Section: Gastroenterology

Original Research Article

PAKISTAN-SPECIFIC RECOMMENDATIONS ON THE ADJUVANT USE OF PROBIOTICS SUCH AS BACILLUS CLAUSII (O/C, SIN, N/R, T) IN ANTIBIOTIC-ASSOCIATED DIARRHEA - CONSENSUS RECOMMENDATIONS FROM EXPERTS IN PAKISTAN

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ABSTRACT

Background: To develop Pakistan-specific, evidence-based consensus recommendations on the use of probiotics, including Bacillus clausii (O/C, SIN, N/R, T), for the prevention and management of antibiotic-associated diarrhea (AAD), considering local healthcare practices, antibiotic utilization patterns, and patient needs.

Materials and Methods: A National Consultative Group (NCG) comprising 11 experts in gastroenterology, pediatrics, family medicine, and internal medicine from across Pakistan was convened. A structured consensus process using the Nominal Group Technique (NGT) was employed. Evidence from published literature was reviewed, and predefined statements were evaluated through structured discussion and anonymized voting. Consensus was defined as ≥75% agreement. The process was moderated by the corresponding author, with the co-authors serving on the steering committee. A single-round consensus meeting was conducted without Delphi rounds.

Results: The expert panel developed eight consensus statements addressing risk stratification, indications for probiotic use, treatment duration, safety considerations, and criteria for probiotic selection in AAD. Probiotics were recommended for patients at high risk of AAD, with initiation alongside antibiotic therapy and continuation during and after antibiotic treatment. Specific high-risk populations and clinical situations requiring caution were identified. Evidence-based selection criteria, including strain specificity, adequate dosing, product stability, and safety profile, were emphasized. Bacillus clausii was recognized as a suitable option for the prevention and management of AAD based on available clinical evidence, safety, and regional applicability.

The panel also supported the adjunctive use of probiotics during H. pylori eradication therapy.
Conclusion: This consensus provides the first Pakistan-specific multidisciplinary recommendations on the use of probiotics in AAD. Adoption of these evidence-based recommendations may improve patient outcomes, enhance treatment adherence, support antibiotic stewardship initiatives, and contribute to mitigating antimicrobial resistance. Bacillus clausii may be considered for the prevention and management of AAD and as an adjunct to H. pylori eradication therapy.
Keywords: Antibiotic-associated diarrhea; Probiotics; Bacillus clausii; Consensus recommendations; Pakistan; Antimicrobial resistance; H. pylori.

INTRODUCTION

Definition

Antibiotic-associated diarrhea (AAD) is defined as three or more loose or watery stools per day associated with antibiotic therapy, typically resulting from disruption of the gut microbiota during antibiotic use or persisting for up to 8 weeks after discontinuation. It may range from mild, self-limiting diarrhea to severe, life-threatening colitis due to Clostridioides difficile infections.[1,2,3]

Burden of AAD

Globally, the incidence of AAD among patients receiving antibiotics ranges between 5–35%,[4] depending on the antibiotic type and patient population. In Pakistan, irrational and prolonged antibiotic use, limited diagnostic stewardship, and over-the-counter antibiotic availability amplify the risk and burden of AAD. This not only increases morbidity but also contributes to healthcare costs, antimicrobial resistance (AMR), and reduced patient compliance with antibiotic therapy.[2,3,5]

Antimicrobial Resistance (AMR) Crisis

Pakistan is facing a rapidly escalating AMR crisis due to unregulated antibiotic use.[6] Preventing AAD through probiotics can help reduce secondary antibiotic prescriptions, improve adherence, and indirectly support antimicrobial stewardship.[2,7]

Rationale for Using Probiotics in AAD

Probiotics, defined as live microorganisms that confer health benefits when administered in adequate amounts, help restore intestinal microbiota disrupted by antibiotic therapy. Evidence from multiple clinical trials supports their role in reducing AAD incidence and severity, enhancing gut barrier function, and modulating immune response.[5,8]

Importance of Bacillus clausii

Bacillus clausii is a spore-forming, polymorphic probiotic known for its resistance to gastric acidity and compatibility with antibiotic therapy. Its four distinct strains (O/C, SIN, N/R, and T) exhibit antimicrobial and immunomodulatory properties, making it a promising candidate for AAD prevention and an adjunct in H. pylori eradication therapy.[8,9,10,11]

Need for a Local Consensus

Despite the existence of global guidelines, Pakistan lacks uniform recommendations tailored to its healthcare realities. This consensus aims to bridge this gap by aligning evidence-based insights with local prescribing behaviors, antibiotic misuse patterns, and patient profiles.[2,7]

This study aims to develop consensus recommendations on the role and scope of probiotics for the prevention and management of AAD in Pakistan through expert agreement and multidisciplinary collaboration.

MATERIALS AND METHODS

Consensus development process: A national consultative group (NCG) comprising 11 experts from gastroenterology, pediatrics, family medicine, and internal medicine was established.

A structured consensus meeting using the nominal group technique (NGT) was conducted to achieve expert agreement on key statements regarding the use of probiotics for AAD.

Literature Review and Statement Development: The members conducted a narrative synthesis of the available literature, including relevant international guidelines, systematic reviews, and clinical studies. The evidence was discussed and used to inform draft statements, which were subsequently refined through expert opinion, structured discussion, and iterative voting. Each expert was asked to independently consider and rate predefined statements, followed by a structured discussion and re-rating to achieve consensus.

Consensus Criteria: The panel agreed to develop practical, context-specific recommendations tailored to Pakistan's healthcare landscape and prescribing practices rather than relying on hypothetical recommendations. The final list of consensus statements was developed through discussion and open voting. Consensus was defined as ≥75% agreement among participants on a given statement.

Finalization of Recommendations: Management guidelines were developed and circulated among the participants for feedback. After incorporating the comments, the draft consensus was shared with the panel members for review and final approval. After unanimous approval from all experts, this paper is submitted for publication.

Efforts were made to minimize bias by ensuring independent expert voting and consensus-based validation. The sponsoring organization had no

influence on the development of statements, voting process, or final wording of the recommendations.

Experts' contribution: Experts contributed through subcommittee discussions and review of draft statements. They provided consultative input and final endorsement of the recommendations, and their clinical expertise guided the refinement of the consensus statements. They also reviewed the final manuscript.

RESULTS

The consensus process resulted in the development of eight key statements addressing the prevention and management of antibiotic-associated diarrhea (AAD) using probiotics. Agreement levels ranged from 82% to 100%, reflecting strong overall consensus among panel members. The finalized recommendations are presented below.

Consensus Statements on the Use of Probiotics for AAD:

Statement 1: Routine Use of Probiotics in AAD Prevention

Consensus Statement:

Probiotics should be co-administered with antibiotics in patients identified as high-risk for AAD as a prophylactic measure based on clinical assessments. The decision to administer probiotics alongside antibiotics should be made at the discretion of the treating physician based on clearly defined risk factors and the patient's individual risk profile.[12,13]

Consensus Level: 100% agreement

Rationale: Experts concluded that routine use in all patients is not cost-effective or evidence-based for low-risk individuals. A targeted, risk-stratified approach ensures optimal resource utilization. Careful risk assessment should be performed based on individual patient history, examination, and clinical investigation to identify high-risk patients.[12]

Statement 2: Identification of High-Risk Patients

Consensus Statement:

The following patient groups are considered at high risk for AAD and should receive probiotics alongside antibiotics:

- Those receiving high-to-moderate-risk antibiotics.
- Those prescribed broad-spectrum and high doses of antibiotics (maximal doses)
- Those on prolonged courses of antibiotic therapy for example, **7–14 days or even several weeks to months**
- Cases involving misuse or overuse of antibiotics.
- Those receiving multiple antibiotics simultaneously (combination of antibiotics: Two or more antibiotics prescribed at the same time, regardless of route of administration)
    - Extremes of age (<2 years or ≥65 years)
- Patients who are currently on or with a **history of H. pylori eradication therapy** (for last 3 months)
- Immunocompromised patients:
- Those with compromised nutritional status (such as children who are wasted, underweight, or have a low BMI) are at higher risk due to reduced immunity resulting from malnutrition, including those taking immunosuppressive medications.
- Obese individuals (BMI ≥30 kg/m²)
- Patients with a history of AAD (at any point in life)
- Patients with a history of *C. difficile* infection (particularly in the last 3 months)
- Hospitalized or ICU patients.
- Patients with chronic comorbidities (diabetes, liver, kidney, cardiac, pulmonary disease)
- Recent **surgery or gastrointestinal procedures** (up to 3 months)
- Patients with IBS or a history of IBS, including those currently receiving therapy.[14]

Consensus Level: 100% agreement

Rationale: Recognizing these clinical scenarios allows early probiotic co-administration to prevent gut microbiota disruption and reduce AAD incidence.[2,12]

Statement 3: Classification by risk of Antibiotic types (as per evidence)

Based on the available clinical evidence, the following classification of antibiotics by AAD risk was agreed upon:

High risk antibiotics: (≥20% AAD incidence)

- **Co-amoxiclav and Penicillins (e.g., Ampicillin, Amoxicillin)**
- **Lincosamides** (e.g., clindamycin)
- **Cephalosporins** (especially 2nd, 3rd, and 4th generation)
- **Carbapenems** (e.g., Meropenem)
- **Fluoroquinolones** (e.g., ciprofloxacin, levofloxacin, moxifloxacin).[1,2,15,16]

Moderate risk antibiotics: (5–15% AAD incidence)

- **Trimethoprim–Sulfamethoxazole**
- **First-generation cephalosporins**
- **Macrolides** (e.g., azithromycin, clarithromycin, erythromycin),[2]

Low risk antibiotics: <5%

- **Chloramphenicol**
- **Nitrofurantoin**
- **Tetracyclines** (e.g., minocycline)
- **Metronidazole**
- **Fosfomycin**
- **Vancomycin**
- **Tobramycin**

Note: The classification of antibiotics by AAD risk is a pragmatic synthesis derived from published clinical studies and pharmacovigilance data. It is intended to support clinical decision-making in the local context and should not be interpreted as a universally standardized or rigid classification system. While metronidazole and vancomycin are also used in the treatment of Clostridioides difficile infection, they may still be associated with a small risk of AAD when used independently, though the incidence is low (with reported rates <5%).[1,2] Nitrofurantoin is

consistently reported in literature as having a low association with gut microbiota disruption and AAD due to its minimal systemic and colonic exposure.[30]

Consensus Level: 91% agreement.

Rationale: Evidence from international studies supports these classifications, although some experts noted variability based on local antibiotic resistance patterns and prescribing practices.

Statement 4: Probiotics for Management of AAD

Consensus Statement:

Given the current scenario and widespread irrational use of antibiotics, probiotics should be initiated promptly upon diagnosis of AAD and continued as clinically appropriate until symptom resolution, as they help restore gut flora balance, shorten the course of diarrhea, and prevent recurrence.[9,12]

Consensus Level: 100% agreement

Recommended Duration (AAD Prevention):

- Probiotic supplementation should be initiated as early as possible, ideally along with or within 48 h of starting antibiotic treatment.
- Continue: Probiotic use is maintained throughout the duration of antibiotic therapy.
- Extend: Continue probiotic supplementation for at least seven days after completing the antibiotic course.

Consensus Level: 100% agreement

Recommended Duration (AAD Treatment):

- Initiate: Probiotic supplementation should be initiated as early as possible after the onset of diarrhea.
- Continue for **at least 7–14 days**, monitoring for symptom improvement.
- Extend: In cases where symptoms persist, probiotics may be continued for up to **three weeks**.

Consensus Level: 100% agreement

Rationale: Timely and sustained probiotic supplementation is strongly associated with reduced AAD frequency and faster recovery in patients with AAD.[5]

Statement 5: Safety Considerations and Contraindications for Probiotic Use

Consensus Statement: Probiotics are generally safe and well tolerated; however, their use should be avoided or exercised with caution in certain high-risk populations.

Probiotics should be used cautiously or avoided in the following situations:

- Severely immunocompromised patients (e.g., neutropenia, post-transplant, advanced HIV)
- Critically ill patients in ICU settings and with central lines (probiotic-associated sepsis risk)
- Premature neonates
- Patients with severe acute pancreatitis
- Cases of severe systemic infection or sepsis[18]

Consensus Level: 100% agreement

Rationale: Probiotic-associated bacteremia and fungemia are rare but have been reported in vulnerable populations. Therefore, careful clinical judgment is required when prescribing probiotics to these groups.[18]

Statement 6: Evidence-Based Criteria for Selection of Probiotics in AAD

Consensus Statement: Only probiotics meeting predefined evidence-based quality and clinical criteria should be recommended for the prevention and management of AAD in Pakistan.

Recommended Qualification Criteria:

• Must contain strain(s) supported by randomized controlled trials (RCTs) specifically in AAD prevention or management

• Minimum effective daily dose consistent with published evidence (e.g., $\geq 2\times10^9$ CFU/day or as per strain-specific data)

• Demonstrated product stability and shelf-life under local storage conditions

• Clear labeling of strain identity (genus, species, strain designation)

• Appropriate formulation (spore-forming vs non-spore) based on clinical context

• Availability of safety data, especially in vulnerable populations

• Evidence available in relevant population groups (adults, children, or both)

Consensus Level: 100% agreement

Rationale: The strain-specific effects of probiotics are well established. The clinical efficacy and safety of these probiotics cannot be extrapolated across strains. Therefore, probiotic selection should be based on high-quality clinical evidence, adequate dosing, and safety.

Statement 7: Role of Bacillus clausii (O/C, SIN, N/R, T) in antibiotic-associated diarrhea.

Consensus Statement: *Bacillus clausii* (O/C, SIN, N/R, and T) may be considered an appropriate option for the prevention and treatment of AAD in Pakistan based on global and regional clinical evidence.

Consensus Level: 82% agreement

Rationale: **Summary of evidence linked to the recommendation statement:**

Evidence is growing for the use of *B. clausii* to prevent AAD, particularly in children undergoing antibiotic therapy. **A pooled analysis of controlled clinical trials** found that *B. clausii* supplementation **significantly reduced the incidence of antibiotic-associated diarrhea in children** compared to antibiotic treatment alone. Across three controlled trials involving children aged **3 months to 14 years** treated for respiratory, genitourinary, or skin infections, the pooled incidence of diarrhea was **1.8% among those receiving B. clausii plus antibiotics versus 6.5% with antibiotics alone** ($p = 0.017$).[14] As shown in Table 1, children receiving Bacillus clausii alongside antibiotics experienced fewer gastrointestinal adverse effects compared with antibiotics alone.

Table 1: Incidence of gastrointestinal problems in children treated with antibiotics and Bacillus species. (group A) versus children treated with antibiotics alone (group B),[24]

	No of children	Nausea	Vomiting	Abdominal pain	Diarrhea	Aphthae	Total
Group A	45	2	0	2	0	0	5
Group B	48	2	1	9	5	1	18
***x^2 = 7.3, p < 0.01**							

Adapted from: De Castro JA, Kesavelu D, Lahiri KR, et al. Recommendations for the adjuvant use of the poly-antibiotic–resistant probiotic Bacillus clausii (O/C, SIN, N/R, T) in acute, chronic, and antibiotic-associated diarrhea in children: consensus from Asian experts. Trop Dis Travel Med Vaccines. 2020;6:21.

A 2019 Cochrane database of systematic review analyzed thirty-three studies with a total of 6,352 pediatric participants to evaluate probiotics for preventing antibiotic-associated diarrhea. The probiotics studied included Bacillus spp., Bifidobacterium spp., Clostridium butyricum, Lactobacillus spp., Lactococcus spp., Leuconostoc cremoris, Saccharomyces spp., and Streptococcus spp. used alone or in combination. The review found that probiotics had a moderate protective effect against AAD (NNT = 9; 95% CI, 7–13) and could reduce diarrhea duration by approximately one day.[29]

Experts acknowledged *the robust evidence base, antibiotic resistance, acid stability, and global clinical validation of B. clausii*.

- **Robust evidence base** from global RCTs, meta-analyses and Asia-Pacific studies.[19,20,21]
- **Poly antibiotic resistance** allows safe concurrent use with commonly prescribed antibiotics in Pakistan. O/C is resistant to chloramphenicol, SIN to neomycin and streptomycin, N/R to novobiocin and rifampin, and T to tetracycline.[22]
- **Acid and bile stability** with spore-forming properties ensures survival during gastric transit.[23]
- It has demonstrated **efficacy in reducing diarrhea duration and frequency**, improving stool consistency, and decreasing hospitalization and healthcare costs.[14]

Regional and Local Relevance:

- Asia-Pacific consensus recommends *B. clausii* as an adjunct to **ORS and zinc** in acute, chronic and antibiotic associated childhood diarrhea, which aligns with current clinical practice in Pakistan.[24]
- Proven **prevention of Clostridium difficile-associated diarrhea** and mitigation of antibiotic-related GI side effects are critical in settings with high antibiotic use.[24]
- Supports the **coadjuvant use in H. pylori eradication**, reducing side effects, and improving the tolerability of therapy, which is relevant given the prevalence of H. pylori in Pakistan.[25,26]
- Recognizing local healthcare resource constraints, *B. clausii* is an effective, safe, and **cost-conscious adjunct therapy**.[14]

However, further local data collection and literature reviews are needed to strengthen national recommendations.[2,10] Any other probiotic strains with sufficient clinical evidence may also be considered based on availability and patient-specific factors.

Statement 8: Probiotics such as Bacillus clausii as Adjuncts in *Helicobacter pylori* Eradication Therapy

Consensus Statement: Probiotics should be used as adjuncts in *H. pylori* eradication regimens, as they have been shown to improve treatment tolerance and minimize gastrointestinal side effects, particularly AAD. The inclusion of probiotics in H. pylori treatment protocols was supported by relevant clinical evidence.[26,27]

Consensus Level: 100% agreement

Rationale: Meta-analyses confirm that probiotics, especially *B. clausii*, reduce antibiotic-related diarrhea, nausea, and bloating during *H. pylori* therapy and may marginally increase eradication rates.[27,28]

In a 2004 randomized, double-blind, placebo-controlled trial involving 120 H. pylori-positive patients, participants received either standard 7-day triple therapy (rabeprazole 20 mg BID, clarithromycin 500 mg BID, amoxicillin 1 g BID) plus ***B. clausii*** (2×10^9 spores TID for 14 days; group A) or triple therapy with placebo (group B). The study found that adding *B. clausii* significantly reduced the incidence of antibiotic-associated diarrhea compared with that of the placebo (PP, $p < 0.05$; ITT, $p < 0.01$).[24]

A 2017 network meta-analysis of 17 RCTs evaluated the addition of probiotics to 14-day triple therapy for H. pylori infection in Asian pediatric patients. The analysis found that probiotic supplementation significantly improved eradication rates (RR = 1.16; 95% CI, 1.07–1.26) and lowered the overall incidence of side effects (RR = 0.40; 95% CI, 0.34–0.48) compared with placebo.[29]

Table 2: Summarizes the expert consensus recommendations on the prevention and management of antibiotic-associated diarrhea (AAD) using probiotics in Pakistan, developed through a structured multidisciplinary agreement

Statement	Topic	Key Consensus Recommendation	Consensus Level
1	Routine Use in Prevention	Probiotics should be co-administered with antibiotics in high-risk patients, based on clinical assessment and physician discretion.	100%
2	High-Risk Patients	Probiotics are recommended in patients with defined risk factors (e.g., broad-spectrum antibiotics, extremes of age, ICU admission, immunocompromised status, poor functional status, recent surgery, IBS, comorbidities, H. pylori therapy, etc.).	100%
3	Antibiotic Risk Stratification	Antibiotics classified into High (≥20%), Moderate (5–10%), and Low (<5%) risk of AAD to guide probiotic use.	91%
4	Management of AAD	Probiotics should be initiated either prophylactically or early in confirmed AAD cases.	100%
4A	Prevention	Start within 48 hours of antibiotic initiation; continue during therapy and up to 7 days post-antibiotics.	100%
4B	Treatment	Start after onset of diarrhea (typically 2–14 days after antibiotics); may continue up to 3 weeks if required.	100%
5	Safety & Contraindications	Avoid in severely immunocompromised patients, ICU patients with central venous lines, premature neonates, severe pancreatitis, and sepsis.	100%
6	Probiotic Selection Criteria	Only strains with RCT evidence, appropriate CFU dose, proven stability, safety profile, and proper labeling should be recommended.	100%
7	Bacillus clausii in AAD	*Bacillus clausii* (O/C, N/R, SIN, T) may be considered a probiotic of choice for prevention and treatment of AAD in Pakistan.	82%
8	H. pylori Adjunct Use	Probiotics, including *Bacillus clausii*, may be used as adjunct therapy in H. pylori eradication to reduce side effects and improve tolerability.	100%

Scope and Implementation

Consensus Statement: The final consensus is endorsed nationally by participating experts and is intended for publication in a peer-reviewed journal. It is expected to serve as a reference for future guideline development on antibiotic-associated diarrhea (AAD) and probiotic use in Pakistan.

DISCUSSION

This consensus represents the first Pakistan-specific multidisciplinary agreement on probiotic use in antibiotic-associated diarrhea (AAD), balancing international evidence with local prescribing practices. It emphasizes targeted prophylaxis and the evidence-based integration of *Bacillus clausii* in antibiotic therapy.

The expert panel underscored the following:

- **Rational antibiotic use:** Irrational and over-the-counter antibiotic prescriptions are widespread in Pakistan, significantly contributing to AAD and antimicrobial resistance (AMR).[17] Implementing probiotics as a preventive adjunct can help reduce unnecessary secondary antibiotic use, indirectly supporting stewardship and national AMR efforts.
- **The incorporation of probiotics as a practical, preventive adjunct** to minimize AAD burden and their role in improving compliance and reducing AMR-related complications.
- **Patient adherence and outcomes:** Probiotics can improve adherence to prescribed antibiotic regimens, reduce treatment discontinuation, and enhance overall patient outcomes by mitigating antibiotic-related gastrointestinal side effects.[3,22]
- **Practicality and accessibility:** Probiotics are cost-effective, easy to administer, and well tolerated, making them suitable for incorporation into routine clinical practice in both urban and rural healthcare settings.
- **Local adaptation of global evidence:** While international guidelines from ESPGHAN, AGA, and WHO provide general recommendations, this consensus contextualizes these findings to Pakistan, considering local practice realities, cultural norms, healthcare infrastructure, economic constraints, and physician awareness.[7,8,9,12]

Limitations

This consensus was developed using a single-round Nominal Group Technique involving 11 experts and was not preceded by a formal Delphi exercise or systematic review. The approach was intentionally chosen to allow timely generation of practical, context-specific recommendations. Although the panel included multiple specialties and representation from different regions of Pakistan, inclusion of additional stakeholder groups in future iterations may further strengthen the comprehensiveness of the recommendations. Moreover, the limited availability of local clinical evidence on probiotic use necessitated partial reliance on established international data. Future real-world studies and periodic updates will be important to refine and contextualize these recommendations as new evidence from Pakistan becomes available.

CONCLUSION

This consensus provides Pakistan-specific, evidence-driven guidance for healthcare professionals on the appropriate use of probiotics, especially *Bacillus clausii*, in preventing and managing AAD. Implementation of these recommendations can support antibiotic stewardship, improve patient outcomes, and contribute to reducing the national burden of antimicrobial resistance.[2,12] Further real-world studies from Pakistan are warranted to validate these recommendations.

Declarations

Clinical trial Number: Not applicable, as this study did not involve interventional clinical trial participants.

Consent to participate: This study involved a structured expert consensus process and did not include patient data or identifiable human subjects. Participation was voluntary, and all responses were anonymized. In accordance with institutional and international guidelines, formal ethical approval was not required for this type of study as it involved expert consensus and did not include human or patient data.

Consent for publication: N/A

Availability of Data and Materials: Not applicable.

Competing interests: Farnaz Khairi is an employee of Hoechst Pakistan. All other authors declare no conflicts of interest.

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Authors' Contributions: FK coordinated the consensus process, organized meetings, managed documentation, and drafted the manuscript. HAC and WQ conceptualized the project, co-chaired the expert panel, and supervised the scientific discussions. KM, ZA, TMM, JUA, MI, EAK, NI, AFS, and FJ participated in the literature review, development and refinement of consensus statements, consensus voting, critical review of the manuscript, and interpretation of the evidence. All authors contributed substantially to the development of the recommendations, critically revised the manuscript for important intellectual content, approved the final version, and fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE).

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