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REVIEW ARTICLE

The role of probiotics in mitigating gastrointestinal side effects of antibiotic treatment in respiratory infections caused by methicillin-resistant Staphylococcus aureus: A novel approach to gut-lung health

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Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of severe respiratory infections, particularly in patients with chronic pulmonary diseases, and its treatment often necessitates prolonged use of broad-spectrum or potent anti-MRSA antibiotics. While these therapies are essential for infection control, they frequently disrupt gut microbiota, leading to dysbiosis and gastrointestinal complications such as antibiotic-associated diarrhea and *Clostridioides difficile* infection. Increasing evidence indicates that antibiotic-induced gut dysbiosis may also influence respiratory immunity through the gut–lung axis, potentially affecting pulmonary inflammation and infection outcomes. Probiotics have emerged as a potential adjunctive strategy to mitigate antibiotic-related gastrointestinal adverse effects by restoring microbial balance, enhancing intestinal barrier integrity, and modulating host immune responses. This narrative review examines current preclinical, indirect clinical, and limited clinical evidence regarding the role of probiotics in alleviating gastrointestinal side effects of antibiotic therapy in MRSA-related respiratory infections and explores their suggestive immunomodulatory effects on pulmonary health via gut–lung immune interactions. Experimental and observational studies indicate that probiotic-mediated restoration of gut microbiota and microbial metabolites, particularly short-chain fatty acids, may exert systemic immunoregulatory effects extending to the lungs. However, direct, high-quality clinical evidence specifically supporting probiotic use in MRSA pneumonia remains limited and preliminary. Overall, probiotics represent a microbiome-centered

supportive approach with biological plausibility but incomplete clinical validation for improving gastrointestinal tolerance to antibiotic therapy and supporting immune homeostasis in MRSA respiratory infections. Further well-designed, MRSA-specific clinical trials incorporating microbiome and immunological endpoints are required before definitive clinical recommendations can be made.

Keywords: Methicillin-resistant Staphylococcus aureus; Probiotics; Respiratory tract infections; Antibiotic-associated diarrhea; Gastrointestinal microbiome

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a multidrug-resistant pathogen that has become a significant cause of respiratory infections such as pneumonia.[1,2] Its importance is especially pronounced in patients with chronic pulmonary diseases—for example, MRSA infection in individuals with chronic lung conditions (like chronic obstructive pulmonary disease or fibrotic lung disease) is associated with worse clinical outcomes.[3] Studies indicate that roughly 20% of hospitalized chronic obstructive pulmonary disease (COPD) patients may be colonized with MRSA, a factor linked to longer hospital stays and higher intensive care needs.[4] Similarly, in fibrotic lung disease, MRSA is frequently isolated from the lungs of hospitalized patients and correlates with increased morbidity and mortality.[1,3] These observations underscore the clinical significance of MRSA-related respiratory infections and the challenges in treating them. Therapeutic options are limited to potent antibiotics (including vancomycin, linezolid), yet overuse of these has driven resistance and reduced efficacy.[5,6] Indeed, MRSA pneumonia carries a high risk of complications and mortality, and treating such infections in vulnerable pulmonary patients remains difficult despite aggressive antibiotic therapy.[3,5]

A less appreciated consequence of intensive antibiotic treatment in MRSA infections is its disruptive impact on the gut microbiota. Broad-spectrum and anti-MRSA antibiotics can perturb the normal gastrointestinal microbiota, leading to *dysbiosis*—a loss of microbial diversity and balance.[7] This dysbiosis underlies common gastrointestinal side effects of antibiotic treatment, notably antibiotic-associated diarrhea (AAD) and *Clostridioides difficile* infection.[7,8] MRSA-targeted regimens are no exception: for instance, while vancomycin is effective against MRSA in the lungs[9], it can simultaneously aggravate gut microbiota imbalance and intestinal barrier damage.[2] Thus, patients receiving antibiotics for MRSA respiratory infections often experience gastrointestinal disturbances such as diarrhea, nausea, and other symptoms of dysbiosis. These side effects not only diminish patient comfort but can also hinder nutrition and recovery, highlighting a need for supportive strategies to protect gut health during treatment.

Probiotics have emerged as a promising approach to maintain gastrointestinal equilibrium in the face of antibiotic therapy. Probiotics are live beneficial microbes that, when administered in adequate amounts, help restore the gut's microbial balance and fortify its integrity. There is robust evidence that probiotics can mitigate the gastrointestinal side effects of antibiotics. Clinical trials and meta-analyses have shown that co-administration of probiotics significantly reduces the incidence of AAD and *C. difficile* colitis.[8] In one analysis, the use of probiotic supplements alongside antibiotics halved the risk of developing *C. difficile* infection.[1,10] Probiotic supplementation is thought to replenish beneficial commensals, prevent pathogen overgrowth, and accelerate the recovery of a healthy gut microbiome after antibiotic-induced perturbation.[11] By preserving microbial diversity and normalizing intestinal function, probiotics can effectively blunt dysbiosis-related symptoms.[1,10] In short, the gastrointestinal benefits of probiotics are well-documented—they offer a safe and practical means to counter antibiotic-induced dysbiosis and its unpleasant sequelae.

While the role of probiotics in maintaining gut health is established, their potential in the specific context of MRSA-related respiratory infections remains underexplored. The current literature lacks focused investigations on whether probiotic use in patients treated for MRSA pneumonia can consistently alleviate antibiotic-associated gastrointestinal side effects or improve overall outcomes. In these patients, an intriguing consideration is the *gut–lung axis* – the bidirectional relationship between gut microbiota and lung health. Imbalances in gut microbial communities have been linked to pulmonary diseases such as asthma and cystic fibrosis, suggesting that changes in the gut microbiome can influence respiratory inflammation and immunity.[12] However, how alterations in the gut microbiome (due to

potent antibiotics or underlying illness) affect respiratory infection severity in MRSA-infected individuals is not fully understood. Emerging evidence hints at a connection; for example, a recent preclinical study demonstrated that restoring gut microbiota with a probiotic mixture in MRSA-infected mice not only corrected dysbiosis but also reduced lung bacterial burden and inflammation.[2,12] This finding supports the concept of a gut–lung interplay in MRSA infection. Yet, clinical research translating this gut–lung axis insight to human MRSA respiratory infections is very limited. No consensus guidelines currently address probiotic use to improve both gastrointestinal tolerance and pulmonary outcomes in MRSA pneumonia, highlighting a significant knowledge gap. Exploring this relationship is important, as it could reveal novel therapeutic avenues—for instance, using probiotics as adjuncts to standard care might simultaneously protect gut integrity and modulate immune responses to infection. Given the increasing attention to the gut–lung connection, more studies are needed to determine if interventions targeting the gut microbiome can positively impact lung infection outcomes.[12] So far, the idea that probiotic therapy could confer benefits beyond the gut, potentially aiding in respiratory recovery for MRSA-infected patients, remains a compelling yet unproven hypothesis.

The purpose of this narrative review is to explore the role of probiotics in alleviating the gastrointestinal side effects of antibiotic treatment in MRSA-related respiratory infections, and to examine their potential impact on respiratory health through the gut–lung axis. Specifically, the review investigates whether adjunct probiotic therapy can reduce antibiotic-induced gastrointestinal complications in patients with MRSA pulmonary infections and whether it might also influence pulmonary outcomes, such as infection severity or recovery. This study aims to address critical gaps in the management of MRSA pneumonia in patients with chronic respiratory diseases. By bridging antimicrobial therapy and microbiome health, this work is clinically and scientifically significant, offering insights into how probiotics may enhance treatment strategies, improve patient care, and contribute to a more integrated approach to gut–lung health.

2. Methods

This narrative review was conducted to synthesize current evidence on the role of probiotics in mitigating gastrointestinal side effects of antibiotic therapy in MRSA–associated respiratory infections, with a particular focus on interactions along the gut–lung axis. A comprehensive literature search was performed using major electronic databases, including PubMed/MEDLINE, Scopus, and Web of Science. Peer-reviewed articles published in English between January 2015 and March 2025 were considered eligible for inclusion. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords such as "Methicillin-Resistant *Staphylococcus aureus*," "Probiotics," "Respiratory Tract Infections," "Antibiotic-Associated Diarrhea," "Gut Microbiome," and "Gut–Lung Axis."

Eligible studies included original experimental research (*in vivo* and *in vitro*), randomized controlled trials, observational clinical studies, systematic reviews, and meta-analyses that investigated antibiotic-induced gastrointestinal dysbiosis, probiotic interventions, or microbiome-mediated immune interactions relevant to respiratory infections. Studies published outside the defined time frame, not involving antibiotic exposure, or lacking relevance to gastrointestinal or respiratory outcomes were excluded. Although priority was given to studies specifically addressing MRSA or multidrug-resistant pathogens, high-quality evidence from related respiratory infection models and critical care populations was included to support mechanistic insights and clinical context. Data were extracted narratively, focusing on study design, population or experimental model, antibiotic regimens, probiotic strains and dosing, gastrointestinal outcomes, respiratory or immunological endpoints, and proposed gut–lung mechanisms.

3. Mechanisms of antibiotic-induced gastrointestinal side effects

3.1. Disruption of gut microbiota by antibiotics

Antibiotic therapy, especially with broad-spectrum agents such as vancomycin, linezolid, β-lactams, and fluoroquinolones, profoundly alters the gut microbial ecosystem, leading to dysbiosis characterized by reduced diversity and a shift in community structure.[13] These antibiotics deplete beneficial commensals, notably *Bifidobacterium*, *Faecalibacterium prausnitzii*, and *Lactobacillus*, while promoting the overgrowth of opportunistic and pathogenic taxa such as *Clostridioides difficile*, *Enterococcus*, *Escherichia*/*Shigella*, and *Proteobacteria*.[14,15] Mechanistically, antibiotics disrupt colonization resistance by eliminating competitive commensals, reducing short-chain fatty acid (SCFA) production, and impairing mucosal barrier integrity, resulting in increased intestinal permeability and susceptibility to pathogen colonization.[14,16–18] This ecological void facilitates the emergence and domination of multidrug-resistant organisms (MDROs), including vancomycin-resistant enterococci (VRE), extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, and MRSA, through horizontal gene transfer and selective pressure.[18-20]

The functional consequences of this disruption are multifaceted. Loss of SCFA-producing bacteria impairs epithelial energy supply and immune modulation, while the depletion of beneficial taxa weakens the gut's ability to resist colonization by pathogens.[21,22] Clinically, these changes manifest as gastrointestinal disturbances, most notably AAD, which can range from mild to severe, especially when associated with *C. difficile* infection.[23] The risk of AAD and *C. difficile* infection is particularly high with agents such as vancomycin, which target Gram-positive organisms and disrupt microbial equilibrium. Furthermore, antibiotic-induced dysbiosis can persist for weeks to months post-therapy, with incomplete recovery of microbial diversity, especially in vulnerable populations such as the elderly or immunocompromised.[24,25]

Restoration strategies have been developed to mitigate these adverse effects. Fecal microbiota transplantation has demonstrated high efficacy in reestablishing microbial diversity and treating recurrent *C. difficile* infections. Probiotics and synbiotics, particularly strains of *Lactobacillus* and *Bifidobacterium*, have shown moderate efficacy in reducing the incidence and duration of AAD and in restoring barrier function, though their benefits are strain- and dose-dependent.[26-28] Next-generation approaches, including defined microbial consortia, engineered probiotics, and phage-based therapeutics, are under investigation to provide targeted restoration of microbial balance and function. The integration of artificial intelligence and multi-omics tools is also emerging to personalize microbiome therapeutics and predict recovery trajectories.[29] Collectively, these findings underscore the profound and lasting impact of antibiotics on gut microbial ecology and highlight the necessity for judicious antibiotic use and innovative restoration strategies to preserve gut health.

3.2. Inflammatory responses and gut dysbiosis

Antibiotic-induced dysbiosis disrupts the colonic microbiota and reduces protective metabolites (such as SCFAs), leading to epithelial barrier breakdown and immune activation.[30,31] Barrier loss allows luminal antigens to provoke mucosal inflammation and cytokine release. In murine models, broad-spectrum antibiotics downregulated tight-junction proteins (ZO-1, occludin) and raised colonic permeability.[31] Consequent immune activation elevates pro-inflammatory mediators: for example, mice treated with ampicillin showed a ~38% rise in colonic interleukin (IL)-6 ($p<0.001$) and increased TNF-α/IL-1β, while anti-inflammatory IL-10 fell.[32] Similarly, AAD models report higher colonic tumor necrosis factor alpha (TNF-α) and IL-6 concentrations, with dysbiosis-driven lipopolysaccharide (LPS) and monocyte chemoattractant protein-1 (MCP-1) upregulation amplifying intestinal inflammation.[33] Excess cytokines (IL-6, TNF-α, IL-1β) induce enterocyte apoptosis and intestinal epithelial cell dysfunction,[34] explaining gastrointestinal symptoms. Clinically, these pathways manifest as diarrhea, bloating, and pain. In patients with irritable bowel syndrome (often dysbiotic), mucosal TNF-α, IL-6, and IL-8 are elevated, and barrier function is impaired.[34] In sum, antibiotic-triggered dysbiosis erodes epithelial integrity and unleashes IL-6/TNF-mediated inflammation, precipitating diarrhea and discomfort.

3.3. Impact on gut-lung axis

Dysbiosis after antibiotics also perturbs the gut–lung axis, altering respiratory immunity. Commensal metabolites (notably SCFAs) reach the lung and modulate immune cells.[35,36] For instance, high-fiber diets (raising SCFAs) limit neutrophil influx and inflammation in viral pneumonia models.[36] Supplementation with gut-derived butyrate protected against MRSA pneumonia by skewing alveolar macrophages to an anti-inflammatory (M2) phenotype and suppressing TNF-α/IL-6 release.[35] Likewise, oral spermidine (a gut polyamine) enhanced survival in MRSA infection by inducing M2 macrophages and reducing pro-inflammatory cytokines.[37] Dysbiosis impairs defense: depletion of gut microbiota (including vancomycin/colistin) depressed dendritic-cell and monocyte function, markedly worsening *P. aeruginosa* lung infection.[38] In humanized mice, antibiotic-perturbed human microbiota weakened inflammatory monocytes' FFAR2/3-dependent killing of MDR *Klebsiella pneumoniae* in the lung.[39] Pathogen-induced dysbiosis can also backfire via immune signals, such as antibiotic-driven *Candida* overgrowth, which activates alveolar macrophage dectin-1, boosting IL-1β and neutrophil-driven lung injury.[40] Notably, restoring gut metabolites reverses damage: gut-derived isovaleric acid from *Prevotella* markedly reduced lung inflammation and tissue damage in influenza infection.[41] Together, these findings show that antibiotic-induced gut dysbiosis impairs lung immunity (via altered immune cell programming and reduced SCFAs), exacerbating respiratory inflammation and infection, including MRSA pneumonia.

As illustrated in Figure 1, antibiotic-induced disruption of the gut microbiota promotes systemic dissemination of pro-inflammatory mediators and immune cells that exacerbate pulmonary inflammation and MRSA persistence, whereas probiotic supplementation restores gut microbial balance and supports immunoregulatory signaling along the gut–lung axis.

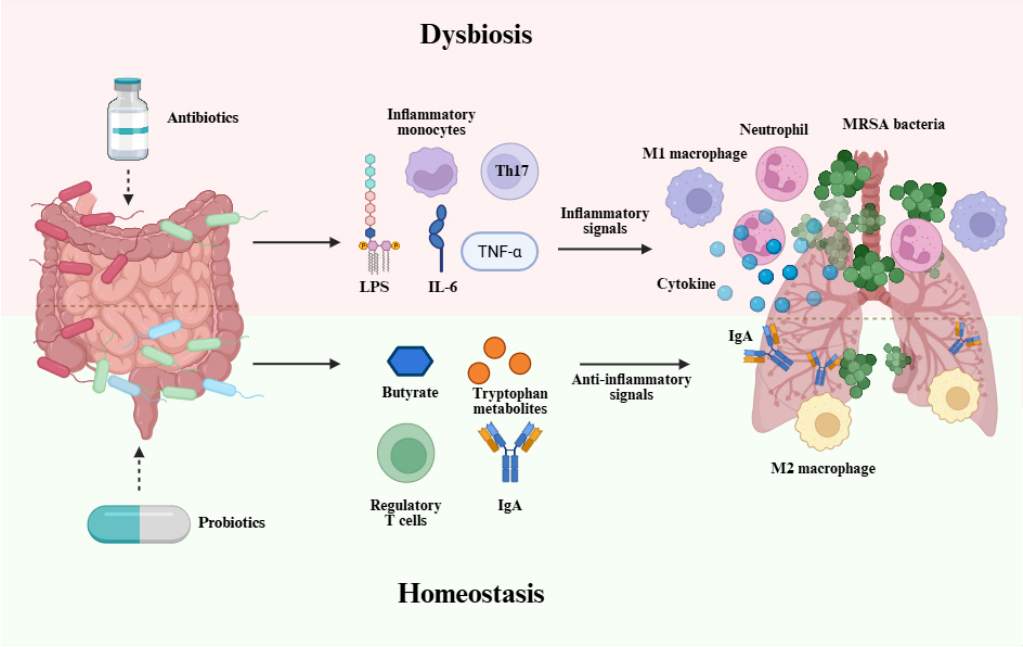


Figure 1. Antibiotic-induced gut dysbiosis and probiotic-mediated modulation of the gut–lung axis in methicillin-resistant Staphylococcus aureus (MRSA) pneumonia. Broad-spectrum or anti-MRSA antibiotic therapy disrupts gut microbial homeostasis, leading to reduced beneficial commensals and overgrowth of pathobionts. This dysbiotic state is associated with increased intestinal permeability and enhanced systemic dissemination of pro-inflammatory mediators, including lipopolysaccharide (LPS), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), inflammatory monocytes, and Th17 cells. Through systemic circulation, these signals reach the lung, where they promote exaggerated inflammatory responses characterized by increased neutrophil recruitment, M1 macrophage polarization, elevated cytokine production, and enhanced MRSA persistence. In contrast, probiotic supplementation restores gut microbial diversity and beneficial taxa, resulting in increased production of short-chain fatty acids (notably butyrate), tryptophan-derived metabolites, regulatory T cells, and IgA. These gut-derived immunoregulatory signals contribute to immune homeostasis in the lung, favoring M2 macrophage polarization, enhanced mucosal IgA responses, reduced bacterial burden, and attenuation of lung inflammation. This schematic highlights the bidirectional gut–lung axis as a key interface linking antibiotic-induced dysbiosis to pulmonary immune dysregulation, and illustrates the potential of probiotics to counterbalance these effects. Created with BioRender. Ahmadinia, M. (2026) https://BioRender.com/mj8mtk3

4. Probiotics as a therapeutic strategy

4.1. Mechanisms of probiotics in gastrointestinal health

Probiotics support the recovery of gut microbial balance (homeostasis) following antibiotic-induced dysbiosis by replenishing commensal taxa and preserving microbial diversity.[42,43] In doing so, they help reconstitute metabolic functions lost after antibiotics. For example, probiotics restore SCFA levels (butyrate, acetate, propionate) that were depleted by antibiotics.[43] These SCFAs strengthen the epithelial barrier and dampen inflammation via increased tight-junction proteins (ZO-1, claudins, occludin) and mucus production.[44,45] Probiotics also modulate host immune signaling: they suppress pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and LPS-mediated pathways (such as TLR4–MyD88–NF-κB) while boosting anti-inflammatory mediators like IL-10.[30,44] Collectively these actions repair barrier integrity and reduce intestinal inflammation. Clinically, this translates to fewer gastrointestinal complications of antibiotic therapy. Numerous trials show probiotic use significantly lowers the incidence and duration of AAD. For instance, *Lactobacillus* and *Bifidobacterium* strains shorten diarrhea episodes and normalize stool consistency in AAD patients.[46,47] Animal studies likewise demonstrate that probiotic supplementation (including *L. plantarum* or *B. lactis*) mitigates antibiotic-induced colitis, restores SCFAs and microbial richness, and reduces endotoxemia.[30,44] Thus, probiotics alleviate antibiotic-driven gut dysbiosis and related morbidity by rebalancing microbiota, repairing the barrier and modulating immune responses.

4.2. Role of probiotics in enhancing gut-lung health

Probiotics modulate both intestinal and pulmonary inflammation via the "gut–lung axis," a bidirectional communication network linking gut microbes, their metabolites and respiratory immunity.[12] Metabolites

produced by gut bacteria—especially SCFAs—enter the bloodstream and reach the lungs, where they enhance alveolar macrophage bactericidal activity and suppress excessive pro-inflammatory cytokine release.[12] In addition, probiotic-driven immune crosstalk occurs through mucosal signaling pathways. For example, oral Bifidobacteria promote Th1/Th2 balance and increase splenic secretion of interferon gamma (IFN-γ), IL-4 and IL-12,[12] whereas *Lactobacillus plantarum* administration reduces lung neutrophil infiltration and IL-6/TNF-α levels and induces regulatory T cells in the airways.[12,30] Through such mechanisms, gut microbes influence lung barrier function and inflammation. Experimental evidence supports these effects: in rats exposed to air pollutants, probiotic treatment attenuated PM2.5-induced lung injury by rebalancing Th17/Treg cells and lowering TNF-α, IL-6 and IL-1β in lung tissue.[48] In viral models, mixed probiotic supplementation (various *Lactobacillus* strains) given before influenza challenge significantly lowered lung viral titers and reduced inflammatory lung damage, while enhancing systemic anti-viral immunity.[49] Clinically, some studies report that probiotics or synbiotics can shorten the course of respiratory infections or reduce incidence of ventilator-associated pneumonia, likely via improved mucosal immunity.[12,50] Overall, probiotics exert protective gut–lung effects by generating immunoregulatory metabolites, strengthening mucosal defenses and modulating systemic cytokine networks, thereby mitigating pulmonary inflammation and enhancing respiratory immune responses.

4.3. Potential benefits in MRSA-induced respiratory infections

Though data are limited, emerging studies suggest probiotics or their metabolites may benefit MRSA pneumonia outcomes. In murine MRSA pneumonia, for instance, oral sodium butyrate (a gut-derived SCFA) markedly reduced lung inflammation: it reshaped the gut–lung microbiota and promoted alternative (M2) activation of alveolar macrophages, thereby dampening inflammatory injury.[35] Similarly, probiotic *Lactobacillus murinus* given to influenza-infected mice decreased susceptibility to secondary MRSA lung infection by bolstering mucosal immunity: treated mice showed significantly lower MRSA lung loads and mortality, associated with a robust T cell–independent IgA response in the airways.[51] These findings imply that probiotics can enhance host defense against MRSA via IgA-mediated neutralization and by skewing lung immune polarization. Importantly, MRSA pneumonia patients often require broad-spectrum anti-MRSA antibiotics, which can induce severe gut dysbiosis and diarrhea. By restoring commensals, probiotics might mitigate these gastrointestinal side effects in such patients, as seen in other settings.[44,47] Mechanistically, probiotics-derived SCFAs and other metabolites likely contribute to this protection: SCFAs not only improve the intestinal barrier and lower systemic endotoxin but also circulate to the lung to restrain inflammation.[12,35]

5. Clinical implications and evidence from studies

5.1. Clinical studies on probiotics in antibiotic-induced gastrointestinal side effects

Antibiotic-associated diarrhea (AAD) is a common complication of broad-spectrum antibiotic therapy, ranging from mild self-limited loose stools to severe colitis. Disruption of the gut microbiota by antibiotics reduces colonization resistance and predisposes to pathogens such as *C. difficile*.[10] A robust body of clinical trials and meta-analyses indicates that probiotic co-administration can mitigate these gastrointestinal adverse effects. Multiple randomized controlled trials (RCTs) have demonstrated a lower incidence of AAD in patients receiving various probiotic strains alongside antibiotics, and these findings have been synthesized in several systematic reviews. For example, a 2017 Cochrane systematic review and meta-analysis of 39 RCTs involving 9,955 participants found that probiotics reduced the risk of *Clostridium difficile*-associated diarrhea in adults and children receiving antibiotics by approximately 60% compared with placebo or no treatment (RR 0.40, 95% CI 0.30–0.52).[52] Similarly, a 2025 meta-analysis including 15 recent trials reported a ~40% relative reduction in AAD incidence with probiotic prophylaxis (RR ~0.60).[53] In practical terms, baseline rates of AAD in adults on antibiotics (often 15–20% or higher) were nearly halved in probiotic-treated groups in these analyses. Notably, the efficacy appears to be dose- and species-dependent; subgroup data suggest higher probiotic doses and multi-strain formulations confer greater protection.[53] Commonly studied preparations—such as *Lactobacillus rhamnosus GG* and the yeast *Saccharomyces boulardii*—have shown significant benefits. An updated quantitative review of *L. rhamnosus GG* trials, for instance, found the overall AAD risk was reduced from ~22% in controls to ~12% with GG (RR ≈ 0.49).[54] Likewise, *S. boulardii* has demonstrated efficacy: in an updated meta-analysis of 21 trials, *S. boulardii* use lowered AAD incidence from ~18.7% to 8.5% (RR 0.47, 95% CI 0.38–0.57), corresponding to a number needed to treat of about 10.[55] These reductions in diarrhea translate into meaningful clinical outcomes such as fewer interruptions of antibiotic therapy and improved patient comfort.[45]

Probiotic prophylaxis is particularly effective against *C. difficile*-associated diarrhea, a severe subset of AAD. In a comprehensive Cochrane review of 39 trials including nearly 10,000 patients, adjunct probiotics reduced the incidence of *C. difficile* infection from 4.0% in the control groups to 1.5% in the probiotic groups (RR 0.40, 95% CI 0.30–0.52).[52] Benefits were most pronounced in high-risk settings: trials with baseline *C. difficile* infection rates >5% saw a ~70% risk reduction (RR ~0.30) with probiotics, whereas those in lower-risk populations showed minimal difference.[52] Another meta-regression analysis confirmed that timing is critical—starting probiotics early, within 48 hours of antibiotic initiation, maximizes efficacy. In hospitalized adults, probiotics begun promptly with antibiotics were associated with over 60% lower odds of *C. difficile* infection.[56]

Despite the overall positive trend, not all trials have shown benefit, underscoring heterogeneity in outcomes. Several large RCTs in specific populations have reported null results, likely reflecting differences in patient age, baseline risk, or probiotic formulation. In particular, the preventive effect appears less robust in elderly patients. A dedicated systematic review of AAD in older inpatients (≥65 years) found no significant reduction with probiotics in that subgroup.[57] Consistent with this, subgroup analyses in meta-reviews have noted that probiotic efficacy is attenuated or absent in older adults while remaining significant in younger patients.[57] This age-dependent effect has been attributed to age-related microbiome changes and higher rates of AAD in the elderly that may not be easily countered by currently tested probiotics.[57] Nevertheless, even in trials where the primary end-point (AAD as strictly defined) was not significantly improved, probiotics often conferred other gastrointestinal benefits. For instance, a recent placebo-controlled trial in 350 children found no significant difference in strict AAD rates between the probiotic and placebo groups, but did observe a reduction in overall antibiotic-related loose stool episodes (32.3% in placebo vs. 20.9% with probiotics, $p<0.05$).[58] Such findings highlight that probiotics may improve stool consistency and minor gastrointestinal symptoms even when not preventing all cases of formal "AAD." Moreover, the lack of effect in some high-profile trials has been partly explained by low baseline event rates or suboptimal probiotic dosing. When probiotic trials enroll populations at relatively low risk of antibiotic-associated gastrointestinal complications, the absolute benefit diminishes.[58,59]

5.2. Application in respiratory infections

Patients with respiratory infections caused by pathogens like MRSA often receive intensive antibiotic regimens, which place them at considerable risk for gastrointestinal side effects. Integrating probiotic prophylaxis into the care of such patients must consider not only the direct gastrointestinal benefits reviewed above, but also any indirect effects on respiratory outcomes via the gut–lung axis. Although no clinical trial has focused exclusively on probiotic use in MRSA pneumonia, related studies in broader respiratory infection populations and critically ill cohorts provide insight into potential applications and limitations.

5.2.1. Antibiotic-associated gastrointestinal protection in respiratory infection patients

Many clinical trials of probiotics have enrolled patients being treated for pneumonia or other respiratory tract infections, given that these conditions frequently require broad-spectrum or combination antibiotic therapy. Subgroup data from prophylaxis trials suggest that the gastrointestinal benefits of probiotics (*e.g.*, reduction in AAD and *C. difficile* rates) are equally applicable to patients with respiratory infections who are receiving antibiotics. For instance, in the previously mentioned 2021 meta-analysis, a large proportion of included subjects were hospitalized for pneumonia or other lung infections,[60] and they experienced the same magnitude of diarrhea risk reduction with probiotics as the overall study population. Similarly, a pediatric trial noted that lower respiratory tract infections were the most common indication for antibiotics in their cohort, and while the probiotic did not significantly change strict AAD incidence, it did improve overall diarrheal outcomes in those children.[58] These findings imply that patients fighting respiratory infections can derive the same prophylactic gastrointestinal advantages from probiotics—such as prevention of *C. difficile* colitis or debilitating diarrhea—as patients treated for other infections. This is particularly relevant in MRSA pneumonia, where standard of care often involves potent anti-MRSA agents (*e.g.*, intravenous vancomycin or linezolid) frequently combined with additional broad-spectrum coverage. Such regimens can be highly disruptive to gut microbiota, and probiotic co-therapy offers a strategy to maintain microbial balance and reduce adverse events. Although direct evidence in MRSA-specific pneumonia is lacking, it is reasonable to extrapolate from the general ICU and hospital data that probiotics could lower rates of AAD and *C. difficile* infection in this setting.[56,60] Indeed, one retrospective analysis in intensive care found that *C. difficile* colitis incidence was notably high in MRSA pneumonia patients on prolonged vancomycin, underlining the need for preventive measures (though specific probiotic data were not reported). By informing such patients of the potential benefits observed in other populations, clinicians can consider probiotics as

an adjunct to mitigate gastrointestinal side effects during anti-MRSA therapy, with the important caveats discussed below.

5.2.2. Impact on respiratory outcomes and the gut–lung axis

Beyond gastrointestinal protection, emerging evidence suggests probiotics might favorably influence pulmonary health via immunomodulation—the so-called gut–lung axis.[50] The gut–lung axis refers to the bidirectional crosstalk between intestinal microbiota and lung immunity: changes in gut microbial composition can alter systemic levels of microbial metabolites and immune cells, thereby affecting the respiratory tract's inflammatory responses.[61] In clinical studies, this interplay is reflected in outcomes like pneumonia severity, ventilator-associated pneumonia incidence, and even frequency of COPD exacerbations. Several trials, though not MRSA-specific, illuminate how probiotics might confer respiratory benefits. In community-acquired pneumonia, a randomized trial in young adults demonstrated that adding a probiotic to antibiotic therapy led to faster clinical recovery. Patients in the probiotic group had a shorter duration of fever and an overall improvement in clinical status compared to those on antibiotics alone.[62]

In critically ill patients with severe respiratory infections, probiotics have been investigated primarily for preventing ventilator-associated pneumonia. Early trials and meta-analyses yielded encouraging results, reporting that prophylactic probiotics could reduce ventilator-associated pneumonia incidence by roughly 30%.[63] Proposed mechanisms include suppression of pathogenic oropharyngeal colonizers and strengthening of gut barrier function to reduce translocation of endotoxins that can fuel lung inflammation.[61,63,64] For example, a 2022 meta-analysis of 18 RCTs (4,893 ICU patients) found that probiotics may reduce the incidence of ventilator-associated pneumonia (RR 0.68, 95% CI 0.55–0.84), alongside shortening ICU stay by ~2 days and reducing total antibiotic days.[63] However, these potential benefits came with important limitations: when the analysis was restricted to the highest-quality trials (double-blinded, low risk of bias), the effect on ventilator-associated pneumonia was no longer statistically significant.[63]

5.2.3. Chronic respiratory diseases and probiotics

Patients with chronic lung diseases, such as COPD or bronchiectasis, often receive recurrent antibiotic courses for infections and may also benefit from probiotic interventions. While data in MRSA-specific chronic infections are absent, parallel research in COPD is illustrative. A recent pilot RCT in moderate-to-severe COPD patients prone to exacerbations tested a 3-month course of *L. rhamnosus GG* against standard care.[65] The probiotic group experienced a significantly longer time to next acute exacerbation compared to controls (median ~249 days vs. 198 days, $p = 0.017$).[65] This suggests that modulating the gut microbiome can reduce the frequency of lung exacerbations, possibly by dampening systemic inflammation or enhancing mucosal immunity in the airways. Notably, all patients in that trial also received influenza and pneumococcal vaccination per guidelines, and the probiotics' added benefit was observed on top of optimal preventive care.[65] While COPD exacerbations are not the same as MRSA pneumonia, both involve an interplay between lung pathogens, host immunity, and often broad-spectrum antibiotics for treatment. The COPD study hints that probiotics could confer resilience against respiratory infections or help maintain remission by means of the gut–lung immune cross-talk. Any extrapolation to MRSA should be made cautiously, but one can hypothesize that a patient recovering from MRSA pneumonia (who may be colonized with MRSA in the gut or airways) could potentially benefit from a probiotic's capacity to restore commensal microbiota and reduce pathogen colonization. In fact, a fascinating line of research has shown that certain probiotics might directly target *S. aureus* colonization. In a 2023 phase II trial, healthy adults colonized with *S. aureus* (including MRSA strains) were given an oral *Bacillus subtilis* probiotic for one month. The probiotic markedly reduced *S. aureus* carriage, eliminating >95% of intestinal colonization and about 65% of nasal colonization compared to placebo.[66]

5.3. Safety and efficacy of probiotics in combination with antibiotics

Across numerous trials, probiotics have demonstrated a strong safety profile when given alongside antibiotics. Meta-analyses report no increase in overall adverse effects with probiotics. For example, in the adult AAD meta-analysis above, the pooled adverse-event rate was identical in probiotic and placebo groups (RR ≈1.00, 95% CI 0.87–1.14).[67] Similarly, the Cochrane review found that probiotic users had no significant excess of minor AEs (RR ≈0.86, 95% CI 0.72–1.01) compared to controls.[52] The most commonly reported effects in both groups were mild gastrointestinal symptoms (bloating, abdominal cramps, flatulence), which were generally infrequent and self-limited. Critically, systematic reviews of ICU and pediatric ICU trials report that no serious adverse effects (*e.g.*, probiotic-associated bacteremia or sepsis) were observed in any randomized study arms.[60,64] For example, a review of critically ill children noted marked reductions in nosocomial pneumonia with probiotics and found that

no adverse effects specifically attributable to the probiotics used (sepsis, bacteremia, *etc*.) were reported in the RCTs.[68]

Large-scale analyses also reinforce probiotic safety. In healthy and ambulatory patients, case reports of probiotic-related bloodstream infection are exceedingly rare. Only isolated instances of *Lactobacillus* or *Bifidobacterium* bacteremia have been documented, almost exclusively in severely immunocompromised or ICU patients with indwelling catheters. In contrast, the vast majority of subjects in clinical trials (even in ICU settings) tolerated probiotics without incident. Furthermore, in critically ill populations where gut translocation is a concern, a recent meta-analysis found that probiotics modestly reduced ICU-acquired infections (RR 0.73, 95% CI 0.58–0.93)[69] without increasing mortality (RR 1.13, 95% CI 0.82–1.55) or diarrhea.

Nevertheless, prudence is warranted in certain high-risk groups. As summarized in pediatric guidelines and Cochrane reviews, no serious probiotic-attributable events were seen in trials of generally healthy children,[70] but a few observational reports describe invasive infections (fungemia or bacteremia) in severely immunodeficient infants or those with central venous catheters. Thus, recommendations often advise avoiding live probiotics in profound neutropenia or shortly after major gastrointestinal surgery. Beyond these rare exceptions, the risk–benefit balance strongly favors probiotic use when the goal is to prevent antibiotic-associated gastrointestinal complications. In practice, probiotics have been co-administered with broad-spectrum antibiotics in countless patients with good tolerability. No adverse drug–probiotic interaction is evident in the literature; on the contrary, studies indicate that probiotics remain active and can engraft even during antibiotic therapy if high enough doses and resistant strains are used.

6. Future directions and limitations

Despite the increasing interest in microbiome-based interventions, significant knowledge gaps persist regarding the role of probiotics in the management of drug-resistant respiratory infections, particularly MRSA-associated pulmonary disease. Most existing studies have focused on gastrointestinal outcomes or heterogeneous, non-MRSA populations, whereas MRSA-specific randomized clinical trials and mechanistic human studies exploring gut–lung immune crosstalk remain limited. Furthermore, substantial heterogeneity in probiotic strains, formulations, dosing schedules, and reported outcomes has impeded the development of standardized, evidence-based clinical recommendations.

Future research should prioritize rigorously designed, randomized controlled trials explicitly enrolling patients with confirmed MRSA respiratory infections. Primary clinical outcomes should be clearly defined and may include time to clinical resolution, duration of antibiotic therapy, rates of microbiological clearance, frequency of infection recurrence, and incidence of antibiotic-related adverse effects. Secondary outcomes could encompass changes in pulmonary function parameters, length of hospital stay, and patient-reported respiratory symptom scores.

To enhance mechanistic insight, future trials should incorporate translational endpoints aimed at elucidating gut–lung axis interactions. These may include quantitative assessment of microbial-derived metabolites (such as SCFAs), longitudinal profiling of systemic and airway inflammatory markers, and immunophenotyping of key innate and adaptive immune cell subsets in peripheral blood and bronchoalveolar lavage fluid. Comparative evaluation of probiotic administration strategies—such as concurrent supplementation with anti-MRSA antibiotics versus post-antibiotic recovery protocols—should also be systematically addressed. Finally, stratification of study populations based on clinically relevant subgroups, including age, baseline disease severity, antibiotic class exposure, and immunological status, is strongly recommended to improve interpretability, identify responders, and facilitate translation into personalized therapeutic approaches.

Despite the potential benefits, several limitations and areas of ongoing debate should be acknowledged. Rare cases of probiotic-associated bacteremia or fungemia have been reported, particularly in critically ill or immunocompromised patients, warranting cautious use in high-risk populations. In addition, the efficacy of probiotics may be influenced by concurrent antibiotic regimens, as certain antibiotics can impair probiotic viability, colonization, and functional activity. Variability in host factors, including age, comorbidities, and baseline microbiome composition, may further contribute to heterogeneous clinical responses. These considerations highlight the need for careful patient selection and antibiotic–probiotic compatibility assessment in future studies.

7. Conclusion

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a leading cause of severe respiratory infections and frequently necessitates intensive antibiotic therapy, which can disrupt gut microbiota and result in clinically relevant gastrointestinal complications. Accumulating evidence suggests that antibiotic-induced dysbiosis may also

influence pulmonary immunity through the gut–lung axis, thereby potentially modulating respiratory inflammation and infection outcomes.

Probiotics represent a theoretically sound and biologically plausible adjunctive intervention, capable of restoring microbial balance, reinforcing intestinal barrier integrity, and modulating host immune responses. However, it is important to emphasize that direct clinical evidence supporting probiotic use specifically in MRSA-associated pneumonia remains limited, and current conclusions rely largely on preclinical studies, indirect clinical data, and mechanistic insights. While these findings are suggestive rather than definitive, they support the rationale for further investigation. Overall, probiotics may offer a supportive strategy to improve gastrointestinal tolerance to anti-MRSA antibiotic regimens and to promote immune homeostasis, but their clinical efficacy in MRSA respiratory infections has yet to be firmly established. Carefully designed MRSA-specific clinical trials are required to clarify their therapeutic role, define optimal usage, and generate evidence-based clinical guidance.

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