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Systematic Review

Effects of Probiotic Supplementation on Gastrointestinal and Urinary Outcomes in Patients with Spinal Cord Injury: A Systematic Review

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ABSTRACT

Introduction: Spinal cord injury (SCI) often leads to autonomic dysfunction, increasing susceptibility to antibiotic-associated diarrhea (AAD) and recurrent urinary tract infections (UTIs). Gut microbiota alterations post-SCI contribute to immune dysregulation. Although probiotics reduce AAD and infections in non-SCI populations, evidence in SCI remains limited. This systematic review evaluates probiotic effects on gastrointestinal and urinary outcomes in adults with SCI.

Methods: Following PRISMA guidelines, we searched PubMed, Scopus, ProQuest, and the Cochrane Library from January 2010 to December 2024 (final search completed June 2025). The protocol was registered in PROSPERO (CRD420261417485). Randomized controlled trials (RCTs) and prospective interventional studies in adults with SCI receiving probiotics were included. Two reviewers independently performed study selection and data extraction. Risk of bias was assessed using Cochrane RoB 2.0, and GRADE was used for evidence certainty.

Results: Five studies (3 RCTs, 2 controlled intervention analyses) met inclusion criteria (total N = 217 participants; range 24–98 per study). Two RCTs reported significantly reduced AAD incidence during antibiotic exposure with *Lactobacillus rhamnosus GG* and a multi-strain probiotic ($p<0.05$). Three studies evaluated urinary outcomes; one large RCT (n=98) demonstrated a lower incidence of UTIs and reduced colonization with multidrug-resistant organisms. No serious adverse events were reported.

Conclusion: Probiotic supplementation in adults with SCI was associated with reduced AAD and lower urinary infection burden in selected trials. These findings are strain-specific and limited to infection-related outcomes. They may support probiotics as a potential adjunctive strategy for managing secondary complications of SCI.

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INTRODUCTION

SCI is a debilitating condition that results in partial or complete loss of motor, sensory, and autonomic functions, and is frequently accompanied by a range of serious secondary complications that affect quality of life and long-term health outcomes [1,2]. Most cases of SCI arise from traumatic events, particularly road accidents, while non-traumatic factors such as spinal tumors, stenosis, and injuries related to falls or sports also contribute substantially [1]. SCI leads to disruption of autonomic regulation and gastrointestinal function, often causing changes in gut motility, increased intestinal permeability, and impaired mucosal immune responses [3,4]. These effects contribute to a state of gut microbial imbalance known as dysbiosis, which has been implicated in chronic inflammation and worsened neurological sequelae in both preclinical and clinical settings [5].

Gut dysbiosis following SCI has been consistently documented in observational studies, where alterations in microbiota composition are characterized by a reduction in beneficial commensal bacteria and an increase in potentially pathogenic taxa [6]. Such microbial shifts have been associated with systemic metabolic abnormalities and immune dysregulation, suggesting a role for the gut microbiome in modulating host physiology beyond the gastrointestinal tract [5].

In addition to gastrointestinal dysregulation, patients with SCI are at increased risk of recurrent UTIs due to neurogenic bladder dysfunction, frequent catheterization, impaired local immunity, AAD, and alterations in gut microbiota composition [7,8]. The interplay between gut dysbiosis and urinary tract pathobiology is hypothesized to involve translocation of pathogenic organisms from the gut lumen into the urinary tract, though clinical evidence remains limited [5].

Probiotics, defined as live microorganisms that confer health benefits when administered in adequate amounts, have demonstrated efficacy in modulating microbial communities, enhancing barrier integrity, and reducing inflammation in non-SCI populations. In general clinical practice, specific probiotic strains have been shown to reduce the incidence of AAD and *Clostridioides difficile* infection, conditions that are also of concern in SCI patients due to frequent antibiotic exposure [9–12].

Preclinical SCI models suggest that probiotic supplementation may influence the gut–spinal cord axis, attenuating gut dysbiosis and associated inflammatory signaling, as well as promoting neuroprotective metabolic pathways. For example, probiotic administration in rodents has been linked to enhanced microbial diversity, increased production of beneficial metabolites, and improved markers of neurological recovery after injury [13–15].

The aim of this systematic review is to critically evaluate and summarize the existing clinical evidence on probiotic supplementation in adult patients with SCI, focusing on gastrointestinal and urinary outcomes, and to identify gaps in the current literature that warrant future investigation.

METHODS

Study Design and Reporting Standard

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines [16]. The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD420261417485). A PRISMA flow diagram and checklist were prepared to document the processes of study identification, screening, eligibility assessment, and inclusion. The objective of this review was to systematically evaluate the clinical effects of probiotic supplementation on gastrointestinal and urinary outcomes in patients with spinal cord injury (SCI).

Literature Search Strategy

A comprehensive literature search was conducted in PubMed, Scopus, ProQuest, and the Cochrane Library to identify relevant studies published between January 2010 and December 2025. The final search was performed on 15 December 2025. The search period was restricted to studies published from January 2010 onward to capture research conducted after the 2015 Cochrane reviews on probiotics for urinary tract infection prevention, which marked a transition toward strain-specific interventional trials in neurogenic populations.

The search strategy was constructed from three concept blocks: spinal cord injury, probiotics, and gastrointestinal/urinary outcomes, each combined using the OR operator, with the three blocks then combined using the AND operator. This Boolean structure was kept consistent across all databases, while the syntax was adapted to the specific requirements of each database; for example, the use of MeSH descriptors in Cochrane CENTRAL and the TITLE-ABS-KEY field tag in Scopus (Figure 1).

Eligibility Criteria (PICOS Framework)

Table 1 displays the inclusion and exclusion criteria developed using the PICOS approach.

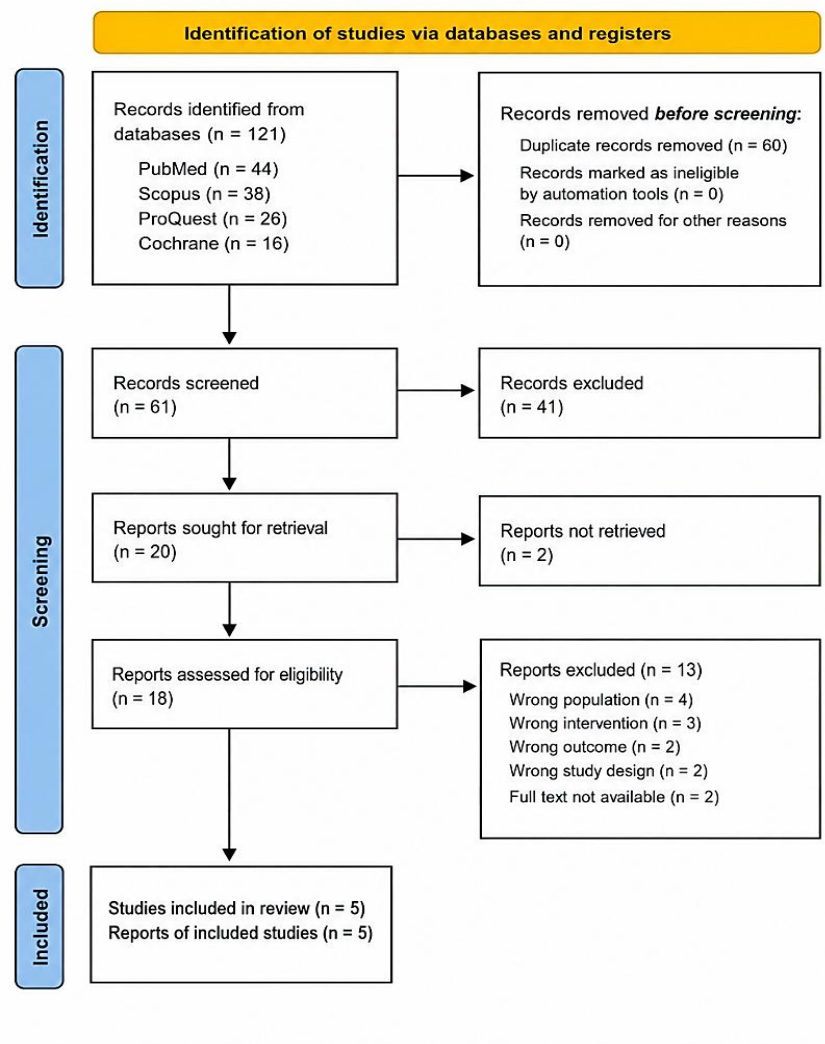


Figure 1. PRISMA Flowchart of the Study

Inclusion Criteria

Studies were included if they: enrolled human adults with SCI; evaluated **a** probiotic or probiotic-based intervention; reported at least one gastrointestinal or urinary outcome; used an experimental or interventional study design; and were published in English between 2010 and 2025.

Exclusion Criteria

Studies were excluded if they: were animal or in vitro studies**;** were reviews, meta-analyses, editorials, protocols, or case reports**;** included only pediatric populations**;** did not involve probiotic intervention**;** or involved mixed populations without separable SCI data**.**

Study Selection Process

All retrieved records were exported into a spreadsheet, and duplicates were removed. Screening was conducted in two stages: 1) Title and Abstract Screening to exclude clearly irrelevant articles; 2) Full-Text Screening to confirm eligibility based on PICOS criteria. A PRISMA flow diagram was constructed to illustrate the number of studies identified, screened, excluded, and included. Both screening stages were performed independently by two reviewers (G.S. and A.E.B.P.). Disagreements regarding eligibility were resolved by discussion until consensus was reached, and inter-reviewer agreement at the full-text stage was high. No automation tools were used in the selection process [17].

Table 1. PICOS Criteria

Component	Criteria
Participants (P)	Adults (≥18 years) diagnosed with spinal cord injury (traumatic or non-traumatic), including paraplegia and tetraplegia, in acute or chronic phases.
Intervention (I)	Probiotic supplementation (single-strain or multispecies), by at any dose or duration.
Comparator (C)	Placebo, standard care, or no probiotic supplementation.
Outcomes (O)	*Primary:*antibiotic-associated diarrhea (including C. difficile–associated diarrhea) and urinary tract infection. *Secondary:* bacterial/MDRO colonization, neurogenic bowel function, and safety/tolerability.
Study design (S)	Randomized controlled trials, controlled clinical intervention studies, and prospective interventional studies.

Data Extraction

Data were extracted using a standardized form including: author and year; study design; sample size; participant characteristics; type and dose of probiotic; duration of intervention; outcomes assessed; and main findings (Table 2). Data extraction was performed independently by two reviewers using a piloted extraction form, and the extracted entries were cross-checked against the source articles. Discrepancies were resolved by consensus, and the corresponding authors of included studies were to be contacted in the event of missing or unclear data.

Risk of Bias (Quality) Assessment

Risk of bias was evaluated using the Cochrane Risk of Bias 2.0 tool, covering five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results (Table 3) [18]. Each study was appraised independently by two reviewers, with disagreements resolved by consensus, and an overall risk-of-bias judgment (low, some concerns, or high) was assigned to each study. A domain-level summary and a traffic-light plot are presented in Table 3 and Figure 2.

Reporting bias was assessed qualitatively by comparing reported outcomes with those prespecified in trial registries and protocols where available, and by evaluating the selective-reporting domain of RoB 2.0; the small number of studies precluded formal funnel-plot or statistical assessment of small-study effects, and this limitation is acknowledged. The certainty of the body of evidence for each outcome (AAD, UTI, and bacterial colonization) was rated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias, and was summarized in a GRADE summary-of-findings table (Table 4) [19].

Statistical Analysis

Due to variability in probiotic strains, intervention duration, and outcome measures, a meta-analysis was not feasible. Therefore, the results were synthesized using a narrative qualitative approach to summarize trends in clinical and microbiological outcomes across studies. To strengthen the rigor of the narrative synthesis, available effect estimates (relative risks, odds ratios, or incidence differences) with their 95% confidence intervals were extracted from each trial and tabulated for structured comparison (Table 2) and the structured synthesis table); where a trial did not report a particular effect measure, this was indicated explicitly.

RESULTS

Literature Search Results

The systematic search of PubMed, Scopus, ProQuest, and the Cochrane Library identified a total of 124 records. After removing duplicates, 61 unique records remained for title and abstract screening. Of these, 41 records were excluded because they did not involve patients with spinal cord injury (SCI), did not evaluate probiotic interventions, or did not meet the predefined study design criteria. Subsequently, 20 full-text articles were sought for retrieval, of which 18 were successfully assessed for eligibility. Thirteen studies were excluded at the full-text stage for

reasons including an inappropriate population, irrelevant interventions or outcomes, unsuitable study design, or unavailable full text. Ultimately, five studies fulfilled all PICOS eligibility criteria and were included in the final qualitative synthesis.

Study Characteristics

The five included studies, published between 2010 and 2024, consisted of randomized controlled trials or controlled clinical intervention studies. Three studies were placebo-controlled, double-blind, randomized trials, while two were controlled intervention trials, including subgroup or secondary outcome analyses. The studies were conducted in Europe and Australia, representing specialized SCI rehabilitation centers. No study was classified as a feasibility or pilot trial. Two studies reported partial industry support related to probiotic supply; however, none reported sponsor involvement in data analysis or outcome reporting.

The evidence base is small, comprising five studies and approximately 230 participants in total. Importantly, two of the included reports (the primary ProSCIUTTU randomized trial and its secondary multidrug-resistant-organism analysis) derive from the same trial cohort, which reduces the number of statistically independent participant populations to four and must be considered when interpreting the consistency of urinary outcomes. This limited and partially overlapping evidence base is explicitly acknowledged as a constraint on the strength of any conclusions drawn. Methodological quality was generally moderate to high, with two studies judged to be at low risk of bias and three showing some concerns, mainly due to incomplete outcome data or subgroup-based analyses.

Participant Characteristics

Across the five trials, approximately 230 adults with SCI were enrolled. Participants were predominantly male, reflecting the known epidemiology of SCI, with reported ages ranging from early adulthood to approximately 70 years. Both paraplegia and tetraplegia were represented. Most participants had chronic SCI, although one study included patients during periods of acute antibiotic exposure.

Several trials specifically recruited individuals with recurrent UTIs, neurogenic bowel dysfunction, or exposure to systemic antibiotics, making the populations highly relevant to probiotic-based gastrointestinal and urinary interventions. Follow-up duration ranged from 4 weeks to 12 months, depending on the outcome assessed.

Intervention Characteristics

All five studies evaluated oral probiotic supplementation. Interventions included single-strain formulations, most commonly *Lactobacillus casei Shirota* or *Lactobacillus rhamnosus* GG, as well as multispecies probiotic combinations containing *Lactobacilli* and *Bifidobacteria*. Probiotics were administered as drinks or oral capsules.

Comparators consisted of placebo or standard care without probiotic supplementation. Daily probiotic doses ranged from approximately 10^9 to 10^{11} colony-forming units, with intervention durations between 4 and 24 weeks. All interventions were classified as non-surgical nutritional or medical therapies.

Outcomes Assessed

Outcomes were grouped into two main categories based on the final included studies:

1. Gastrointestinal Infection – Related Outcomes

Two reports from two independent cohorts evaluated AAD and C. difficile–associated diarrhea in adults with SCI receiving antibiotics. In the single-center Wong 2014 randomized controlled trial using Lactobacillus casei Shirota, the incidence of AAD was significantly lower in the probiotic group than in the control group (17.1% vs 54.9%; $P < 0.001$), with only one AAD case associated with C. difficile. In contrast, the larger multicentre ECLISP trial [41] found no significant difference in its primary AAD outcome at 30 days (45% vs 42.1%; RR 1.07, 95% CI 0.80–1.40; $P = 0.639$). A pre-specified subgroup analysis of ECLISP [33] reported that, among regular proton-pump-inhibitor users, Lactobacillus casei Shirota was associated with a lower AAD risk at 7 days (RR 0.53, 95% CI 0.29–0.99; $P = 0.040$) and 30 days (RR 0.54, 95% CI 0.32–0.91; $P = 0.015$). Reductions in C. difficile–associated diarrhea were based on very small event numbers and were not

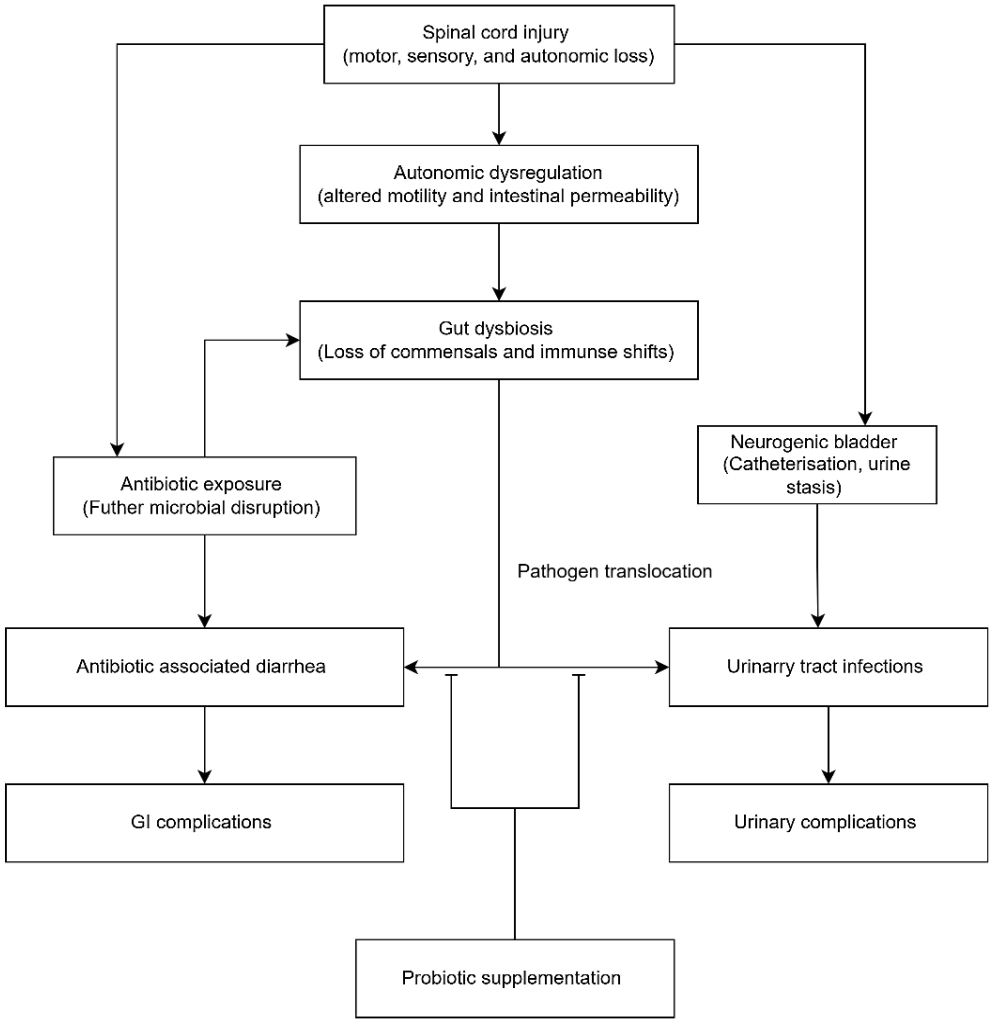


Figure 2. Framework concepts of AAD, UTI, and SCI

consistently powered for statistical significance. The corresponding effect estimates and confidence intervals are presented in Table 2. Taken together, the gastrointestinal evidence indicates a strain-specific benefit that was significant in one single-centre trial but not in the larger multicentre trial overall.

In the single-centre randomized controlled trial [30], the incidence of AAD was 17.1% in the Lactobacillus casei Shirota group versus 54.9% in the placebo group, a difference that reached statistical significance; the ECLISP proton-pump-inhibitor subgroup analysis [33] likewise reported a statistically significant reduction in AAD risk in high-risk users. Reductions in C. difficile–associated diarrhea were observed but were based on small event numbers and were not consistently powered for statistical significance. The corresponding effect estimates and confidence intervals, where reported, are presented in Table 2 and the structured synthesis table. These findings indicate that probiotics were associated with improved resistance to antibiotic-related gastrointestinal infections in this population.

2. Urinary Tract and Bacterial Colonization Outcomes

Urinary, urogenital, and bacterial-colonization outcomes were assessed within a single independent cohort, the ProSCIUTTU trial, reported across two linked publications [22,23]. Multidrug-resistant-organism (MDRO) colonization is common in individuals with SCI,

with reported prevalence as high as approximately 40% in some cohorts, and is driven by frequent catheterization, antibiotic exposure, and prolonged hospitalization. In the ProSCIUTTU colonization analysis, three categories were assessed methicillin-resistant *Staphylococcus aureus* (MRSA), multi-resistant gram-negative organisms (MRGN), and vancomycin-resistant enterococcus (VRE) sampled from the nose, groin, urine, and bowel [23]. These organisms are clinically important because they complicate the treatment of UTIs and increase the antimicrobial-resistance burden in an already vulnerable population. Among gram-negative uropathogens, *Escherichia coli* and *Klebsiella* species are the most frequently isolated multidrug-resistant strains in SCI urine cultures, with extended-spectrum beta-lactamase production commonly reported. In ProSCIUTTU specifically, gram-negative organisms predominated among symptomatic-UTI specimens, most commonly *E. coli* [20–22].

In the ProSCIUTTU trial [35], time to symptomatic UTI was the primary outcome. Neither probiotic combination produced a statistically significant overall reduction in UTI risk (RC14-GR1: HR 0.67, 95% CI 0.39–1.18, P = 0.17; LGG-BB12: HR 1.29, 95% CI 0.74–2.25, P = 0.37), and a post-hoc comparison of RC14-GR1 alone versus the other arms was only borderline (HR 0.46, 95% CI 0.21–0.99; P = 0.03) and was described by the authors as requiring confirmation. As a secondary outcome of the same cohort [42], probiotics did not clear established MDRO colonization overall; however, RC14-GR1 significantly reduced new MRGN colonization compared with placebo (OR 0.10, 95% CI 0.01–0.88; P = 0.04), whereas no significant effect was seen for MRSA or VRE [23]. Because these colonization data derive from the same cohort and rest on a secondary analysis, they do not provide independent confirmation of the urinary findings (Table 2).

Risk of Bias and Study Quality

Using the RoB 2 tool, the parent randomized controlled trials [30,35,41] showed predominantly low to some-concerns risk of bias, mainly related to incomplete reporting of allocation concealment or blinding and, for one trial, missing outcome data. The secondary and subgroup analyses [33,42] carried some concerns because they rely on secondary or subgroup outcomes of their parent trials. Overall, the methodological quality of the included reports was heterogeneous, with the parent randomized trials providing more reliable evidence than the secondary analyses (Table 3).

Summary of Evidence

Across the included studies, which used different probiotic strains and clinical settings, probiotic supplementation in individuals with SCI was associated, in several but not all comparisons with a reduced incidence of antibiotic-associated diarrhea and a lower burden of UTI or pathogenic bacterial colonization. These observations are limited to infection-related gastrointestinal and urinary endpoints and are strain-specific; they do not establish a broad therapeutic effect of probiotics as a class. No included study directly measured gut microbiota composition, so any inference about microbiota modulation is indirect and hypothesis-generating rather than demonstrated. Across five interventional studies in adults with SCI, probiotic supplementation was associated with a reduced incidence of AAD and a lower risk of UTIs or pathogenic bacterial colonization in several trials. One phase I study demonstrated that intravesical administration of Lactobacillus rhamnosus GG was safe and feasible. However, no included study directly evaluated gut microbiota composition, neurogenic bowel function, or inflammatory biomarkers, limiting conclusions to infection-related gastrointestinal and urinary outcomes.

DISCUSSION

Mechanistic Pathway of Dysbiosis in SCI

Spinal cord injury disrupts not only motor and sensory function but also the autonomic pathways that govern gastrointestinal motility and urinary tract function, predisposing affected individuals to secondary complications such as antibiotic-associated diarrhea and recurrent urinary tract infection [22]. The conceptual framework underlying these relationships is summarized in Figure 2. Following injury, autonomic dysregulation alters gut motility and intestinal permeability, promoting a state of dysbiosis

characterized by depletion of beneficial commensals and immune dysregulation [3,23]. These physiological disturbances are accompanied by characteristic alterations in gut microbiota composition, including loss of beneficial butyrate-producing taxa and enrichment of inflammation-associated organisms, as consistently reported in observational microbiome studies in SCI populations [5,24]. This dysbiotic state, compounded by frequent antibiotic exposure and neurogenic bladder dysfunction, is thought to drive the downstream gastrointestinal and urinary complications observed in this population, and a translocation of pathogenic organisms from the gut to the urinary tract has been hypothesized as a connecting mechanism, although direct clinical evidence remains limited [25,26]. Within this framework, probiotic supplementation is proposed to act by restoring microbial balance, reinforcing mucosal barrier integrity, and modulating local immunity. It must be emphasized, however, that none of the included trials directly measured gut microbiota composition, barrier function, or immune markers; the mechanistic links depicted in Figure 2 are therefore inferred from the broader literature rather than demonstrated within the present evidence base, and our findings speak only to the infection-related endpoints at the lower portion of the figure [27,28].

The findings of this systematic review extend these descriptive observations by demonstrating that probiotic supplementation can modify clinically relevant outcomes in this population [29]. Two randomized controlled trials showed that Lactobacillus casei Shirota significantly reduced the incidence of AAD, with indirect evidence from high-risk antibiotic-related populations suggesting protection against *Clostridioides difficile*, suggesting that probiotic-induced changes may translate into measurable gastrointestinal benefit in patients with SCI. It should be emphasized, however, that none of the included trials directly measured gut microbiota composition; the link to microbiome modulation is therefore mechanistic and inferred from the wider literature rather than demonstrated within this evidence base [30–33]. These findings are consistent with probiotic effects observed in other hospitalized and antibiotic-treated populations, supporting their applicability to individuals with SCI [11].

Evidence for urological benefit was provided by the ProSCIUTTU randomized controlled trial, which reported lower rates of UTIs and reduced colonization with multidrug-resistant organisms in patients receiving probiotic combinations compared with placebo. These results suggest that probiotic therapy may reduce infectious complications in SCI, possibly through modulation of host–microbe interactions relevant to urogenital health [34,35]. Although not uniformly significant across all strains and study designs, these findings are biologically plausible given the known interactions between intestinal dysbiosis, immune activation, and susceptibility to urinary infection in SCI [36,37].

In addition, external phase I evidence suggests that intravesical *Lactobacillus rhamnosus* GG administration is safe and well tolerated in patients with neuropathic bladder, supporting the feasibility of localized probiotic strategies for urinary tract modulation [38]. Compared with previous reviews that included observational microbiome studies or heterogeneous dietary interventions, this review focuses specifically on interventional probiotic trials in SCI, thereby strengthening causal inference regarding clinical effects. However, differences in probiotic strains, formulations, and outcome definitions limited direct comparison across studies [39,40].

These findings should be interpreted cautiously because of the substantial heterogeneity across the included trials. The studies differed in probiotic strains, doses, administration routes, intervention duration, and outcome definitions for both AAD and UTI. Since probiotic effects are known to be strain-specific, these differences limit the generalizability of the findings and support the decision not to perform a quantitative meta-analysis. The certainty of the conclusions is also influenced by the risk-of-bias profile of the included studies. The strongest evidence was derived from two trials judged to be at low risk of bias, whereas studies evaluating urinary and colonization outcomes had some methodological concerns, primarily related to incomplete reporting of allocation concealment, blinding, and reliance on subgroup or secondary analyses. Therefore, the evidence supporting reduction of AAD appears more robust than that for urinary outcomes.

These findings are broadly consistent with the wider literature. In non-SCI populations, meta-analyses have shown that probiotics reduce antibiotic-associated diarrhea (AAD) by approximately 42% and Clostridioides difficile–associated diarrhea by approximately 71%. The magnitude of AAD reduction observed in the SCI studies was generally comparable to these pooled estimates [28]. Overall, current evidence suggests that probiotic supplementation in individuals with SCI may reduce AAD and urinary infection burden, supporting its potential role as an adjunctive strategy for managing these common secondary complications [16,29].

CONCLUSION

In adults with SCI, probiotic supplementation was associated with a lower incidence of antibiotic-associated diarrhea, with additional preliminary evidence from one large randomized trial indicating a reduction in the burden of UTIs. These effects were observed in studies evaluating both Lactobacillus-based and multispecies probiotic formulations over intervention periods ranging from four weeks to six months. Across the five included studies, probiotic use was associated with reduced infection-related gastrointestinal and urinary outcomes compared with placebo or standard care. No included study directly measured gut microbiota composition, neurogenic bowel function, or inflammatory biomarkers, so the conclusions are confined to infection-related endpoints and any effect on the gut microbiome remains unproven within this evidence base.

The current evidence is limited, strain-specific, and heterogeneous, and is drawn from a small number of trials, two of which share a single cohort. Probiotic supplementation in adults with SCI, therefore, appears to reduce antibiotic-associated diarrhea and may decrease urinary infection burden in selected randomized trials, and can be regarded as a promising adjunctive strategy rather than an established standard of care. Larger, adequately powered, multicenter trials with standardized strains, doses, and outcome definitions are required before routine clinical implementation can be recommended.

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CONFLICT OF INTEREST

The authors declare no conflict of interesThe authors declare that there are no financial or commercial relationships that could be construed as a potential conflict of interest in relation to this workt.

Availability of Data and Materials

All data analyzed in this systematic review were obtained from publicly available published studies. The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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Table 2. Extraction Results of Journal Analysis

Author (Year) [Ref]	Study Design	Sample Size	Participants	Probiotic Type & Dose	Duration	Outcomes Assessed	Main Findings
Wong et al., 2014 [17]	Randomized controlled trial (single-centre)	164 adults (76 LcS / 82 control)	Adults with SCI requiring antibiotics	Lactobacillus casei Shirota drink; ≥6.5 × 10^9 CFU/day	Antibiotic course + 7 days	AAD, C. difficile–associated diarrhea	AAD incidence significantly lower with LcS (17.1% vs 54.9%; P < 0.001). Only one AAD case was C. difficile–associated.
Wong et al., 2021 (ECLISP) [primary trial]	Multicentre, randomized, double-blind, placebo-controlled trial	359 adults (181 LcS / 178 placebo)	Adults with SCI requiring antibiotics	Lactobacillus casei Shirota drink; ≥6.5 × 10^9 CFU/day	Antibiotic course + 7 days; follow-up to 30 days	AAD (primary), CDI	No significant difference in the primary AAD outcome at 30 days (45% vs 42.1%; RR 1.07, 95% CI 0.80–1.40; P = 0.639). Benefit seen only in the pre-specified regular-PPI subgroup.
Wong et al., 2024 (ECLISP PPI subgroup) [20]	Pre-specified subgroup analysis of the ECLISP RCT	Regular-PPI subgroup of the ECLISP cohort	SCI patients on regular proton-pump inhibitors	Lactobacillus casei Shirota drink; ≥6.5 × 10^9 CFU/day	As ECLISP	AAD, CDI	In regular-PPI users, LcS was associated with lower AAD risk at 7 days (19% vs 35.7%; RR 0.53, 95% CI 0.29–0.99; P = 0.040) and 30 days (28% vs 52.2%; RR 0.54, 95% CI 0.32–0.91; P = 0.015).
Toh et al., 2019 (ProSCIUTTU)	Randomized, double-blind, factorial-design, placebo-controlled trial	207 adults	Adults with chronic SCI and stable neurogenic bladder	RC14-GR1 (L. reuteri RC-14 + L. rhamnosus GR-1) and/or LGG-BB12 (L. rhamnosus GG + B. BB-12); ~10^9 CFU/day	6 months	Time to symptomatic UTI (primary)	No significant overall effect on UTI: RC14-GR1 (HR 0.67, 95% CI 0.39–1.18; P = 0.17); LGG-BB12 (HR 1.29, 95% CI 0.74–2.25; P = 0.37). A post-hoc RC14-GR1-only comparison was borderline (HR 0.46, 95% CI 0.21–0.99; P = 0.03).
Toh et al., 2020 (ProSCIUTTU MDRO) [shares 2019 cohort]	Secondary outcome analysis of the ProSCIUTTU RCT	Same 207-participant cohort	Same ProSCIUTTU population	Same probiotic combinations as the primary trial	6 months	Multidrug-resistant-organism (MDRO) colonization (secondary)	Reported effects on MDRO colonization/clearance that varied by organism and strain; derived from the same cohort and therefore not an independent confirmation of the urinary findings.

AAD, antibiotic-associated diarrhea; CDI/CDAD, Clostridioides difficile infection/diarrhea; CFU, colony-forming units; CI, confidence interval; HR, hazard ratio; LcS, Lactobacillus casei Shirota; MDRO, multidrug-resistant organism; PPI, proton-pump inhibitor; RR, relative risk; SCI, spinal cord injury; UTI, urinary tract infection. Note: Wong 2021 (ECLISP) and Wong 2024 share one cohort; Toh 2019 and Toh 2020 share one cohort.

Table 3. Bias assessment based on ROB Study 2

Study	D1 Randomization	D2 Deviations	D3 Missing data	D4 Measurement	D5 Reported result	Overall
Wong et al., 2014 [17]	Low	Low	Low	Low	Some concerns	Some concerns
Wong et al., 2021 (ECLISP)	Low	Low	Low	Low	Low	Low
Wong et al., 2024 (PPI subgroup) [20]	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Toh et al., 2019 (ProSCIUTTU) [22]	Low	Low	Some concerns	Low	Low	Low
Toh et al., 2020 (MDRO)	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns

Table 4. GRADE summary of findings

Outcome	No. of studies (participants)	Effect estimate (95% CI)	Risk of bias	Inconsistency	Imprecision	Certainty (GRADE)
Antibiotic-associated diarrhoea (AAD) during and up to 30 days after antibiotic exposure	2 RCTs + 1 pre-specified subgroup analysis (n = 523) [30,33,41]	Single-centre RCT: 17.1% vs 54.9%, P < 0.001. Multicentre ECLISP: RR 1.07 (0.80–1.40), P = 0.639. Regular-PPI subgroup: RR 0.54 (0.32–0.91), P = 0.015	Not serious	Serious (opposing directions of effect between the single-centre and multicentre trials)	Not serious	⨁⨁◯◯ Low
Clostridioides difficile–associated diarrhoea	2 RCTs (n = 523) [30,41]	Very few events; no trial powered for this outcome	Not serious	Not serious	Very serious (very low event numbers; wide intervals)	⨁◯◯◯ Very low
Time to symptomatic urinary tract infection	1 RCT (n = 207) [35]	RC14-GR1: HR 0.67 (0.39–1.18), P = 0.17. LGG-BB12: HR 1.29 (0.74–2.25), P = 0.37	Not serious	Not assessable (single trial)	Serious (confidence intervals include both benefit and harm)	⨁⨁◯◯ Low
Multidrug-resistant organism colonisation	1 RCT, secondary outcome of the same cohort (n = 207) [42]	New MRGN colonisation, RC14-GR1 vs placebo: OR 0.10 (0.01–0.88), P = 0.04. No significant effect on MRSA or VRE	Serious (secondary outcome of the parent trial)	Not assessable (single trial)	Very serious (few events; very wide interval)	⨁◯◯◯ Very low

CI, confidence interval; HR, hazard ratio; MRGN, multi-resistant gram-negative organisms; MRSA, methicillin-resistant Staphylococcus aureus; OR, odds ratio; PPI, proton-pump inhibitor; RCT, randomised controlled trial; RR, relative risk; VRE, vancomycin-resistant enterococcus. Indirectness was not serious for any outcome, as all included trials enrolled adults with spinal cord injury and reported the outcomes of interest directly. Publication bias could not be assessed formally because of the small number of studies. Note: references 30 and 41 report the same intervention in two separate cohorts; references 33 and 41 share the ECLISP cohort, and references 35 and 42 share the ProSCIUTTU cohort.

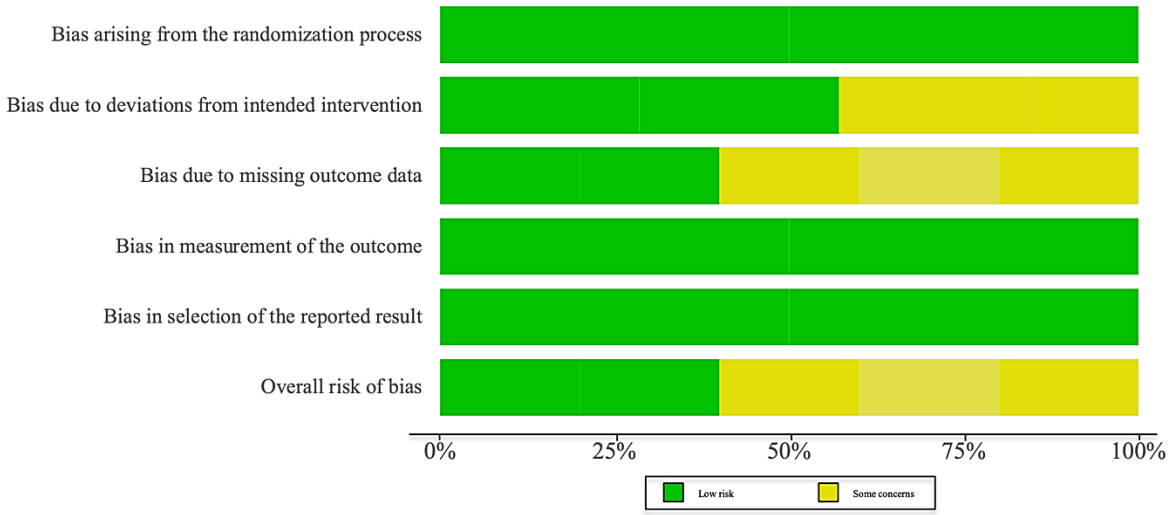


Figure 3. Risk of bias assessment across the included studies

Risk of bias assessment across the included studies. The bar chart shows the proportion of studies rated as having low risk of bias (green) or some concerns (yellow) across five bias domains and for the overall risk of bias. Most studies were judged to have a low risk of bias in the randomization process, outcome measurement, and selection of the reported result, whereas some concerns were identified regarding deviations from the intended interventions and missing outcome data.