources of dietary fibre to patients with confirmed intestinal permeability.	⊕⊕
Macronutrient ratio recommendations			
1.6	EBR	People with intestinal permeability should consider consuming the Acceptable Macronutrient Distribution Range of protein (15-25%), fats (20-35%) and carbohydrates (45-65%) in accordance with the Australian Dietary Guidelines.	⊕⊕⊕⊕
1.7	EBR	People with intestinal permeability should consider consuming a diet moderate in fat and limit high consumption of long-chain saturated fatty acids.	⊕⊕⊕⊕
1.8	EBR	People with intestinal permeability should consider NOT consuming a diet high in free fructose.	⊕⊕⊕⊕
Energy intake recommendations			
1.9	EBR	People with intestinal permeability may consider consuming the estimated energy requirements in accordance with the Australian Dietary Guidelines.	⊕⊕⊕
1.10	EBR	Clinicians may consider using a kilojoule restricted diet in the short-term treatment of people with confirmed intestinal permeability when clinically appropriate (e.g., obesity).	⊕⊕⊕
Gluten-free diet recommendations			
1.11	EBR	Clinicians should only advise a strict gluten-free diet during the treatment of people with confirmed intestinal permeability if clinical symptoms or pathology indicate a gluten intolerance, sensitivity or allergy.	⊕⊕⊕⊕⊕
1.12	EBR	Clinicians should aim to advise a gluten-free diet during the short-term treatment of people with confirmed intestinal permeability that report clinical symptoms in response to the consumption of gluten after the investigation for gluten intolerance, sensit ivity or allergy has been carried out	⊕⊕⊕⊕⊕
1.13	EBR	Clinicians should aim to offer a low gluten diet for the management of people with confirmed intestinal permeability that report no clinical symptoms or pathology indicating a gluten intolerance, sensitivity or allergy.	⊕⊕⊕⊕⊕
Probiotic, prebiotic and synbiotic supplementation recommendations			
Probiotics			
2.1	EBR	There is insufficient evidence to form a recommendation on the use of probiotics as a collective group for the treatment of people with intestinal permeability.	∅
2.2	EBR	Clinicians may consider using *Saccharomyces cerevisiae var boulardii (Saccharomyces boulardii)* supplementation in the treatment of people with intestinal permeability.	⊕⊕⊕

2.3	EBR	Clinicians may consider the use of effective probiotics for a minimum of 3 months when treating people with intestinal permeability.	⊕⊕⊕
2.4	PP	Clinicians may consider researching probiotic strains for their effectiveness before using them to treat people with intestinal permeability.	⊕
2.5	PP	Clinicians may consider the use of probiotics which are supported by pre-clinical research in conjunction with other treatment interventions for the management people with intestinal permeability.	⊕
Probiotic drink			
2.6	EBR	People with intestinal permeability should consider trialling and if tolerated, consume fermented milk products such as kefir.	⊕⊕⊕⊕
2.7	EBR	People with intestinal permeability may consider NOT consuming Yakult light®.	⊕⊕⊕
Prebiotics			
2.8	EBR	There is insufficient evidence to form a recommendation on the use of prebiotics as a collective group for the treatment of people with intestinal permeability.	∅
2.9	PP	Clinicians may consider researching specific prebiotic for their effectiveness before using them in the treatment of people with intestinal permeability.	⊕
2.10	PP	Clinicians may consider trialling and if tolerated, recommend patients to use prebiotic which are supported by pre-clinical research in conjunction with other treatment interventions for the management people with intestinal permeability.	⊕
2.11	PP	Clinicians may consider NOT using polydextrose in the treatment of people with intestinal permeability.	⊕
Synbiotic			
2.12	EBR	Clinicians may consider the use of effective synbiotic in the treatment of people with intestinal permeability.	⊕⊕⊕
2.13	EBR	Clinicians may consider the use of effective synbiotic for a minimum of 3 months when treating people with intestinal permeability.	⊕⊕⊕
2.14	EBR	Clinicians may consider NOT using polydextrose and *Bifidobacterium animalis ssp. lactis* 420 in the treatment of people with intestinal permeability.	⊕⊕⊕
2.15	PP	Clinicians may consider the use of specific synbiotic which are supported by pre-clinical research in conjunction with other treatment interventions for the management people with intestinal permeability.	⊕
NSAID induced intestinal permeability			
2.16	EBR	Clinicians may consider NOT using probiotics for the treatment of people with nonsteroidal anti-inflammatory drug induced intestinal permeability.	⊕⊕⊕
2.17	EBR	Clinicians may consider NOT using prebiotics for the treatment of people with nonsteroidal anti-inflammatory drug induced intestinal permeability.	⊕⊕⊕
2.18	EBR	Clinicians may consider NOT using synbiotics for the treatment of people with nonsteroidal anti-inflammatory drug induced intestinal permeability.	⊕⊕⊕
Amino acid supplementation recommendations			
Glutamine			
3.1	EBR	Clinicians should offer glutamine supplementation for the treatment of people with intestinal permeability.	⊕⊕⊕⊕⊕
3.2	CBR	Clinicians may consider the use of glutamine supplementation in conjunction with other treatment interventions for the management of people with intestinal permeability.	⊕⊕
NSAID-induced intestinal permeability			
3.3	EBR	Clinicians should consider the use of short-term lactoferrin supplementation for the treatment of people with nonsteroidal anti-inflammatory drug induced intestinal permeability.	⊕⊕⊕⊕
Plant-based medicine supplementation recommendations			
4.1	EBR	There is insufficient evidence to form a recommendation on the use of plant-based medicines as a collective group for the treatment of people with intestinal permeability.	∅
4.2	PP	Clinicians may consider the use of plant-based medicines which are supported by pre-clinical research in conjunction with other treatment interventions for the management people with intestinal permeability.	⊕

Essential fatty acid supplementation recommendations			
5.1	EBR	There is insufficient evidence to form a recommendation on the use of essential fatty acid supplementation for the treatment of people with intestinal permeability.	∅
Mineral supplement recommendations			
6.1	EBR	Clinicians may consider using zinc supplementation in the treatment of people with intestinal permeability.	⊕⊕⊕

Abbreviations: CBR = Consensus-based recommendation; EBR = evidence-based recommendation; NSAID = nonsteroidal anti-inflammatory drug; PP = practice point.

10. DIETARY CHOICES

10.1 CLINICAL QUESTIONS

Clinical Question 1: In Australian adults with increased intestinal permeability, what are the benefits of dietary choices for the treatment of increased intestinal permeability?

Clinical Question 2: In Australian adults with increased intestinal permeability, what are the harms, cautions and contraindications for dietary choices?

10.2 CLINICAL NEED FOR THE QUESTION

The consumption of some food products such as alcohol,[12-15] gluten,[16-19] and dairy[20,21] are suggested to negatively affect intestinal integrity. In contrast, other food products such as dietary fibre, including prebiotics, display a beneficial action on intestinal integrity.[22] Considering the opinions of clinicians that commonly treat patients with IP, dietary modification is the most frequently used treatment intervention used in the management of IP.[5] These clinicians were found to employ diverse dietary interventions while treating patients with IP, including the reduced consumption of alcohol, gluten, dairy while incorporating organic foods, apple cider vinegar, bone broth, lemon water and fermented foods. The opinions of clinicians appear to align with opinions of Australian adults with suspected IP. Dietary products are the preferred method for treating IP; over 80% of Australian adults with suspected IP report they prefer to be treated using dietary modification.[4] This population also choose to allocate their finances to dietary interventions regardless of their income manageability, with many of them prescribing the dietary change themselves. To further support the need for dietary recommendations, patients expect that clinicians should have a comprehensive understanding of dietary treatment interventions to manage IP.[7]

10.3 SUMMARY OF EVIDENCE

A review of the literature found 22 studies addressing the two clinical questions (CQ.1 and CQ.2) regarding the impact of dietary intake on intestinal integrity. The risk of bias (RoB) assessment found the identified systematic review had a high RoB (n = 1),[23] while the seven randomised control trials were found to have some RoB; n = 5 with moderate RoB[24-28] and n = 2 with low RoB.[29,30] The 14 non-randomised clinical trials had moderate (n = 7),[31-37] serious (n = 4),[37-40] or critical (n = 3) RoB.[41-43] A summary of the evidence is provided here with a full review of the literature found in the Technical Report.

Four studies reported on the impact of alcohol consumption on IP, five studies explored the effect of dietary fibre on intestinal integrity, ten studies were included evaluating energy intake and macronutrient distribution on intestinal integrity, and four studies evaluating the effects of a gluten-free diet on IP. There is sufficient evidence to suggest dietary modifications can influence intestinal integrity, with some changes supporting health and integrity and others causing a detrimental effect to IP. However, a major limitation is the lack of high-quality research, even though the included articles utilising a non-randomised clinical trial study design. Studies on alcohol consumption most notably saw a lack of high-quality research, as such there is insufficient evidence to suggest complete avoidance of alcohol is necessary during the treatment of IP.[23,37,38,44] There is potential benefit in limiting alcohol consumption in specific health conditions, however the combination of low-quality evidence and mixed results suggests further randomised controlled trials and longitudinal research is required before evidence-based recommendations can be made.[23,37,38,44]

There is moderate-quality evidence to suggest the consumption of dietary fibre supports intestinal integrity and improves IP.[27-29,36,43] Although limited evidence is available on the type and amount of dietary fibre, consuming a diverse range of dietary fibre with prebiotic properties appears to benefit intestinal integrity.[27,36,43] However, the fortification of wheat-based products with prebiotics (inulin or beta-glucan) results in mixed effects on IP.[27,28] There is limited low to moderate-quality evidence that patients at risk of IP or have confirmed IP should follow a gluten-free diet during IP treatment.[24,30,41,42] Instead, evidence suggests that patients at risk of IP could tolerate a low amount of gluten (<16g/day).[24] However, patients with positive HLA-DQ2/8, the genetic predisposition for coeliac disease, may not tolerate the consumption of gluten-containing products with a more significant impact on IP found in patients with positive HLA-DQ2/8 compared to negative HLA-DQ2/8 after the consumption of a gluten-containing diet.[30]

The evidence evaluating energy intake and macronutrient distribution was of low-quality.[25,26,31-36,39,40] In terms of energy intake, kilojoule restriction of 3,350-6700kJ/day has been found to improve IP[36,39] while overfeeding with either estimated energy requirements plus 4,180kJ/day[40] or 116% estimated energy requirements saw no significant effect on IP.[26] In contrast with this latter finding, increased energy intake (>10,945 kJ/day) was found to be an independent risk factor for IP.[23] Although the distribution of macronutrients was found to have mixed results, a trend suggests a high-fat diet may have a detrimental effect on intestinal integrity. Total fat percentage was found to be an independent risk factor for IP.[23] Although short-term (<15 days) consumption of a high-fat diet (41-55% of estimated energy requirements from fats) does not appear to significantly impact intestinal integrity,[25,31,40] a slightly high-fat diet (35% of estimated energy requirements from fats) over a longer period (12 weeks) saw a significant impact on IP.[35] The only other macronutrient distribution ratio identified to influence intestinal integrity potentially was simple carbohydrates.[26,33] Although increased simple carbohydrate consumption saw mixed results, the most significant impact on intestinal integrity was the consequence of fructose consumption rather than other simple carbohydrates.[26,33]

Table 4 Recommendations: Dietary Based

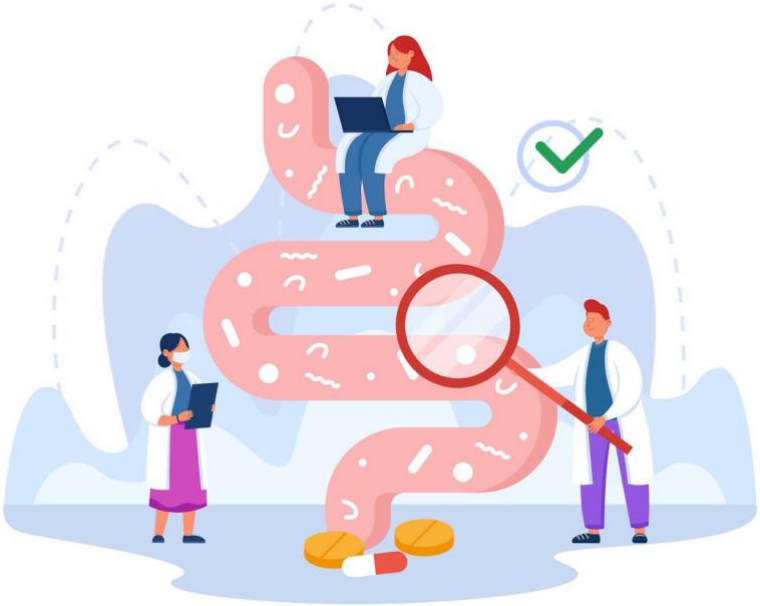
No.	Category	Recommendation	Strength
Alcohol recommendations			
1.1	EBR	People with intestinal permeability should consider consuming no more than 10 standard alcoholic drinks a week and no more than 4 standard alcoholic drinks on any one day in accordance with the Australian Dietary Guidelines during the treatment of intestinal permeability.	⊕⊕⊕⊕
1.2	CBR	People with intestinal permeability may consider limiting or avoiding alcohol consumption during the short-term treatment of intestinal permeability.	⊕⊕
Dietary fibre recommendations			
1.3	EBR	People with intestinal permeability should consider trialling and if tolerated, consume a diet high in dietary fibre from a diverse range of sources.	⊕⊕⊕⊕
1.4	CBR	Clinicians are advised to trial and if tolerated, recommend patients to consume 38g for men and 28g for female of dietary fibre daily while treating patients with intestinal permeability.	⊕⊕
1.5	CBR	Clinicians are encouraged to recommend gluten-free sources of dietary fibre to patients with confirmed intestinal permeability.	⊕⊕
Macronutrient ratio recommendations			
1.6	EBR	People with intestinal permeability should consider consuming the Acceptable Macronutrient Distribution Range of protein (15-25%), fats (20-35%) and carbohydrates (45-65%) in accordance with the Australian Dietary Guidelines.	⊕⊕⊕⊕
1.7	EBR	People with intestinal permeability should consider consuming a diet moderate in fat and limit high consumption of long-chain saturated fatty acids.	⊕⊕⊕⊕
1.8	EBR	People with intestinal permeability should consider NOT consuming a diet high in free fructose.	⊕⊕⊕⊕
Energy intake recommendations			
1.9	EBR	People with intestinal permeability may consider consuming the estimated energy requirements in accordance with the Australian Dietary Guidelines.	⊕⊕⊕
1.10	EBR	Clinicians may consider using a kilojoule restricted diet in the short-term treatment of people with confirmed intestinal permeability when clinically appropriate (e.g., obesity).	⊕⊕⊕
Gluten-free diet recommendations			
1.11	EBR	Clinicians should only advise a strict gluten-free diet during the treatment of people with confirmed intestinal permeability if clinical symptoms or pathology indicate a gluten intolerance, sensitivity or allergy.	⊕⊕⊕⊕⊕
1.12	EBR	Clinicians should aim to advise a gluten-free diet during the short-term treatment of people with confirmed intestinal permeability that report clinical symptoms in response to the consumption of gluten after the investigation for gluten intolerance, sensitivity or allergy has been carried out	⊕⊕⊕⊕⊕
1.13	EBR	Clinicians should aim to offer a low gluten diet for the management of people with confirmed intestinal permeability that report no clinical symptoms or pathology indicating a gluten intolerance, sensitivity or allergy.	⊕⊕⊕⊕⊕

Abbreviations: CBR = Consensus-based recommendation; EBR = evidence-based recommendation; PP = practice point.

10.4 JUSTIFICATION

Recommendations were informed by the best available evidence on the impact dietary intake can have on intestinal integrity. The guideline development group carefully considered the available literature and the importance patients with IP place of dietary treatments for the management of IP while forming each recommendation. As Australian adults with suspected IP report the desire to use dietary modifications as the primary treatment interventions in the management of IP, recommendations were formulated regardless of the low grade identified. As diet is not a short-term fix but rather a long-term solution, recommendations considered the length of included studies and the possible long-term health outcomes. While many studies involved healthy adults without IP or associated conditions, the recommendations also considered the potential effect diet might have on population groups with IP or disease associated with impaired IP.

With the available evidence and the current advice clinicians are currently providing patients with IP, the recommendation regarding alcohol consumption should follow the Australian Dietary Guidelines. However, to align with clinician's current views and preclinical research, a consensus-based recommendation was developed whereby patients with IP may limit or avoid alcohol consumption during the treatment period for IP.



Whilst limited evidence was found on the precise amount of dietary fibre required to provide a beneficial effect, the available evidence supports the consumption of a diverse range of dietary fibre. There is moderate-quality evidence indicating no harmful effects after the consumption of dietary fibre among individuals with suspected IP. Therefore, the best available recommendation is to follow the suggested dietary target for dietary fibre according to the Australian Dietary Guidelines. Prioritising the consumption of low gluten sources of dietary fibre was included to complement the recommendations related to gluten consumption. Guiding patients to consume a strict gluten-free diet limits the consumption of major food groups and increases social stress involved in gluten avoidance. Therefore, evidence and consensus suggest a low gluten diet rather than a strict gluten-free diet may provide the best outcomes for individuals with IP.

The recommendation to follow the Acceptable Macronutrient Distribution Range in accordance with the Australian Dietary Guidelines is based on the findings that deviations from these reference ranges may results in worsening of IP. Furthermore, many of the included studies used a variation of the Acceptable Macronutrient Distribution Range as the control diet while exploring macronutrients ratio. Although there is conflicting evidence on the effect of a high-fat diet in the short-term (<15 days), the advice not to follow a high-fat diet is supported by the long-term (>12 weeks) effect of a slightly high-fat diet on both serum and stool zonulin. Limiting the consumption of excess fructose is supported by the available literature and the Australian Dietary Guidelines. Although total kilojoule intake is suggested to influence intestinal integrity, following the Australian Dietary Guidelines regarding kilojoule intake remains the best option for people with IP. However, while under the care of a clinician, there may be benefits for a short-term kilojoule restricted diet.

11. PROBIOTIC, PREBIOTIC AND SYNBIOTIC SUPPLEMENTATION

11.1 CLINICAL QUESTIONS

Clinical Question 3: In Australian adults with increased intestinal permeability, what are the benefits of oral probiotic, prebiotic or synbiotic supplementation for the treatment of increased intestinal permeability?

Clinical Question 4: In Australian adults with increased intestinal permeability, what are the harms, cautions and contraindications for oral probiotic, prebiotic or synbiotic supplementation use?

11.2 CLINICAL NEED FOR THE QUESTION

Probiotics and prebiotics may influence intestinal integrity by changing the environment of the gastrointestinal system.[45,46] Mechanistic research indicate probiotics may increase gene expression of ZO-1, ZO-2, claudin-1, occluding, which are involved in tight junction modulation in the small intestine.[46] Other probiotics may stabilise the mucosal barrier by increasing mucin expression.[46] While gliadin-induced IP has been suggested to be reduced by the use of probiotics increasing ZO-1, claudin-1, and occluding gene expression.[47] Some probiotics can produce bacteriocins, antimicrobial peptides that inhibit pathogenic bacteria, thereby modifying the microbiome so that pathogenic bacteria are unable to stimulate IP.[48] While less is known about prebiotic effect on intestinal integrity, mechanistic research suggests prebiotics may mitigate the impact of lipopolysaccharide on intestinal integrity and protect the mucosa from inflammation.[45]

Australian adults with suspected IP preferred the use of dietary supplements such as probiotics and prebiotics managing IP.[7] Specifically, the use of dietary supplements is the third most preferred treatment method for IP, with many people with IP frequently using dietary supplements (73%) for the management of IP.[4,7] Dietary supplements are most frequently prescribed by a naturopath, with over 70% of probiotic and prebiotic supplementation prescribed by a clinician.[4] This population group reports spending an average of AUD $2,175 on dietary supplements annually.[7] The economic burden of using dietary supplements does not appear to prohibit this populations' use of dietary supplements.[7] Almost 90% of Australian adults with suspected IP perceive that it is important for clinicians to be knowledgeable about dietary supplements.[7] The most frequently used dietary supplement in people with IP are probiotics, with prebiotics as a close third.[4] Saccharomyces boulardii is the most frequently prescribed probiotic for IP management by clinicians.[5] From the Saccharomyces boulardii supplements used by this population group, 85% is reported to be prescribed by a clinician.[4] Supplementation with Saccharomyces boulardii is reported as an independent predictor of a greater number of days each week that IP affects daily living, suggesting patients with more severe IP use Saccharomyces boulardii.[4] At the same time, Australian adults with suspected IP that report an improved IP are more likely to use dietary supplements.[4] Clinicians frequently to treat IP, with almost 80% of clinicians reporting they always prescribe probiotics to patients with IP.[5] Although limited evidence is available on the type of probiotics clinicians use, multi-strain probiotics are more frequently used than single-strain probiotics.[5] Clinicians also use prebiotic fibres such as resistant starch, pectin and slippery elm in the treatment of patients with IP.[5] The use of synbiotic (a combination of prebiotic and probiotic) by individuals with IP have not been investigated in the literature.

The mechanistic evidence suggests potential benefits of probiotic and prebiotic supplementations and a collective summary of the available literature is required. Furthermore, as both clinicians and individuals with suspected IP report the frequent use of probiotics and prebiotics, structured recommendations are necessary to ensure optimal care is provided.

11.3 SUMMARY OF EVIDENCE

A literature review found 33 studies addressing the two clinical questions (CQ.3 and CQ.4) regarding the effect of probiotic, prebiotic and synbiotic on intestinal integrity. The risk of bias (RoB) assessment found the identified systematic reviews had a high RoB (n = 1)[49] and low RoB (n = 1),[50] while the 27 randomised control trials were found to have high (n = 15),[51-65] some (n = 6)[66-71] and low (n = 6)[72-77] RoB. The four non-randomised clinical trials had moderate RoB (n = 3)[78-80] and serious RoB (n = 1).[81] A summary of the evidence is provided here with a full review of the literature found in the Technical Report.

Although there is substantial evidence (n = 19)[49-52,56-61,63,64,67-69,71,72,74,78] investigating the effect of probiotics on intestinal integrity, the heterogeneity of these studies presents difficulties synthesising the research. The research on multi-strain probiotics their effect on intestinal integrity was mixed. Most studies found no significant difference in stool zonulin, serum zonulin, and dual sugar test after probiotic supplementation. The quantity of each probiotic strain may influence the effectiveness of supporting IP; however, further studies are required.[63] One commercially available probiotic, Saccharomyces boulardii was found to decrease IP by 33.33% at 12 weeks.[67] Furthermore, intervention duration of less than three months had a significant impact on the effects of probiotics on serum zonulin, with greater improvement seen in studies lasting for three months then any longer (coefficient = 33.23 [95% CI: 0.30, 66.16]; p=0.048). One type of probiotic with a sufficient amount of studies with similar designs was probiotic drinks. Kefir milk and fermented milk were both found to have a beneficial effect on IP.[69,71] Three further studies examined 65ml of milk drink (Yakult light®) containing Lactobacillus casei Shirota 108/ml (6.5 x 109 CFU) three times daily and found no significant effect on IP.[56,58,61] These results were consistent across multiple assessment methods (stool zonulin, serum zonulin and dual sugar), time points (12 weeks and six months) and disease states (metabolic syndrome and liver cirrhosis).[56,58,61]

The use of prebiotics in the treatment of IP was met with mixed evidence in the limited studies found (n = 6).[49,62,65,76,77,80.] Synthesis of the available evidence was not possible due to the diverse prebiotics fibres used in the identified studies, including pectin (n = 2),[65,80] arabinoxylan (n = 2),[76,77] inulin (n = 1),[49] inulin-type fructans (n = 1),[49] polydextrose (n = 1),[62] slippery elm (n = 1)[80] and guar gum (n = 1).[80] However, the effect of prebiotics on intestinal integrity appears to be influenced by the type of prebiotic used. For instance, inulin or inulin-type fructans were found to decreased either LPS or exotoxin levels[49] while others such as arabinoxylan[76,77] and pectin[65] were found to have no effect on IP.

The evidence evaluating synbiotic supplementation found moderate quality of evidence.[50,53,55,62,70,73,79,81] Most studies (n = 5)[50,53,55,62,73] used a diverse range of probiotics and prebiotics with only three studies identified as having the same or similar ingredients.[78,79,81] The variety of synbiotic combinations used in the included studies made synthesising the evidence difficult. A meta-analysis found synbiotic supplementation significantly reduced serum zonulin compared to placebo (weighted mean difference = -10.55 [95% CI: -17.76, -3.34]; p=0.004), with a study duration of less than three months identified to have a significant impact on the effects of synbiotic on serum zonulin (coefficient = 33.23 [95% CI: 0.30, 66.16]; p=0.048). The three studies identified as having the same or similar ingredients used a combination of inulin, corn starch and fructooligosaccharides with a multi-strain probiotic (7.5 x 109 CFU).[78,79,81] All three studies demonstrated a beneficial effect of symbiotic therapy on intestinal integrity. Mixed results were found for other synbiotic combinations, with some such as 250mg of tara gum and Streptococcus thermophilus (1 x 107 CFU) found to improve IP after 4 weeks[73] while other combinations of 2.4g of partially hydrolysed guar gum and 1.6g of inulin, Lactobacillus reuteri (1 x 108 CFU) twice daily round to have no effect after 3 months (p=0.737).[53] Furthermore, one study identified synbiotic supplementation containing 12g of polydextrose and *Bifidobacterium animalis* ssp. lactis 420 (1010 CFU) resulted in a significant increase in serum lipopolysaccharide compared to placebo after six months (+9.1±40 vs −26±108; p=0.007).[62]

Four high-quality studies investigated the effects of probiotic (n = 2), prebiotic (n = 1) and synbiotic (n = 1) supplementation on nonsteroidal anti-inflammatory drugs (NSAIDs) induced IP.[54,66,70,75] All included studies used the same designs to induce IP with NSAIDs. This study design involved participants taking 75mg of a NSAID nine hours before measuring IP and another 50mg one hour prior to measuring IP. Five probiotic formulations measured across two short-term studies found no significant change in NSAID induced IP.[54,75] A six-week trial of two different prebiotics (12g of arabinoxylan or 12g of oat β-glucan) found no significant difference in arabinoxylan group or oat β-glucan in preventing NSAID induced IP.[66] Synbiotic supplement containing fructooligosaccharides and a multi-strain probiotic resulted in similar outcomes as prebiotic and probiotic with no significant difference.[70]

Table 5 Recommendations: Probiotic, prebiotic and synbiotic supplementation

No.	Category	Recommendation	Strength
Probiotics			
2.1	EBR	There is insufficient evidence to form a recommendation on the use of probiotics as a collective group for the treatment of people with intestinal permeability.	∅
2.2	EBR	Clinicians may consider using *Saccharomyces cerevisiae var boulardii (Saccharomyces boulardii)* supplementation in the treatment of people with intestinal permeability.	⊕⊕⊕
2.3	EBR	Clinicians may consider the use of effective probiotics for a minimum of 3 months when treating people with intestinal permeability.	⊕⊕⊕
2.4	PP	Clinicians may consider researching probiotic strains for their effectiveness before using them to treat people with intestinal permeability.	⊕
2.5	PP	Clinicians may consider the use of probiotics which are supported by pre-clinical research in conjunction with other treatment interventions for the management people with intestinal permeability.	⊕
Probiotic drink			
2.6	EBR	People with intestinal permeability should consider trialling and if tolerated, consume fermented milk products such as kefir.	⊕⊕⊕⊕
2.7	EBR	People with intestinal permeability may consider NOT consuming Yakult light®.	⊕⊕⊕
Prebiotics			
2.8	EBR	There is insufficient evidence to form a recommendation on the use of prebiotics as a collective group for the treatment of people with intestinal permeability.	∅
2.9	PP	Clinicians may consider researching specific prebiotic for their effectiveness before using them in the treatment of people with intestinal permeability.	⊕
2.10	PP	Clinicians may consider trialling and if tolerated, recommend patients to use prebiotic which are supported by pre-clinical research in conjunction with other treatment interventions for the management people with intestinal permeability.	⊕
2.11	PP	Clinicians may consider NOT using polydextrose in the treatment of people with intestinal permeability.	⊕
Synbiotic			
2.12	EBR	Clinicians may consider the use of effective synbiotic in the treatment of people with intestinal permeability.	⊕⊕⊕
2.13	EBR	Clinicians may consider the use of effective synbiotic for a minimum of 3 months when treating people with intestinal permeability.	⊕⊕⊕
2.14	EBR	Clinicians may consider NOT using polydextrose and *Bifidobacterium animalis ssp. lactis* 420 in the treatment of people with intestinal permeability.	⊕⊕⊕
2.15	PP	Clinicians may consider the use of specific synbiotic which are supported by pre-clinical research in conjunction with other treatment interventions for the management people with intestinal permeability.	⊕
NSAID induced intestinal permeability			
2.16	EBR	Clinicians may consider NOT using probiotics for the treatment of people with nonsteroidal anti-inflammatory drug induced intestinal permeability.	⊕⊕⊕
2.17	EBR	Clinicians may consider NOT using prebiotics for the treatment of people with nonsteroidal anti-inflammatory drug induced intestinal permeability.	⊕⊕⊕
2.18	EBR	Clinicians may consider NOT using synbiotics for the treatment of people with nonsteroidal anti-inflammatory drug induced intestinal permeability.	⊕⊕⊕

Abbreviations: CBR = Consensus-based recommendation; EBR = evidence-based recommendation; NSAID = nonsteroidal anti-inflammatory drug; PP = practice point.

11.4 JUSTIFICATION

Recommendations were informed by the best available evidence on the impact probiotics, prebiotics and synbiotics may have on intestinal integrity. The guideline development group carefully considered the available literature and the importance patients with IP place on supplementation for the management of IP while forming each recommendation. The heterogeneity of the available evidence impacted the grade and the ability to form evidence-based recommendations.

As probiotics are unique, with each strain able to have a different clinical and physiological effect, no collective recommendation was formed for all probiotics. Instead, two practice points were developed to provide clinicians with direction when prescribing probiotics in treating IP. As the evidence on probiotics is an expanding area of research, the two practice points were designed to safeguard the longevity of the IP Guideline. The focus of these two recommendations were for clinicians to undertake their own research for beneficial strains and use pre-clinical research when choosing a probiotic. In response to the evidence supporting the use of *Saccharomyces boulardii* and clinicians frequently prescribing this probiotic, an evidence-based recommendation was developed. Another single-strain probiotic *Akkermansia muciniphila* demonstrated promising results, however, no recommendation was developed as this strain is not available in the Australian market.

Each type of prebiotic has a unique structure and associated action; therefore, no collective recommendation was formed for all prebiotics as a collective group. As prebiotics are known to have a beneficial effect on many health conditions associated with IP, advising practitioners not to prescribe a prebiotic supplement could be met with resistance. Therefore, three practice points were created to provide clinicians with direction for the prescription of prebiotics in the treatment of IP. Two of these practice points encourage clinicians to research beneficial types of prebiotics and use pre-clinical research where necessary. As the evidence on prebiotics and the effect on the microbiome is an expanding area of research, these two practice points can ensure the IP Guideline is relevant for clinicians. The other practice point was developed to address the potential adverse effects of supplementing with polydextrose. Although polydextrose is not a frequently prescribed prebiotic, this recommendation may further direct clinicians until further research confirms the safety in people with IP.

Unlike probiotic and prebiotic supplementation, the evidence supporting the use of synbiotic therapy for the treatment of IP suggests a beneficial effect. Therefore, an evidence-based recommendation was created to reflect the evidence. Furthermore, like probiotic and prebiotic supplementation, a practice point was developed, endorsing clinicians to prescribe synbiotic supplementation based on pre-clinical research if they were to use synbiotic in clinical practice. According to the research, a synbiotic formula containing polydextrose and Bifidobacterium animalis ssp. lactis 420 has the potential to exacerbate IP. This led to the recommendation for clinicians to avoid this combination until further research confirms the safety in people with IP.

Regarding NSAID induced IP, there is consistent research across different probiotics and prebiotics intervention studies providing evidence to recommend clinicians not to use probiotics, prebiotics, or synbiotics to prevent NSAID induced IP. Therefore, this resulted in three practice points to support clinicians and reflect the level of research.

12. AMINO ACID

12.1 CLINICAL QUESTIONS

Clinical Question 5: In Australian adults with increased intestinal permeability, what are the benefits of oral amino acid supplementation for the treatment of increased intestinal permeability?

Clinical Question 6: In Australian adults with increased intestinal permeability, what are the harms, cautions and contraindications for oral amino acid supplementation use?

12.2 CLINICAL NEED FOR THE QUESTION

Amino acids, especially glutamine, may have potential benefits on the intestinal integrity.[82] Glutamine is a major energy source for intestinal epithelial, promoting enterocyte proliferation and protects the epithelium from apoptosis.[82] Glutamine may increase the expression of zonula occludens-1 (ZO-1), ZO-2, ZO-3, and claudin-1, therefore, enhancing tight junction integrity.[83,84] Caco-2 cell monolayer in vitro study design suggests glutamine may prevent alcohol-induced IP.[15] Glutamine has been suggested to enhances the transactivation of heat shock factor-1 and induces heat shock factor-1 expression, therefore protect the intestinal epithelium against oxidative stress and inflammation.[85] Another amino acid with potential clinical application is lactoferrin is an iron-binding glycoprotein that is naturally found in human breast milk.[86] Mechanistic research on lactoferrin indicates a potential antibacterial and anti-inflammatory action with the supplementation used an adjuvant therapy in gastrointestinal disorders.[86]

Australian adults with suspected IP report preferring dietary supplements including amino acids such as glutamine managing IP.[7] Specifically, the use of dietary supplements is the third most preferred treatment method for IP, with many people with IP frequently using dietary supplements (73%) for the management of IP.[4,7] Dietary supplements are most frequently prescribed by a naturopath, with over 70% of glutamine supplementation prescribed by a clinician and the other 30% self-prescribed.[4] In addition, almost 90% of Australian adults with suspected IP perceive that it is important for clinicians to be knowledgeable about dietary supplement.[7] This population group reports spending an average of AUD $2,175 on dietary supplements annually.[7] The economic burden of using dietary supplements does not appear to prohibit this populations' use of dietary supplements.[7] Glutamine is the fifth most frequently used dietary supplement in people with IP, with amino acid complex also used to a lesser extent.[4] While clinicians frequently use glutamine in the management of patients with IP, with 73% of clinicians always using glutamine.[5]

The mechanistic evidence indicates a potential benefit of amino acids, especially glutamine.[82] As both clinicians and people with suspected IP report the frequent use of amino acids, a collective summary of the available literature and structured recommendations are necessary to ensure optimal care is provided.

12.3 SUMMARY OF EVIDENCE

A literature review found four studies addressing the two clinical questions (CQ.5 and CQ.6) regarding the effect of amino acids on intestinal integrity. The risk of bias (RoB) assessment found the three randomised control trials to have low RoB (n = 3).[87-89] The one non-randomised clinical trials had moderate RoB.[80] A summary of the evidence is provided here with a full review of the literature found in the Technical Report.

A total of three studies exploring the effects of glutamine on altered IP were included.[80,87,89] The use of glutamine supplementation in people with IP saw consistent beneficial effects on intestinal integrity. All studies involved participants with a gastrointestinal disorder, and they were assessed for IP through the dual sugar test. The supplementation of glutamine in people with diarrhoea-predominant irritable bowel syndrome demonstrated a significant decrease in IP compared to baseline after two months (0.11±0.03 vs. 0.04±0.01; p<0.0001).[87] Furthermore, there is a significant correlation between irritable bowel syndrome severity and improvement of IP in people taking glutamine (r=0.72; p<0.001).[87] Another RCT investigated the effect of 0.5g/kg of glutamine on ideal body weight per day in Crohn's disease patients currently in remission.[89] This study found glutamine supplementation reduced lactulose/mannitol ratio (LMR) median value from 0.071 (0.041–0.254, range) to 0.029 (0.006–0.090, range) after two months.[89] Furthermore, the control group also had a significant improvement in IP from a median value of 0.067 (0.040–0.136, range) to 0.033 (0.009–0.077, range), possibly influenced by the placebo supplement containing a large amount of whey protein. No significant difference was found between the glutamine group and whey protein group after two months (median value 0.029 vs. 0.033; p>0.05).[89] An Australian based study explored the effects of 2.5g of glutamine in combination with prebiotics, other intestinal supportive herbal medicine, and nutrients on IP.[80] This study found a significant decrease between baseline and 12 weeks in LMR (0.04±0.004 vs. 0.03±0.001; p<0.0001).[80]

One article investigated the effects of lactoferrin on NSAID induced intestinal integrity. Healthy males had IP induced by consuming 75mg NSAID 9 hours prior and 50mg 1 hour prior to undertaking the dual sugar test. The intervention involved participants consuming 5g of lactoferrin three times (24, 9 and 1 hour before the dual sugar test). Lactoferrin supplementation was found to significantly decrease NSAID-induced IP compared to NSAIDs and placebo (0.028 vs. 0.036; p<0.05).

Table 6 Recommendations: Amino acid supplementation

No.	Category	Recommendation	Strength
Glutamine			
3.1	EBR	Clinicians should offer glutamine supplementation for the treatment of people with intestinal permeability.	⊕⊕⊕⊕
3.2	CBR	Clinicians may consider the use of glutamine supplementation in conjunction with other treatment interventions for the management of people with intestinal permeability.	⊕⊕
NSAID-induced intestinal permeability			
3.3	EBR	Clinicians should consider the use of short-term lactoferrin supplementation for the treatment of people with nonsteroidal anti-inflammatory drug induced intestinal permeability.	⊕⊕⊕⊕

Abbreviations: CBR = Consensus-based recommendation; EBR = evidence-based recommendation; NSAID = nonsteroidal anti-inflammatory drug.

12.4 JUSTIFICATION

Recommendations were informed by the best available evidence on the impact amino acids may have on IP. The guideline development group carefully considered the available literature and the importance patients with IP place on supplementation for the management of IP while forming each recommendation.

There is consistent evidence supporting the use of glutamine in people with IP. Although one study found a significant improvement in the glutamine group from baseline to two months, this same study found no significant difference between the control and glutamine supplementation. Key characteristics in the study design such as demographic and control supplement (a large amount of whey protein) could potentially explain this finding and therefore did not affect the grading of the recommendation. Although whey protein, a complex source of amino acids, could be considered as a potential therapeutic intervention based on this study,[89] the conflicting result seen with Zhou et al,[87] resulted in no recommendation considered. A consensus-based recommendation was developed considering the whole system approach clinicians follow in managing people with IP. This recommendation suggests glutamine be considered as a part of other treatment interventions rather than the sole ingredient. Although the grade for the recommendation for lactoferrin was allocated a B, the Working Group downgraded the strength of the recommendation from a strong recommendation to a recommendation considering this intervention is less used in clinical practice, and only one study was included.

13. PLANT-BASED MEDICINE

13.1 CLINICAL QUESTIONS

Clinical Question 7: In Australian adults with increased intestinal permeability, what are the benefits of oral plant-based medicine supplementation for the treatment of increased intestinal permeability?

Clinical Question 8: In Australian adults with increased intestinal permeability, what are the harms, cautions and contraindications for oral plant-based medicines use?

13.2 CLINICAL NEED FOR THE QUESTION

Plant-based medicines are reported to influence the function of the gastrointestinal system and may modulate the integrity of the small intestine.[90] Herbal therapy is suggested to support IP by reducing the effect of endotoxins, changing the expression of tight junction proteins and contributing to the mucus layer of the gastrointestinal tract.[91,92] Mechanistic research on individual herbal therapies such as Aloe barbadensis Mill (aloe vera) suggest that it may potentially enhance the expression of intestinal zonula occludens (ZO)-1.[93] While other herbal medicines, including Curcuma longa (turmeric) is reported to regulate the expression of ZO-1 and claudin-1.[94]

Australian adults with suspected IP report preferring dietary supplements such as herbal medicine for managing IP.[7] Specifically, the use of dietary supplements is the third most preferred treatment method for IP, with many people with IP frequently using dietary supplements (73%) for the management of IP.[4,7] Dietary supplements are most frequently prescribed by a naturopath, with over 70% of herbal mixtures prescribed by a clinician.[4] Clinicians frequently prescribe herbal medicine to treat IP, with many reporting they always prescribe Curcuma longa (73%), Allium sativum (52%), Ulmus rubra (51%), Zingiber officinale (50%), Aloe barbadensis Mill (48%), Althaea officinalis (44%) and Gentiana lutea (44%) in patients with IP.[5] Clinicians treating people with IP will generally use a combination of herbal products as part of a whole system treatment approach.[5]

People with IP report spending an average of $2,175 AUD on dietary supplements annually.[7] The financial cost of dietary supplements and peoples financial status, does not appear to affect this populations' decision in using dietary supplements.[7] The second most frequently used dietary supplement in people with IP are herbal mixtures.[4] The herbal products most commonly used by people with IP are Curcuma longa, Ulmus rubra (slippery elm) and Aloe barbadensis Mill.[4] Australian adults with suspected IP that report an improved IP are more likely to use dietary supplements.[4] Almost 90% of Australian adults with suspected IP report that the knowledge and understanding of dietary supplements are important for clinicians to understand.[7] The mechanistic evidence indicates a potential benefit of herbal medicine.[90,93] As clinicians and individuals with suspected IP report the frequent use of herbal medicine, a collective summary of the available literature and structured recommendations are necessary to the provision of optimal care.

13.3 SUMMARY OF EVIDENCE

A literature review found five studies addressing the two clinical questions (CQ.7 and CQ.8) regarding the effect of plant-based medicines on intestinal integrity. The risk of bias (RoB) assessment found the four randomised control trials to have high (n = 3)[57,95,96] and low (n = 1)[74] RoB. The one non-randomised clinical trials had moderate RoB.[80] A summary of the evidence is provided here with a full review of the literature found in the Technical Report.

A total of five studies exploring the effects of a diverse range of plant-based medicines on intestinal integrity were included.[57,74,80,95,96] The use of plant-based medicines in people with IP resulted in mixed outcomes with three out of the five studies reporting no significant effect. One study exploring the effects of pomegranate extract in overweight and obese adults found after three weeks, pomegranate extract significantly reduced lipopolysaccharide-binding protein compared to placebo ($p<0.001$).[96] While an Australian based study exploring the effects of a mix of herbal medicines (aloe vera 2.5mg, slippery elm 500mg, guar gum 100mg, pectin 100mg and peppermint oil 3mg) and amino acids in patients with a functional gastrointestinal disorder found a significant decrease between baseline and 12 weeks in lactulose/mannitol ratio (0.04±0.004 vs 0.03±0.001; $p<0.0001$).[80] Three other studies investigating the effects of plant-based medicines on IP found no significant impact. These studies used a combination of herbal ingredients. One of these studies used multi-herbal formula in healthy adults over eight weeks and found a significant difference in serum zonulin between placebo and the intervention group.[95] Another herbal combination containing barley grass and oat grass juice had no significant impact on lactulose/mannitol ratio between baseline and 12 weeks ($p>0.05$).[74] Similar results were seen with a traditional Japanese formula known as Bofutsushosan.[57] The study found no significant effect between baseline and five week in lactulose/mannitol ratio (2.7±1.9 vs 2.2±1.5; $p=0.391$).[57]

Table 7 Recommendations: Plant-based medicine supplementation

No.	Category	Recommendation	Strength
4.1	EBR	There is insufficient evidence to form a recommendation on the use of plant-based medicines as a collective group for the treatment of people with intestinal permeability.	∅
4.2	PP	Clinicians may consider the use of plant-based medicines which are supported by pre-clinical research in conjunction with other treatment interventions for the management people with intestinal permeability.	⊕

Abbreviations: EBR = evidence-based recommendation; PP = practice point.

13.4 JUSTIFICATION

Recommendations were informed by the best available evidence on the impact plant-based medicine may have on intestinal integrity. The guideline development group carefully considered the available literature and the importance patients with IP place on supplementation for the management of IP while forming each recommendation. The limited available literature and heterogeneity of the available evidence impacted the grade and the ability to develop evidence-based recommendations.

Plant-based medicines are unique, with every herbal ingredient able to have a different clinical and physiological effect. Therefore, no collective recommendation was developed for all herbal therapies. Instead, the development of one practice point to provide clinicians with direction when prescribing plant-based medicines in treating IP was formulated. This practice point was developed as plant-based medicines are frequently used in clinical practice and no safety concerns were identified. Furthermore, as the evidence on herbal therapies is an expanding area of research, the practice point was designed to provide confidence in the IP Guideline. The focus of this practice point is for clinicians to undertake their own research for beneficial herbal therapies and use pre-clinical research when prescribing to patients with IP. Although one research study identified pomegranate extract as a potential therapy for the management of IP, important characteristics such as the high RoB and only using lipopolysaccharide-binding protein as a marker for IP, no recommendation could be developed.

14. ESSENTIAL FATTY ACID

14.1 CLINICAL QUESTIONS

Clinical Question 9: In Australian adults with increased intestinal permeability, what are the benefits of oral essential fatty acid supplementation for the treatment of increased intestinal permeability?

Clinical Question 10: In Australian adults with increased intestinal permeability, what are the harms, cautions and contraindications for oral essential fatty acid use?

14.2 CLINICAL NEED FOR THE QUESTION

Essential fatty acids are a group of polyunsaturated fatty acids, including two types of omega-3 docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) with the other being omega-6. These essential fatty acids, especially omega-3, are thought to prevent changes to IP by inhibiting the production of pro-inflammatory cytokines.[97] Mechanistic research suggests omega-3 may normalise the expression of zonula occludens (ZO)-1 and occluding in the intestine.[98] Australian adults with suspected IP report preferring dietary supplements such as omega-3 for managing IP.[7] Specifically, the use of dietary supplements is the third most preferred treatment method for IP, with many people with IP frequently using dietary supplements (73%) for the management of IP.[4,7] Dietary supplements are most frequently prescribed by a naturopath, with over 66% of omega-3 prescribed by a clinician.[4] People with IP report spending an average of $2,175 AUD on dietary supplements annually.[7] The financial cost of dietary supplements and peoples financial status, does not appear to affect this populations' decision in using dietary supplements.[7] One third of people with IP report using omega-3 in the treatment of IP.[4] Australian adults with suspected IP that report an improved IP are more likely to use dietary supplements.[4] Almost 90% of Australian adults with suspected IP report that it is important for clinicians to understand dietary supplements in the context of IP management and treatment.[7] Due to this early mechanistic evidence and the frequent use of omega-3 supplements reported by both patients and clinicians, exploration of the evidence regarding essential fatty acid supplementation for people with IP is needed.

14.3 SUMMARY OF EVIDENCE

A literature review found one study addressing the two clinical questions (CQ.9 and CQ.10) regarding the effect of essential fatty acid supplementation on intestinal integrity. The risk of bias (RoB) assessment found this trial to have high RoB.[59] A summary of the evidence is provided here with a full review of the literature found in the Technical Report.

A total of one study exploring the effects of essential fatty acid supplementation on intestinal integrity was included.[59] This randomised, double-blind placebo-controlled trial assessed the effects of four study arms: omega-3, probiotic, omega-3 and probiotic or placebo over 21 weeks in pregnant women.[59] The omega-3 supplement contained 2g of omega-3 (79.6% DHA and 9.7% EPA) twice daily. The study found no significant effect in serum zonulin between early and late pregnancy with omega-3 supplementation (mean change: +5.2±11.2ng/ml; 95%CI +2.0, +8.5; p>0.05). Furthermore, lipopolysaccharide (LPS) had no significant change between early and late pregnancy with omega-3 supplementation (mean change: +0.06±0.11EU/ml; 95%CI +0.023, +0.088; p>0.05).

Table 8 Recommendations: Essential fatty acid supplementation

No.	Category	Recommendation	Strength
5.1	EBR	There is insufficient evidence to form a recommendation on the use of essential fatty acid supplementation for the treatment of people with intestinal permeability.	∅

Abbreviations: EBR = evidence-based recommendation.

14.4 JUSTIFICATION

Recommendations were informed by the best available evidence on the impact essential fatty acid supplementation may have on intestinal integrity. The guideline development group carefully considered the available literature and the importance patients with IP place on supplementation for the management of IP while forming the recommendation. There is insufficient evidence to recommend the use of essential fatty acid supplementation in people with IP, with only included study finding no significant change in markers of IP.

15. MINERAL SUPPLEMENTATION

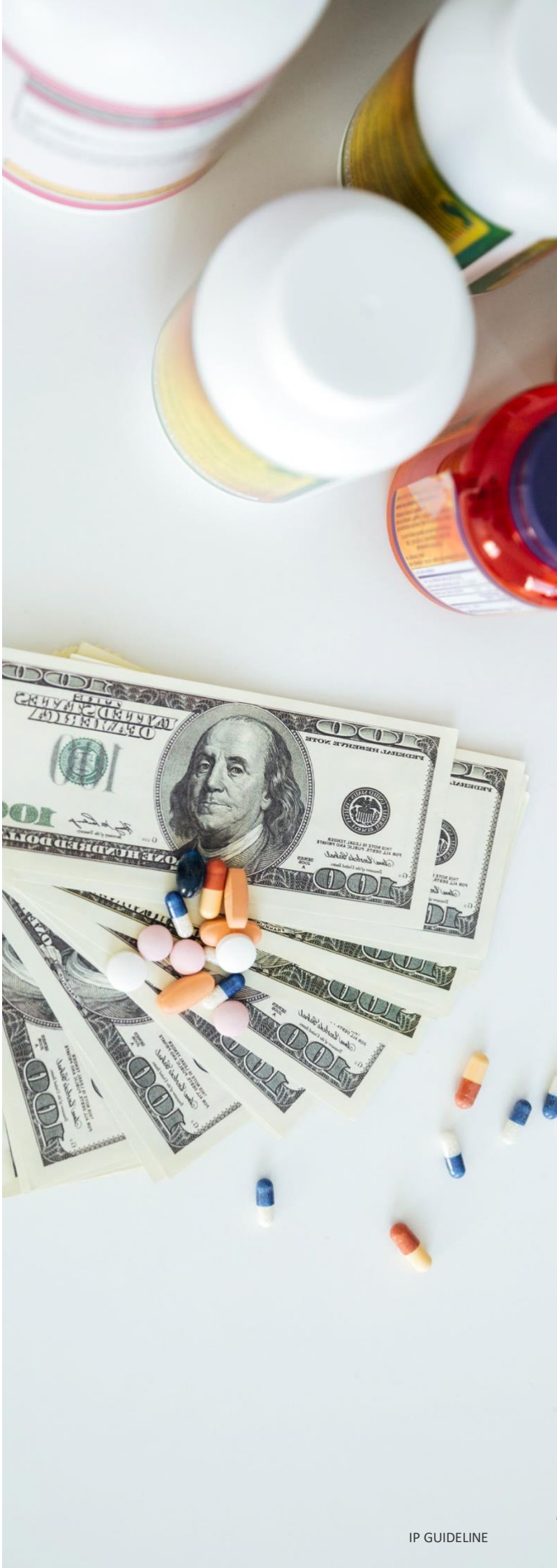
15.1 CLINICAL QUESTIONS

Clinical Question 11: In Australian adults with increased intestinal permeability, what are the benefits of oral mineral supplementation for the treatment of increased intestinal permeability?

Clinical Question 12: In Australian adults with increased intestinal permeability, what are the harms, cautions and contraindications for oral mineral supplementation use?

15.2 CLINICAL NEED FOR THE QUESTION

Minerals, especially zinc, are essential for tight juntion maintenance, with mechanistic research sug- gesting zinc may prevent the breakdown of tight junction proteins and enhance the expression of zonula occludens (ZO)-1.[99-101] Australian adults with suspected IP report preferring dietary supplements such as minerals, including zinc and magnesium for managing IP.[7] Specifically, the use of dietary supple- ments is the third most preferred treatment meth- od for IP, with many people with IP frequently using dietary supplements (73%) for the management of IP.[4,7] Dietary supplements are most frequently pre- scribed by a naturopath, with over 80% of zinc prescribed by a clinician.[4] Furthermore, zinc is the most prescribed dietary supplement in the treatment of people with IP.[5] People with IP report spending an average of $2,175 AUD on dietary supplements annually.[7] The financial cost of dietary supplements and peoples financial status, does not appear to affect this populations' decision in using dietary supplements.[7] Over 20% of people with IP report using zinc in the treatment of IP.[4] Australian adults with suspected IP that report an improved IP are more likely to use dietary supplements.[4] Almost 90% of Australian adults with suspected IP report that it is important for clinicians to understand dietary supplements in the context of IP management and treatment.[7] Due to this early mechanistic evidence and the frequent use of zinc supplementation reported by both patients and clinicians, exploration of the evidence regarding mineral supplementation for people with IP is needed.



15.3 SUMMARY OF EVIDENCE

A literature review found two studies addressing the two clinical questions (CQ.11 and CQ.12) regarding the effect of oral mineral supplementation on intestinal integrity. The risk of bias (RoB) assessment found the one non-randomised clinical trial to have a moderate RoB.[59] A summary of the evidence is provided here with a full review of the literature found in the Technical Report.

Only one non-randomised clinical trial met the inclusion criteria and was included.[102] This study explored the effects of zinc supplementation in 12 Crohn's disease patients currently in remission with a lactulose mannitol ratio >0.035. The study involved zinc supplementation containing 25mg of elemental zinc three times daily for eight weeks. After the study period, there was a significant decrease in IP from baseline to eight weeks (0.041±0.003 vs. 0.026±0.005; p= 0.0028). Furthermore, at the end of the eight weeks, the lactulose-mannitol ratio normalised in 75% of participants.

Table 9 Recommendations: Mineral supplementation

No.	Category	Recommendation	Strength
6.1	EBR	Clinicians may consider using zinc supplementation in the treatment of people with intestinal permeability.	⊕⊕⊕

Abbreviations: EBR = evidence-based recommendation.

15.4 JUSTIFICATION

Recommendations were informed by the best available evidence on the impact mineral supplementation may have on intestinal integrity. The guideline development group carefully considered the available literature and the importance patients with IP place on supplementation for the management of IP while forming the recommendation. One evidence-based recommendation was developed to reflect the available literature and the importance clinicians place on zinc supplementation.

16. VITAMIN SUPPLEMENTATION

16.1 CLINICAL QUESTIONS

Clinical Question 13: In Australian adults with increased intestinal permeability, what are the benefits of oral vitamin supplementation for the treatment of increased intestinal permeability?

Clinical Question 14: In Australian adults with increased intestinal permeability, what are the harms, cautions and contraindications for oral vitamin supplementation use?

16.2 SUMMARY OF EVIDENCE

A literature review found no studies addressing the two clinical questions (CQ.13 and CQ.14) regarding the effect of vitamin supplementation on intestinal integrity. Therefore, no recommendation was developed.

17. COLOSTRUM SUPPLEMENTATION

17.1 CLINICAL QUESTIONS

Clinical Question 15: In Australian adults with increased intestinal permeability, what are the benefits of oral colostrum supplementation for the treatment of increased intestinal permeability?

Clinical Question 16: In Australian adults with increased intestinal permeability, what are the harms, cautions and contraindications for oral colostrum supplementation use?

17.2 SUMMARY OF EVIDENCE

A literature review found no studies addressing the two clinical questions (CQ.15 and CQ.16) regarding the effect of colostrum supplementation on intestinal integrity. Therefore, no recommendation was developed.

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