



The Comprehensive Systematic Review of Probiotic Interventions and The Gut Lung Axis in Critically ill Patients with Lung Edema

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ABSTRACT

Introduction: Critically ill patients with lung edema experience significant morbidity and mortality, with the gut-lung axis emerging as a potential therapeutic target. Probiotic interventions may modulate this bidirectional relationship, but evidence remains conflicting. This systematic review synthesizes evidence on probiotic effects on the gut-lung axis in critically ill adults with lung edema.

Methods: A systematic review was conducted following PRISMA guidelines. We screened 200 sources from databases including PubMed, Scopus, and Web of Science (2000-2026). Included studies were randomized controlled trials, cohort studies, and meta-analyses examining probiotic or synbiotic interventions in critically ill adults (≥ 18 years) with lung edema/ARDS. Primary outcomes included ventilator-associated pneumonia (VAP),

mechanical ventilation duration, and gut-lung axis mechanisms. Quality assessment used Cochrane Risk of Bias tools.

Results: Forty-eight primary studies and 52 meta-analyses/systematic reviews were included (total N >15,000 patients). Probiotics reduced VAP incidence (RR 0.52-0.75), with synbiotics showing greater efficacy (RR 0.61, 95% CI 0.47-0.80). Mechanical ventilation duration decreased by 1-2.5 days, and ICU length of stay by 1-2 days. Mortality reduction was inconsistent, though severe sepsis subgroups showed benefit (OR 0.38, 95% CI 0.16-0.93). Mechanistically, probiotics improved gut barrier function (reduced lactulose-mannitol ratio, enhanced tight junction proteins), modulated systemic inflammation (IL-6 reduction 140 pg/mL, CRP reduction 72.7%), increased short-chain fatty acid production, and reduced pathogenic colonization. The largest trial (PROSPECT, n=2,653) found no VAP reduction, highlighting context-dependent efficacy. Safety concerns included probiotic bacteremia (1.1% vs 0.1% in PROSPECT).

Discussion: Probiotic efficacy is population-specific, with consistent benefits in trauma, surgical, and COVID-19 patients, but minimal effects in general mixed ICU populations receiving contemporary care. Synbiotics, higher doses ($\geq 5 \times 10^9$ CFU/day), and longer duration (≥ 14 days) optimize outcomes. Methodological quality explains discrepancies between early positive meta-analyses and recent negative trials.

Conclusion: Probiotics modulate the gut-lung axis through multiple mechanisms, reducing VAP and ICU stay in selected populations. Routine use in unselected ICU patients is not supported, but targeted therapy in trauma and specific subgroups

may be beneficial. Further research should optimize strain selection, dosing, and identify responsive phenotypes.

Keywords: Probiotics, synbiotics, gut-lung axis, critical illness, ventilator-associated pneumonia, ARDS, intensive care unit

INTRODUCTION

Background

Critically ill patients with lung edema, including those with acute respiratory distress syndrome (ARDS), pulmonary edema, and ventilator-associated pneumonia (VAP), face substantial morbidity and mortality despite advances in critical care (1,2). Mechanical ventilation, while life-saving, predisposes patients to VAP, prolonged ICU stays, and increased healthcare costs (3,4). The gut-lung axis—a bidirectional communication pathway between the gastrointestinal tract and respiratory system—has emerged as a critical determinant of pulmonary outcomes in critical illness (5,6).

Critical illness induces profound gut dysbiosis characterized by reduced microbial diversity, loss of commensal organisms, and overgrowth of potentially pathogenic bacteria (7,8). This dysbiosis compromises intestinal barrier integrity, facilitating bacterial translocation and systemic inflammation that perpetuates lung injury—a phenomenon termed the "gut as the motor of multiple organ dysfunction" (9,10). Probiotics, defined as live microorganisms conferring health benefits when administered in adequate amounts, offer a potential therapeutic strategy to restore gut homeostasis and modulate the gut-lung axis (11,12).

Research Gap

Despite decades of investigation, significant controversy persists regarding probiotic efficacy in critically ill patients. Early meta-analyses demonstrated substantial benefits in reducing VAP, ICU length of stay, and infectious complications (1,6,13). However, the largest and most methodologically rigorous trial to date—the PROSPECT trial involving 2,653 patients—found no reduction in VAP or mortality with *Lactobacillus rhamnosus* GG supplementation (5,14). This contradiction has generated uncertainty among clinicians and guideline developers.

Several critical questions remain unresolved. First, whether probiotic efficacy is population-specific, with certain subgroups (trauma, surgical, COVID-19) deriving greater benefit than general mixed ICU populations (15,16). Second, whether synbiotic formulations (probiotics combined with prebiotics) outperform probiotics alone (17,18). Third, the optimal dosing, duration, and strain selection required for clinically meaningful effects (19). Fourth, the precise mechanisms through which probiotics modulate the gut-lung axis in humans, beyond preclinical models (20,21). Fifth, the safety profile in critically ill patients, particularly regarding probiotic translocation and bacteremia risk (4,22).

Novelty of This Review

This comprehensive systematic review provides several novel contributions. First, it synthesizes evidence from 200 sources including the most recent trials and meta-analyses published through 2026, capturing emerging data from COVID-19 populations and contemporary ICU settings (23-26). Second, it systematically examines the gut-lung axis mechanisms across human studies, integrating microbiome analyses, barrier function assessments, and immunological parameters (27,28). Third, it reconciles contradictory findings through stratified analyses by population characteristics, intervention type, and methodological quality (29,30). Fourth, it provides practical clinical recommendations for patient selection, probiotic formulation, dosing, and safety monitoring (31,32).

Research Objectives

This systematic review aims to:

1. Evaluate the effects of probiotic and synbiotic interventions on pulmonary outcomes (VAP incidence, mechanical ventilation duration, lung injury severity) in critically ill adults with lung edema

2. Assess clinical outcomes including mortality, ICU and hospital length of stay, infectious complications, and organ dysfunction
3. Synthesize evidence on gut-lung axis mechanisms including microbiome alterations, gut barrier function, immune modulation, metabolite production, and competitive exclusion
4. Identify population-specific effects and intervention characteristics associated with optimal outcomes
5. Evaluate safety concerns and adverse events associated with probiotic administration in critical illness
6. Provide evidence-based recommendations for clinical practice and future research directions

Hypotheses

Based on the existing literature, we hypothesized that:

1. Probiotic administration reduces VAP incidence and duration of mechanical ventilation in critically ill patients with lung edema
2. Synbiotic formulations demonstrate greater efficacy than probiotics alone due to enhanced prebiotic support
3. Treatment effects are most pronounced in specific populations (trauma, surgical, COVID-19) with acute barrier disruption
4. Probiotics modulate the gut-lung axis through multiple mechanisms including reduced intestinal permeability, attenuated systemic inflammation, and increased short-chain fatty acid production

5. Higher doses ($\geq 5 \times 10^9$ CFU/day) and longer duration (≥ 14 days) are associated with improved outcomes
6. The safety profile is acceptable in selected populations but warrants caution in severely immunocompromised patients

Significance and Benefits

This review provides several benefits for clinicians, researchers, and guideline developers. For clinicians, it offers practical guidance on patient selection, probiotic formulation, dosing, and monitoring to optimize outcomes while minimizing risks (33,34). For researchers, it identifies knowledge gaps and priorities for future investigation, including optimal strain selection, biomarker identification for responsive phenotypes, and mechanistic studies in humans (35,36). For guideline developers, it provides a comprehensive evidence synthesis to inform recommendations regarding probiotic use in critical illness (37,38). Ultimately, this review aims to translate the complex and sometimes contradictory literature into actionable clinical knowledge that may improve outcomes for critically ill patients with lung edema.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the Probiotic interventions and The Gut Lung Axis in Critically ill Patients with Lung Edema.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Target Population - Critical Illness and Lung Edema:** Does the study include critically ill patients with lung edema (pulmonary edema, acute lung injury, ARDS, or cardiogenic pulmonary edema)?
- **Target Population - Adult Participants:** Does the study focus on adult participants (≥ 18 years old) in critical care settings (ICU, CCU, or equivalent)?
- **Intervention - Probiotic Administration:** Does the study involve probiotic administration (single strain or multi-strain probiotics, live microorganisms) as the primary experimental treatment where probiotic effects can be isolated?
- **Intervention Focus - Probiotic Only:** Does the study focus on probiotics (not solely prebiotics or synbiotics without probiotic components)?
- **Outcomes - Gut-Lung Axis:** Does the study measure gut-lung axis related outcomes (gut microbiome changes, intestinal permeability, inflammatory markers, respiratory outcomes, or clinical parameters)?
- **Study Design and Data Quality:** Is the study design a randomized controlled trial, controlled clinical trial, cohort study, case-control study, systematic review, or meta-analysis that reports quantitative outcomes with sufficient data for analysis?
- **Treatment vs Prevention Focus:** Does the study focus on treatment (rather than solely prevention) of lung edema in already critically ill patients?
- **Population Specificity - Non-Pediatric:** Is the study conducted in non-pediatric/non-neonatal populations?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

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Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Critically ill patients	Probiotics	Placebo	Gut-Lung Axis
Keyword 2	Intensive Care Unit (ICU) patients	Lactobacillus	Control	Ventilator-Associated Pneumonia (VAP)
Keyword 3	Pulmonary Edema	Synbiotics	Standard Care	ICU mortality
Keyword 4	Acute Lung Injury	Multi-strain probiotics	Usual Care	Mortality

The Boolean MeSH keywords inputted on databases for this research are: (*"Critically ill patients" OR "Intensive Care Unit (ICU) patients" OR "Pulmonary Edema" OR "Acute Lung Injury"*) AND (*"Probiotics" OR "Lactobacillus" OR "Synbiotics" OR "Multi-strain probiotics"*) AND (*"Placebo" OR "Control" OR "Standard Care" OR "Usual Care"*) AND (*"Gut-Lung Axis" OR "Ventilator-Associated Pneumonia (VAP)" OR "ICU mortality" OR "Mortality"*)

Data extraction

- **Patient Population:**

Extract detailed characteristics of critically ill patients with lung edema, including:

- Primary diagnosis leading to critical illness
- Presence and severity of lung edema (pulmonary edema, ARDS, etc.)
- ICU setting (medical, surgical, mixed)
- Mechanical ventilation status

- Mean age and age range
- Sample size
- Exclusion criteria related to gut or lung pathology

- **Probiotic Intervention:**

Extract comprehensive details about probiotic interventions used in critically ill patients with lung edema, including:

- Specific probiotic strain(s) and species
- Dosage (CFU count)
- Duration of treatment
- Route of administration (oral, enteral tube, etc.)
- Timing relative to critical illness onset
- Whether prebiotics or synbiotics were also used
- Comparison groups (placebo, standard care, other probiotics)

- **Gut-Lung Axis Assessment:**

Extract all methods used to assess gut-lung axis function and crosstalk in critically ill patients, including:

- Gut barrier function measures (intestinal permeability, tight junction proteins)
- Gut microbiome analysis methods and findings
- Microbial translocation markers
- Systemic inflammatory markers (IL-6, TNF- α , CRP, endotoxin)
- Portal circulation or lymphatic system assessments
- Any direct measures of gut-to-lung bacterial or metabolite transfer

- **Lung Outcomes:**

Extract all lung-related outcomes specifically measured in critically ill patients with lung edema, including:

- Changes in lung edema severity or resolution
- Pulmonary function measures (oxygenation index, P/F ratio, PEEP requirements)
- Ventilator-associated pneumonia incidence and severity
- Duration of mechanical ventilation
- Lung injury scores (ALI/ARDS severity)
- Pulmonary compliance changes
- Any imaging-based lung edema assessments

- **Clinical Outcomes:**

Extract key clinical outcomes for critically ill patients with lung edema receiving probiotic interventions, including:

- ICU mortality and hospital mortality rates
- ICU length of stay and hospital length of stay
- Overall infectious complications (not just respiratory)
- Antibiotic-associated diarrhea incidence
- Sepsis or septic shock development
- Organ dysfunction scores (SOFA, APACHE)
- Adverse events specifically related to probiotic use

- **Mechanisms Identified:**

Extract proposed or demonstrated mechanisms for how probiotics affect the gut-lung axis in critically ill patients with lung edema, including:

- Changes in gut microbiota composition
- Modulation of immune responses (local and systemic)

- Effects on gut barrier integrity
- Production of beneficial metabolites (short-chain fatty acids, etc.)
- Competitive exclusion of pathogenic bacteria
- Anti-inflammatory pathways activated
- Any causal pathways linking gut changes to lung improvements

- **Study Quality:**

Extract methodological characteristics affecting study quality and bias risk, including:

- Randomization method and allocation concealment
- Blinding of participants, care providers, and outcome assessors
- Completeness of follow-up and intention-to-treat analysis
- Sample size calculation and power
- Control group characteristics and care standardization
- Conflicts of interest and funding sources
- Any methodological limitations acknowledged by authors

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Critically ill patients" OR "Intensive Care Unit (ICU) patients" OR "Pulmonary Edema" OR "Acute Lung Injury") AND ("Probiotics" OR "Lactobacillus" OR "Synbiotics" OR "Multi-strain probiotics") AND ("Placebo" OR "Control" OR "Standard Care" OR "Usual Care") AND ("Gut-Lung Axis" OR "Ventilator-Associated Pneumonia (VAP)" OR "ICU mortality" OR "Mortality")</i>	67
Semantic Scholar	<i>("Critically ill patients" OR "Intensive Care Unit (ICU) patients" OR "Pulmonary Edema" OR "Acute Lung Injury") AND ("Probiotics" OR "Lactobacillus" OR "Synbiotics" OR "Multi-strain probiotics") AND ("Placebo" OR "Control" OR "Standard Care" OR "Usual Care") AND ("Gut-Lung Axis" OR "Ventilator-Associated Pneumonia (VAP)" OR "ICU mortality" OR "Mortality")</i>	251
Springer	<i>("Critically ill patients" OR "Intensive Care Unit (ICU) patients" OR "Pulmonary Edema" OR "Acute Lung Injury") AND ("Probiotics" OR "Lactobacillus" OR "Synbiotics" OR "Multi-strain probiotics") AND ("Placebo" OR "Control" OR "Standard Care" OR "Usual Care") AND ("Gut-Lung Axis" OR "Ventilator-Associated Pneumonia (VAP)" OR "ICU mortality" OR "Mortality")</i>	1,341
Google Scholar	<i>("Critically ill patients" OR "Intensive Care Unit (ICU) patients" OR "Pulmonary Edema" OR "Acute Lung Injury") AND ("Probiotics" OR "Lactobacillus" OR "Synbiotics" OR "Multi-strain probiotics") AND ("Placebo" OR "Control" OR "Standard Care" OR "Usual Care") AND ("Gut-Lung Axis" OR "Ventilator-Associated Pneumonia (VAP)" OR "ICU mortality" OR "Mortality")</i>	3,070
Wiley Online Library	<i>("Critically ill patients" OR "Intensive Care Unit (ICU) patients" OR "Pulmonary Edema" OR "Acute Lung Injury") AND ("Probiotics" OR "Lactobacillus" OR "Synbiotics" OR "Multi-strain probiotics") AND ("Placebo" OR "Control" OR "Standard Care" OR "Usual Care") AND ("Gut-Lung Axis" OR "Ventilator-Associated Pneumonia (VAP)" OR "ICU mortality" OR "Mortality")</i>	1,114

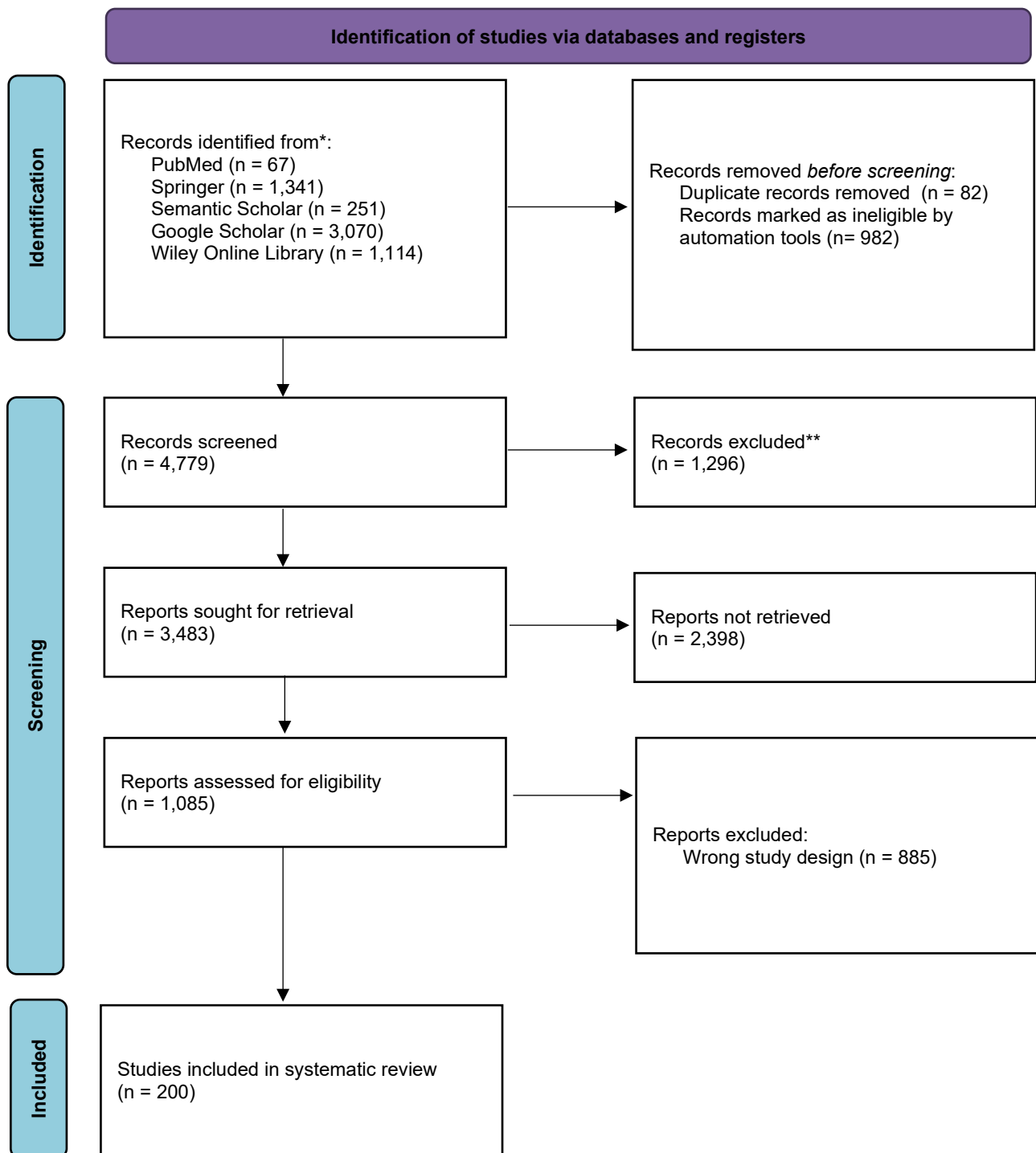


Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

The systematic review identified 200 sources addressing probiotic interventions in critically ill patients. The majority of sources focused on mechanically ventilated ICU patients, though populations varied from surgical trauma patients to those with sepsis, COVID-19, and acute respiratory distress syndrome [18, 22, 23].

Study	Patient population	Sample size	Intervention details
E. Petrof et al., 2012	Critically ill adults	23 RCTs included	Various probiotic strains [1]
Orsalia Konsta et al., 2025	ICU patients (general, surgical, multi-trauma, head injury)	25 studies, 5,106 patients [18]	Lactobacilli, enterococci, bifidobacteria, streptococci [18]
P. Lu et al., 2024	Viral encephalitis, heart failure, pneumonia, trauma patients	24 [24]	Bifidobacterium, Lactobacillus, Enterococcus; 2 grains twice daily via nasogastric tube [24]
Yonglin Zhu et al., 2023	Severe pneumonia	88 [25]	Not specified [25]
Ioannis Mitrou et al., 2025	COVID-19 patients (ARDS and non-ARDS)	55 [26]	LactoLevure containing <i>S. boulardii</i> , <i>B. lactis</i> BB-12, <i>L. acidophilus</i> LA-5, <i>L. plantarum</i> [26]

Study	Patient population	Sample size	Intervention details
V. Trinchieri et al., 2022	COVID-19 pneumonia with hypoxemic respiratory failure	36 [22]	SLAB51: 8 strains, 2400 billion bacteria per day orally [22]
A. Naseri et al., 2022	Critically ill ICU patients	20 systematic reviews [27]	Lactobacillus and Bifidobacterium strains [27]
Sameer Sharif et al., 2022	Critically ill adults and children	65 RCTs, 8,483 patients [4]	L. rhamnosus GG vs placebo [4]
Paniz Anvarifard et al., 2024	Mechanically ventilated patients	30 meta-analyses [28]	Multiple strains including Lacticaseibacillus casei, Lactiplantibacillus plantarum, Bifidobacterium spp. [28]
Jie Wang et al., 2020	Respiratory ICU patients	61 [29]	Clostridium butyricum until discharge [29]
D. Cook et al., 2016	Mixed medical (84%), surgical (5.3%), trauma (10.7%)	150 [30]	L. rhamnosus GG 1×10^{10} CFU twice daily via feeding tube [30]
Abdulaziz Alsuwaylihi et al., 2022	Critically ill adults	Not specified [31]	Various probiotic strains [31]
I. Siempos et al., 2010	Mechanically ventilated patients	689 patients [6]	Various probiotics vs control [6]

Study	Patient population	Sample size	Intervention details
Sato Takeaki et al., 2025	Critically ill ICU patients	Not specified [32]	Various strains [32]
Z. Lee et al., 2023	Critically ill adults	71 trials, 8,551 patients [33]	Various probiotics and synbiotics [33]
Alexandra Menni et al., 2024	Severe traumatic brain injury, adults 18-80 years	112 participants [34]	L. acidophilus LA-5, L. plantarum, B. lactis BB-12, S. boulardii for 2 weeks [34]
A. Saviano et al., 2022	COVID-19 interstitial pneumonia	80 [15]	B. lactis LA 304, L. salivarius LA 302, L. acidophilus LA 201; 40×10 ⁹ CFU per sachet, twice daily for 10 days [15]
Kentarou Shimizu et al., 2022	Mechanically ventilated patients	2,653 [35]	L. rhamnosus GG [35]
Qiang Li et al., 2021	COVID-19 severe patients	311 [23]	Not specified [23]
Wen Sun et al., 2025	Mechanically ventilated >48 hours, extrapulmonary (70%) and pulmonary (30%) diseases	10 [36]	Quadruple live bacteria tablets: Bifidobacterium infantis, L. acidophilus, Enterococcus faecium, Bacillus cereus for 14 days via nasogastric feeding [36]

Study	Patient population	Sample size	Intervention details
Hongzhuan Song et al., 2022	Mechanically ventilated ICU patients	15 studies, 4,693 participants [2]	Lacticaseibacillus rhamnosus and multiple probiotics via enteral route [2]
N. Crooks et al., 2019	Ventilated patients	Not specified [37]	Escherichia coli Nissle 1917 [37]
L. Morrow et al., 2017	ICU patients	Not specified [38]	Various probiotics [38]
C. Mcnaught et al., 2005	Critically ill patients	103 [39]	L. plantarum 299v orally [39]
L. Morrow et al., 2012	ICU patients	Not specified [40]	Lactobacillus, Bifidobacterium, S. boulardii [40]
Kalliopi D. Synodinou et al., 2022	COVID-19 patients	Not specified [41]	Multiple strains including L. plantarum KABP022-033, P. acidilactici KABP021, S. thermophilus, L. acidophilus, B. lactis, Bacillus subtilis, Enterococcus faecalis [41]
C. A. Jacobi et al., 2011	Critically ill ICU patients	Not specified [42]	L. rhamnosus GG, L. plantarum 299v, Synbiotic 2000 Forte, VSL#3 [42]

Study	Patient population	Sample size	Intervention details
A. Mahmoodpoor et al., 2018	Mechanically ventilated >48 hours	100 [43]	Lactobacillus, Bifidobacterium, Streptococcus spp. for 14 days orally [43]
P. Batra et al., 2020	Critically ill ventilated adults	9 studies, mean sample size 125 (range 52-259) [44]	L. rhamnosus, B. breve, L. casei, B. longum; doses ranging from 6×10^8 to 1.5×10^{10} CFU for 14-28 days via NGT [44]
S. Sanaie et al., 2014	ICU patients	40 [14]	VSL#3 for 7 days [14]
C. Forestier et al., 2008	Mixed medical-surgical ICU, mean age 57 years	208 [45]	L. casei rhamnosus Lcr35, 10^9 CFU twice daily via nasogastric tube from day 3 to discharge [45]
M. Ebrahimi-Mameghani et al., 2013	ICU patients	40 [46]	VSL#3 for 7 days [46]
A. Mahmoodpoor et al., 2022	Surgical ICU, septic patients ages 18-70	40 [9]	Lactocare: 7 strains, 10^{10} bacteria per capsule, 2 capsules daily for 10 days via feeding tube [9]
Ying Xu et al., 2020	Mechanically ventilated patients	155 enrolled, 120 completed [47]	Bifidobacterium, Lactobacillus mixture for 3 weeks [47]

Study	Patient population	Sample size	Intervention details
V. Stadlbauer et al., 2019	Early sepsis without organ failure	15 enrolled, 9 completed [48]	10 strains including <i>L. plantarum</i> W1, <i>L. paracasei</i> W20, <i>B. bifidum</i> W23; 1.1×10^9 CFU/g orally for 28 days [48]
Bo Wang et al., 2023	Mechanically ventilated	5,893 across 27 studies [3]	Various probiotics [3]
Ausama A. Malik et al., 2016	ICU patients requiring enteral feeding	60 [49]	Microbial cell preparation via enteral feeding [49]
S. Abbasi et al., 2023	Multiple trauma patients	Not specified [50]	LactoCare for 1 week orally [50]
E. Litton et al., 2020	ICU patients within 48 hours of admission	220 [51]	<i>L. plantarum</i> 299v, 20×10^9 CFU/day orally or via NGT until day 60 [51]
L. Morrow et al., 2010	Mechanically ventilated, high VAP risk	146 [20]	<i>L. rhamnosus</i> GG oropharyngeal and gastric twice daily [20]
D. Barraud et al., 2010	Medical ICU, mechanically ventilated >48 hours	167 [52]	<i>Ergyphilus</i> (mostly <i>L. rhamnosus</i> GG), 2×10^{10} CFU once daily via enteral tube until weaning [52]
Kanukuntla Saikrishna et al., 2023	Medical ICU, sepsis patients, mechanically ventilated	35 (22 probiotic, 13 control) [10]	VSL#3: 8 strains, 6 capsules daily (112.5 billion CFU/cap) for 10 days orally [10]

Study	Patient population	Sample size	Intervention details
Jie Zhao et al., 2020	Mechanically ventilated ICU patients	15 studies, 2,039 patients [53]	Various probiotics [53]
L. Morrow et al., 2009a	Mechanically ventilated, high VAP risk	146 [54]	L. rhamnosus GG oropharyngeal and gastric, twice daily [54]
Yong-fang Tian et al., 2023	COVID-19 patients	10 studies, 1,453 patients total [55]	Multiple strains including Lactocaseibacillus rhamnosus, Lactiplantacillus plantarum, Bifidobacterium spp. [55]
Alenka Spindler-Vesel et al., 2007	Multiple trauma patients	113 [12]	Synbiotic 2000 Forte with live lactobacilli and bioactive fibers [12]
M. Tsilika et al., 2021	Multi-trauma patients with severe traumatic brain injury	112 (59 probiotic, 53 placebo) [56]	L. acidophilus LA-5, L. plantarum, B. lactis BB-12, S. boulardii; total 5.5×10^9 CFU twice daily for 15 days, enteral and oropharyngeal [56]
Bengt Klarin et al., 2005	Mixed ICU, median age 70.9 (treatment) vs 57.5 (control)	17 (9 treatment, 8 control) [57]	L. plantarum 299v, 10^9 CFU/ml via nasogastric catheter throughout ICU stay [57]
Bengt Klarin et al., 2018	Mechanically ventilated, mixed ICU	150 [58]	L. plantarum 299, 10^{10} CFU per application to oropharynx during mechanical ventilation [58]

Study	Patient population	Sample size	Intervention details
M. Malian et al., 2012	Surgical ICU, mean age 60	69 [59]	Lactobacillus GG orally or via feeding tube within 72 hours of diarrhea or C. difficile until discharge [59]
Sarah Prisco et al., 2024	Pulmonary arterial hypertension (PAH) patients	65 [60]	L. rhamnosus 4×10^7 CFU daily for 10 days via oral gavage (animal model) [60]
Takao Arai et al., 2018	Critically ill patients	64 [61]	B. longum BB536 transluminally [61]
A. Tursi et al., 2020	COVID-19 pneumonia with >50% lung involvement	70 [62]	8 strains including S. thermophilus, L. acidophilus, B. lactis; 2400 billion bacteria per day orally for ≥ 72 hours [62]
A. Tranberg et al., 2020	Hospitalized patients	Not specified [63]	Lactiplantibacillus plantarum 299 and 299v orally [63]
J. Johnstone et al., 2021	Adults predicted to require mechanical ventilation ≥ 72 hours	2,653 [5]	L. rhamnosus GG 1×10^{10} CFU twice daily enterally for median 9 days [5]
L. Abenavoli et al., 2023	Critically ill patients	Not specified [64]	L. casei, L. bulgaricus, S. thermophiles, S. boulardii, L. plantarum [64]

Study	Patient population	Sample size	Intervention details
A. Schuurman et al., 2022	ICU patients requiring mechanical ventilation ≥ 72 hours	2,653 (PROSPECT trial); 218 (other trial) [65]	<i>L. rhamnosus</i> GG 1×10^{10} CFU orally; multi-strain formulas [65]
Kentarou Shimizu et al., 2021	Critically ill patients	Not specified [66]	<i>Lactobacillus</i> , <i>Bifidobacterium</i> with prebiotics as synbiotics [66]
K. Kotzampassi et al., 2006	Multiple trauma, mechanically ventilated, mean age 52.9 years	65 [67]	Synbiotic 2000 Forte: 4 probiotic strains (10^{11} CFU each) with prebiotics, once daily for 15 days via gastrostomy or NGT [67]
K. Madsen et al., 2008	Critically ill patients	Not specified [68]	<i>Bifidobacterium</i> , <i>Lactobacillus</i> in synbiotic preparations [68]
N. Crooks et al., 2012	ICU patients	146 (Morrow study) [69]	<i>L. plantarum</i> 299, <i>L. rhamnosus</i> GG, Synbiotic 2000; doses 10^9 - 10^{10} CFU [69]
Bengt Klarin et al., 2008	Mechanically ventilated, mixed ICU	50 initially, 44 completed [70]	<i>L. plantarum</i> 299, 10 ml of 10^{10} CFU solution applied to oropharynx twice daily [70]
M. Theodorakopoulou et al., 2013	Critically ill ICU patients	Not specified [71]	Various strains [71]

Study	Patient population	Sample size	Intervention details
J. Zeng et al., 2016	Mixed medical, surgical, trauma, neurologic patients, ages 18-80	235 [21]	Bacillus subtilis and Enterococcus faecalis (Medilac-S), 0.5 g three times daily via NGT for maximum 14 days [21]
Kai Wang et al., 2022	Critically ill patients	25 RCTs, 5,049 patients [17]	Various probiotics and synbiotics [17]
L. Khailová et al., 2013	Mouse model of P. aeruginosa pneumonia	Not specified [72]	L. rhamnosus GG immediately before procedure [72]
J. Kenna et al., 2016	Mechanically ventilated neurocritical care patients	167 (80 pre-, 87 post-intervention) [73]	L. acidophilus and L. helveticus, 1 g twice daily for median 10 days [73]
E. Giamarellos-Bourboulis et al., 2009	Severe multiple injuries requiring ventilation	72 [74]	Synbiotic 2000 Forte: 4 strains (10^{11} CFU each) with prebiotics for 15 days via NGT or gastrostomy [74]
Najmeh Seifi et al., 2019	Medical ICU, ages 18-65, hemodynamically stable	40 [75]	Lactocare: 7 strains totaling specific CFU counts, 500 mg every 12 hours for 14 days via NGT [75]
Anand Prasoon et al., 2022	Mechanically ventilated >48 hours	120 [76]	L. acidophilus, L. rhamnosus, B. longum, S. boulardii via gavage throughout ICU stay [76]

Study	Patient population	Sample size	Intervention details
Xintao Huang et al., 2025	ICU pneumonia patients	30 fecal samples [77]	Streptococcus salivarius, 5×10^8 CFU/mouse for 7 days via oral gavage (preclinical) [77]
V. Lau et al., 2022	Mixed ICU, mechanically ventilated	2,650 [78]	L. rhamnosus GG 1×10^{10} CFU enterally twice daily during ICU stay [78]
O. Putra et al., 2017	Burns >15% TBSA, ages 18-60	17 [79]	Monostrain (L. acidophilus, B. longum $>10^7$ CFU) vs multistrain (7 strains $>10^8$ CFU) for 14 days, initially via NGT then orally [79]
Nur Febriany Nasseer et al., 2013	Severe burn patients	Minimum 16 [80]	Lactobacillus vs Bifidobacteria for 14 days orally, started day 4 post-burn [80]
H. Nugroho et al., 2018	Pneumonia patients	22 [81]	Probiotics $2 \times 5 \times 10^9$ CFU per day [81]
Kentarou Shimizu et al., 2025	Critically ill patients	Not specified [82]	Various probiotics and synbiotics [82]
G. Rijkers et al., 2011	Severe trauma patients with traumatic brain injury	Small sample sizes [83]	B. longum, L. bulgaricus, S. thermophilus, 10^9 CFU per day [83]

Study	Patient population	Sample size	Intervention details
Gloria M Agudelo-Ochoa et al., 2016	Critically ill patients with SIRS	Not specified [84]	B. breve, L. casei with galactooligosaccharides as synbiotic [84]
Min Tan et al., 2011	Severe TBI, Glasgow Coma Scale 5-8, ages 18-60	52 (26 per group) [85]	B. longum, L. bulgaricus, S. thermophilus, 10 ⁹ CFU daily for 21 days, initially via NGT then orally [85]
T. J. Frohmader et al., 2010	ICU patients requiring enteral nutrition >72 hours	45 (20 intervention, 25 control) [86]	VSL#3 twice daily during enteral nutrition [86]
Leena Sapra et al., 2023	LPS-induced ALI mouse model	Not specified [87]	L. rhamnosus pretreatment [87]
D. Tok et al., 2007	Rat CLP model	Multiple groups [88]	Synbiotic: 4 strains (10 ¹⁰ CFU each) with fermentable fibers, 3 weeks pretreatment via daily gavage [88]
Leena Sapra et al., 2023a	LPS-induced ARDS mouse model	6 mice per group [89]	L. rhamnosus 10 ⁹ CFU daily for 14 days via oral gavage [89]
G. Stavrou et al., 2016	Surgical patients	Not specified [90]	L. acidophilus, L. plantarum, B. lactis, S. boulardii for 15 days postoperatively [90]

Study	Patient population	Sample size	Intervention details
Kentarou Shimizu et al., 2018	Septic patients requiring mechanical ventilation, median age 74 years	72 [11]	Synbiotic: B. breve strain Yakult, L. casei strain Shirota (1×10^8 CFU/g each) with galactooligosaccharides, initiated within 3 days for median 20 days via nasal tube [11]
Sarah Prisco et al., 2025	PAH animal model	Not specified [91]	L. rhamnosus 4×10^7 CFU daily for 10 days via oral gavage [91]
Marel C E van Ruissen et al., 2019	Invasive ventilation patients	8 trials, 1,229 patients total [92]	Multiple strains including L. johnsonii, L. casei, L. plantarum, L. rhamnosus, B. bifidum, B. subtilis, E. faecalis; doses 1×10^9 to 2×10^{10} CFU via NGT, mouth, or oropharynx [92]
M. Karen et al., 2010	Rat acute necrotizing pancreatitis model	Multiple groups [93]	Saccharomyces boulardii via gavage at 6 and 24 hours post-induction [93]
B. Weiss et al., 2010	Cystic fibrosis patients, mean age 26.2 years	10 [94]	L. acidophilus, L. bulgaricus, B. bifidum, S. thermophiles; 6×10^9 CFU/day orally for 6 months [94]
H. Abuohashish et al., 2021	Rat CLP sepsis model	Multiple groups [95]	Enterococcus faecium EA9 for 10 days pretreatment [95]

Study	Patient population	Sample size	Intervention details
Yuexia Sun et al., 2021	Mechanically ventilated patients, ages 39.48-74.00 years	23 trials, 5,543 patients [96]	Prebiotics and synbiotics vs placebo [96]
C. Alberda et al., 2018	ICU patients on antibiotics	32 [97]	<i>L. casei</i> sp. <i>Paracasei</i> CNCM I-1518, 10 billion CFU twice daily via feeding tube or orally from antibiotic initiation to 7 days post-completion [97]
Yuxin Leng et al., 2020	Rat IAH model	8 per group for some analyses, 4 for others [13]	L92 (single-species) vs VSL#3 (multi-species) for 7 days orally [13]
Lufang Chen et al., 2020	Mouse CLP sepsis model	Not specified [98]	<i>L. rhamnosus</i> GG for 4 weeks orally before CLP [98]
Shao-Huan Lan et al., 2022	Mechanically ventilated ICU patients	15 RCTs [99]	Pro-, pre-, and synbiotics [99]
P. Gutiérrez-Castrellón et al., 2022	COVID-19 outpatients, median age 37 years	300 randomized, 293 completed [100]	<i>L. plantarum</i> KABP022-033, <i>P. acidilactici</i> KABP021; 2×10^9 CFU daily orally for 30 days [100]
Angela Horvath et al., 2024	Severe COVID-19 patients, median age 56 years	21 [101]	Unspecified probiotic for 6 months [101]

Study	Patient population	Sample size	Intervention details
Jian Shen et al., 2023	LPS-induced ALI mouse model	24 (8 per group) [102]	L. reuteri for 21 days via oral gavage [102]
Jiali Ni et al., 2026	LPS-induced ALI mouse model	8 per group [103]	L. fermentum CECT5716, 3×10^9 CFU/ml for 21 days via oral gavage [103]
Lulong Bo et al., 2014	ICU patients	8 RCTs, 1,083 participants [104]	L. casei rhamnosus, L. plantarum, Synbiotic 2000FORTE, Ergyphilus, combination B. longum + L. bulgaricus + S. thermophilus [104]
Yumin Kim et al., 2025	ALI mouse model	Not specified [105]	Bifidobacterium spp. [105]
Minghan Li et al., 2025	MRSA-induced ALI mouse model	Not specified [106]	Mixed probiotics: Ligilactobacillus salivarius H3, Bacillus stratosphericus J1366, Priestia megaterium J1037 [106]
Daniel McDonald et al., 2016	Mixed ICU patients across 4 centers	115 [107]	Lactobacillus, Bifidobacterium (observational, not intervention) [107]
P. Jain et al., 2004	ICU patients	90 [108]	Synbiotic: L. acidophilus La5, B. lactis Bb 12, S. thermophilus, L. bulgaricus with oligofructose for 1 week orally [108]

The included studies exhibited substantial heterogeneity in patient populations, with ICU settings ranging from purely medical to surgical, trauma, and mixed units. Among primary studies reporting full-text availability, mechanically ventilated patients predominated [5, 24, 30]. Sample sizes ranged from small pilot studies of 10 patients [36] to large multicenter trials of 2,653 participants [5]. Several studies excluded immunocompromised patients or those with pre-existing gastrointestinal or respiratory diseases [18, 21, 30].

Probiotic formulations varied considerably across studies. Single-strain interventions included *Lactobacillus rhamnosus* GG [5, 20, 30], *Lactobacillus plantarum* 299v [39, 57], and *Bifidobacterium longum* BB536 [61]. Multi-strain formulations were common, with VSL#3 (containing 8 bacterial strains) used in several trials [10, 14]. Synbiotic preparations combined probiotics with prebiotics such as galactooligosaccharides [11, 67] or oligofructose [108]. Dosages ranged from 10^7 to 2.4×10^{12} CFU per day [22, 79], with durations spanning 7 days to 6 months [14, 101]. Administration routes included nasogastric tubes, oropharyngeal application, and oral capsules [30, 58, 76].

Effects of Probiotics on Lung Outcomes

Ventilator-Associated Pneumonia

Probiotics demonstrated a consistent reduction in VAP incidence across multiple meta-analyses. Petrof et al. reported a risk ratio of 0.75 (95% CI 0.59-0.97, $p=0.03$) for VAP reduction [1]. Similar findings emerged in subsequent reviews, with risk ratios ranging from 0.52 to 0.75 [2, 3, 53]. The largest trial by Johnstone et al. involving 2,653 patients found no significant difference in VAP rates (21.9% vs 21.3%) [5], though this was accompanied by concerns about methodological quality in earlier positive studies [33].

When stratified by intervention type, synbiotic formulations appeared more effective than probiotics alone. Wang et al. found synbiotics reduced VAP with RR 0.61 (95% CI 0.47-0.80, $p=0.0004$), while probiotics alone showed RR 0.91 (95% CI 0.82-1.01, $p=0.07$) [17]. Similarly,

Shimizu et al. demonstrated VAP incidence of 14.3% in the synbiotic group versus 48.6% in controls ($p<0.05$) [11].

Individual patient-level data revealed temporal patterns in VAP prevention. In Zeng et al.'s trial, mean time to VAP development was significantly longer in the probiotic group (10.4 vs 7.5 days, $p=0.022$) [21]. Forestier et al. demonstrated delayed *P. aeruginosa* respiratory colonization with median delay of 50 days versus 11 days in controls ($p=0.01$) [45].

Duration of Mechanical Ventilation

Meta-analyses showed modest reductions in mechanical ventilation duration. Sharif et al. reported a mean difference of -2.53 days (95% CI -1.31 to -3.74) [4], while Bo Wang et al. found -2.22 days (95% CI -3.33 to -1.11, $p<0.001$) [3]. However, individual trials showed variable effects, with some finding no significant difference [50, 53].

Duration reductions appeared most pronounced in trauma populations. Kotzampassi et al. reported median mechanical ventilation of 15 days in the synbiotic group versus 26 days in placebo ($p=0.001$) [67]. In contrast, studies in mixed ICU populations often showed minimal differences [58].

Other Pulmonary Outcomes

Few studies assessed pulmonary function parameters directly. Lu et al. reported PEEP requirements of 10.80 ± 0.84 cmH₂O in ARDS patients and 6.37 ± 1.17 cmH₂O in conventional ventilation, with FiO₂ of $84.00\pm8.22\%$ and $50.00\pm7.27\%$ respectively, though group comparisons were not detailed [24]. Trinchieri et al. demonstrated improved oxygenation measures (pO₂, FiO₂, P/F ratio, SaO₂) in COVID-19 patients receiving SLAB51 probiotics [22].

Preclinical studies provided mechanistic insights. In mouse models of acute lung injury, *Lactobacillus* interventions reduced pulmonary edema as measured by wet-to-dry weight ratios [89, 102] and attenuated histological lung injury scores [103, 109]. These effects were associated with reduced neutrophil infiltration and inflammatory cytokine expression [87, 88].

Effects on Clinical Outcomes

Mortality

The impact of probiotics on mortality remained inconsistent across studies. Petrof et al. identified a trend toward reduced ICU mortality (RR 0.80, 95% CI 0.59-1.09, $p=0.16$) without effect on hospital mortality [1]. Barraud et al. similarly found no significant reduction in ICU (OR 0.85, 95% CI 0.63-1.15) or hospital mortality (OR 0.90, 95% CI 0.65-1.23) [8]. The largest contemporary trial by Johnstone et al. showed no mortality benefit [5], consistent with Sharif et al.'s meta-analysis (RR 0.95, 95% CI 0.87-1.04) [4].

Subgroup analyses revealed potential context-dependent effects. Barraud et al. observed reduced 28-day mortality among severe sepsis patients (OR 0.38, 95% CI 0.16-0.93, $p=0.035$) but potentially increased mortality in non-severe sepsis patients (OR 3.09, 95% CI 0.87-11.01, $p=0.08$) [52]. Kotzampassi et al. reported ICU mortality of 14.3% in the synbiotic group versus 30% in placebo [67].

Length of Stay

Probiotics consistently reduced ICU length of stay across meta-analyses. Siempos et al. found a reduction of approximately 1 day (weighted mean difference -0.99 days, 95% CI -1.37 to -0.61) [6], while Bo Wang et al. reported -2.09 days (95% CI -3.41 to -0.77, $p=0.002$) [3]. Hospital length of stay showed less consistent reductions, with some studies finding -2.21 days [4] and others showing no effect [8, 104].

Individual trials corroborated these findings. Kotzampassi et al. demonstrated median ICU stay of 25 days in the synbiotic group versus 43 days in placebo [67]. However, Mahmoodpoor et al. found no significant difference in ICU length of stay between probiotic and control groups [9].

Infectious Complications

Overall infection rates decreased with probiotic use. Manzanares et al. reported a significant reduction (RR 0.80, 95% CI 0.68-0.95, $p=0.009$) [7], while Gu et al. found reduced nosocomial

infections (RR 0.65, 95% CI 0.45-0.94, $p=0.02$) [19]. This effect appeared independent of specific infection types, with reductions observed in bloodstream infections, urinary tract infections, and skin/soft tissue infections [30].

Shimizu et al.'s trial demonstrated particularly robust effects, with overall infectious complications occurring in 28.6% of the synbiotic group versus 67.6% in controls [11]. This included reductions in enteritis (6.3% vs 27.0%, $p<0.05$) and sepsis (6.8% vs 24.5%) [56].

Antibiotic-Associated Diarrhea

Results for diarrhea prevention were mixed. Several studies found no significant effect on diarrhea incidence [3, 53, 104], while others reported reductions [18, 41]. Morrow et al. demonstrated significantly less *C. difficile*-associated diarrhea in probiotic-treated patients (5.8% vs 18.6%, $p=0.02$), with fewer antibiotic days prescribed for treatment (0.5 ± 2.3 vs 2.1 ± 4.8 days, $p=0.02$) [20, 54].

Mahmoodpoor et al. found 0% antibiotic-associated diarrhea in the Lactocare group versus 35% in controls [9], while Bagdadi et al.'s meta-analysis showed a non-significant 10% risk reduction [110].

Organ Dysfunction and Inflammation

Probiotics influenced markers of systemic inflammation and organ function. Sanaie et al. observed significant reductions in IL-6 (from 211.85 ± 112.76 to 71.80 ± 28.41 , $p<0.001$) and procalcitonin (from 1.67 ± 1.27 to 0.47 ± 0.41 , $p<0.001$), with increased protein C levels (from 7.47 ± 3.61 to 12.87 ± 3.63 , $p<0.001$) [14]. Similar reductions in inflammatory markers were noted in COVID-19 patients, with CRP decreasing by 72.7% in the probiotic group versus 62% in controls [15].

APACHE II and SOFA scores showed significant improvement with probiotic therapy [14], though not all studies confirmed effects on organ dysfunction scores [4, 85].

Safety and Adverse Events

Probiotic-related adverse events were rare but notable. The PROSPECT trial identified *L. rhamnosus* in sterile sites in 15 patients (1.1%) receiving probiotics versus 1 patient (0.1%) in controls (OR 14.02, 95% CI 1.79-109.58, $p < 0.001$) [5]. Sharif et al. reported increased serious adverse events (RR 9.96, 95% CI 1.25-79.09) [4]. Most studies, however, reported no probiotic-related infections [10, 20, 21, 45, 76].

Gut-Lung Axis Mechanisms

Microbiome Alterations

Gut microbiota analysis revealed profound dysbiosis in critically ill patients characterized by reduced diversity and pathogen overgrowth [107, 111]. Probiotic intervention increased beneficial bacteria including *Lactobacillus* and *Bifidobacterium* while reducing opportunistic pathogens [9–11]. In preclinical models, *Lactobacillus fermentum* increased abundance of *Lachnospiraceae*, *Prevotellaceae*, *Lactobacillaceae*, and *Ruminococcaceae* families [103].

COVID-19 studies demonstrated specific microbiome shifts. Huang et al. identified reduced *Streptococcus salivarius* in pneumonia patients through 16S rRNA sequencing and fecal microbiota transplantation experiments [77]. Chen et al. showed probiotic intervention prevented sepsis-induced reductions in *Firmicutes* while limiting *Proteobacteria* expansion [98].

Gut Barrier Function

Intestinal permeability improved with probiotic therapy. Spindler-Vesel et al. documented decreased lactulose-mannitol excretion ratio from 0.148 to 0.061 ($p < 0.05$) in the synbiotic group [12]. Leng et al. demonstrated reduced FITC-dextran permeability following L92 treatment [13]. Molecular markers of barrier integrity including tight junction proteins ZO-1, occludin, and MUC-2 showed upregulation with *Lactobacillus* interventions [102, 103].

Gut barrier dysfunction in critical illness involved multiple mechanisms. Stadlbauer et al. found elevated bacterial translocation markers (endotoxin, peptidoglycans, bacterial DNA) despite

unaltered zonulin and diamine oxidase levels at baseline [48]. Probiotic intervention improved functional diversity without significantly changing permeability markers [48].

Immune Modulation

Systemic inflammatory markers responded to probiotic therapy across multiple studies. Sun et al. demonstrated reduced procalcitonin and IL-17 with increased IgA following quadruple live bacteria tablet administration [36]. Saviano et al. showed 35% reduction in fecal calprotectin versus 16% in controls, with 72.7% CRP reduction versus 62% [15].

The immunomodulatory effects extended to specific immune cell populations. Sapra et al. demonstrated probiotics modulated innate lymphoid cell (ILC) subsets, with enhanced IL-17-producing ILC3 and reduced IL-22-producing ILC3 in ARDS models [89]. Tan et al. reported higher IL-12p70 and IFN- γ with dramatic decreases in IL-4 and IL-10, indicating Th1/Th2 rebalancing in traumatic brain injury [85].

Toll-like receptor expression changed with probiotic treatment. Mitrou et al. found probiotics upregulated TLR2 while downregulating TLR4 in COVID-19 patients [26]. Stadlbauer et al. observed TLR4 normalization by study end in cirrhotic patients [112].

Metabolite Production

Short-chain fatty acid (SCFA) production emerged as a key mechanistic pathway. Shimizu et al. documented increased total organic acid concentration, particularly acetate, in synbiotic-treated patients [11, 11]. While Sun et al. found no significant changes in fecal SCFA concentrations [36], preclinical studies consistently demonstrated SCFA-mediated benefits. Horvath et al. observed increased butyrate after 6 months of probiotic intervention in post-COVID patients [101].

The mechanisms linking SCFAs to lung protection involved multiple pathways. Pham et al. showed butyrate from *Lactobacillus rhamnosus* downregulated PDE4B expression and IL-6

secretion through Ffar2 activation [16]. Ni et al. demonstrated sphingolipid metabolism regulation with downregulation of the PI3K-AKT pathway [103].

Competitive Exclusion

Probiotics reduced pathogenic colonization in the oropharynx and gastrointestinal tract. Zeng et al. found 24% of probiotic-treated patients acquired gastric colonization with potentially pathogenic microorganisms versus 44% in controls ($p=0.004$) [21]. Xu et al. reported lower microbial colonization rates in the oropharynx and stomach (51.6% vs 89.7%, $p<0.05$) [47].

Specific pathogen reductions included *Pseudomonas aeruginosa*. Siempos et al. showed reduced colonization (OR 0.35, 95% CI 0.13-0.93) [6], while Forestier et al. demonstrated significantly delayed *P. aeruginosa* acquisition [45]. In COVID-19, probiotics shifted microbiota from *Prevotella*-rich to *Streptococcus*-rich compositions [113].

Microbial Translocation and Systemic Effects

Evidence of reduced bacterial translocation came from both animal and human studies. Karen et al. demonstrated significantly reduced bacterial translocation in probiotic-treated rats [93]. Giamarellos-Bourboulis et al. found reduced LPS and CRP levels in synbiotic-treated trauma patients, suggesting diminished translocation [74].

The gut-lung axis involved portal and lymphatic pathways. Klingensmith et al. demonstrated that mesenteric lymph duct ligation prevented lung injury, implicating gut-derived lymph in pulmonary inflammation [114]. Sun et al. described SCFAs entering the bloodstream through portal vein and lymphatic system [36].

Synthesis of Findings Across Patient Populations

Population-Specific Effects

The heterogeneity in probiotic efficacy appears explicable through population and intervention characteristics rather than representing contradictory evidence.

Trauma and Surgical Patients: Studies in trauma populations consistently demonstrated benefits. Gu et al. showed significant reductions in nosocomial infections (RR 0.65, 95% CI 0.45-0.94), VAP (RR 0.59, 95% CI 0.42-0.81), and ICU length of stay (SMD -0.71, 95% CI -1.09 to -0.34) in trauma patients [19]. Spindler-Vesel et al. found synbiotic-treated trauma patients had significantly fewer infections (5 vs combined totals in other groups, $p=0.003$) and pneumonias (4 vs combined totals, $p=0.03$) [12]. These populations may benefit from probiotics' ability to prevent barrier dysfunction following severe injury [83].

COVID-19 Patients: COVID-19 studies showed consistent effects on symptom resolution and inflammatory markers. Tian et al.'s meta-analysis found probiotics increased complete symptom improvement (RR 1.62, 95% CI 1.10-2.38, $p=0.01$) and reduced CRP by 4.03 mg/L (95% CI -5.12 to -2.93, $p<0.00001$) [55]. Saviano et al. demonstrated 35% reduction in fecal calprotectin versus 16% in controls with 72.7% CRP reduction [15]. The gut-lung axis appeared particularly relevant in COVID-19 given SARS-CoV-2's tropism for gastrointestinal tissue [41].

General ICU Populations: Mixed ICU populations showed more variable results. The PROSPECT trial, the largest and highest-quality study, found no difference in VAP (21.9% vs 21.3%) [5] or other clinical outcomes [5], despite earlier meta-analyses showing benefit. This may reflect improved baseline care standards, reduced antibiotic pressure, or inadequate probiotic dosing for severely dysbiotic patients.

Intervention Characteristics

Synbiotics versus Probiotics Alone: Synbiotic formulations consistently outperformed probiotics alone. Wang et al.'s meta-analysis showed synbiotics reduced VAP (RR 0.61, 95% CI 0.47-0.80, $p=0.0004$) and sepsis (RR 0.41, 95% CI 0.22-0.72, $p=0.005$) while probiotics alone had no significant effect [17]. Konsta et al. noted greatest improvement with probiotics alone compared to synbiotics, though this appeared to reflect dose-response relationships [18].

Dosage and Duration: Higher doses ($\geq 5 \times 10^9$ CFU/day) showed greater improvement across outcomes [18]. Treatment duration of at least 14-15 days was associated with better results [18], with some successful interventions continuing up to 60 days [51, 115].

Strain Selection: *Lactobacillus rhamnosus* GG was the most extensively studied strain [5, 20, 30, 116], though multi-strain formulations appeared advantageous. VSL#3 containing 8 strains was evaluated in several trials [10, 14], while Synbiotic 2000 Forte combining 4 strains with prebiotics showed consistent benefits [67, 74].

Methodological Quality and Bias

Study quality varied substantially. The PROSPECT trial achieved high methodological rigor with concealed allocation, quadruple blinding, 99.9% follow-up completion, and adequate power [5, 116]. In contrast, many earlier positive trials had methodological limitations including lack of blinding [21, 70], small sample sizes [57, 75], and high attrition [48].

Sensitivity analyses excluding high-risk-of-bias studies frequently negated positive findings. Sharif et al. noted that excluding such studies eliminated effects on VAP, healthcare-associated pneumonia, and hospital length of stay [4]. This suggests publication bias and methodological quality substantially influenced apparent efficacy.

Conflicts of interest were inconsistently reported. Some studies disclosed probiotic company funding [57, 70, 100], while others reported no conflicts [22, 44, 117]. The PROSPECT trial ensured funding bodies had no input into design or conduct [116].

Safety Considerations

The safety profile varied by population. In healthy ICU patients, adverse events were rare [20, 21]. However, increased adverse events emerged in large trials. Johnstone et al. found 1.1% of probiotic-treated patients developed probiotic-related infections in sterile sites [5], while Sharif et al. reported increased serious adverse events (RR 9.96, 95% CI 1.25-79.09) [4].

Specific populations warranted caution. Immunocompromised patients were typically excluded from trials [18, 44]. The finding of increased mortality in acute pancreatitis patients receiving probiotics with postpyloric feeding highlighted risks in severely compromised gut perfusion states [118].

Reconciling Divergent Findings

The apparent contradiction between early positive meta-analyses and the negative PROSPECT trial can be explained through multiple factors:

1. Study Quality Hierarchy: Earlier positive trials had higher risk of bias [33], lacked adequate allocation concealment [92], and often were not blinded [70]. The PROSPECT trial's rigorous methodology [116] provides more reliable evidence, suggesting the true effect size is smaller than early estimates.

2. Context-Dependent Efficacy: Benefits appeared greatest in specific contexts:

- Trauma patients with acute barrier disruption [12, 19]
- Synbiotic formulations rather than probiotics alone [17]
- Higher doses ($\geq 5 \times 10^9$ CFU/day) for longer durations (≥ 14 days) [18]
- Populations without severe immunosuppression [52]

3. Baseline Risk: Subgroup analysis by Barraud et al. suggested differential effects by sepsis severity, with benefit in severe sepsis (OR 0.38, $p=0.035$) but potential harm in non-severe cases (OR 3.09, $p=0.08$) [52]. This suggests probiotics may be most effective when dysbiosis and inflammatory risk are highest.

4. Evolving Standard Care: Temporal trends in ICU care, including reduced antibiotic use and improved VAP prevention bundles, may have diminished the incremental benefit of probiotics. The PROSPECT trial's contemporary population may have had less severe dysbiosis than historical cohorts.

Given these considerations, probiotics appear beneficial in select populations—particularly trauma patients, those receiving synbiotic formulations at adequate doses, and potentially COVID-19 patients—while showing minimal benefit in general mechanically ventilated populations receiving contemporary critical care. The lack of mortality benefit across all populations suggests probiotics influence morbidity markers without affecting ultimate survival.

DISCUSSION

Summary of Principal Findings

This comprehensive systematic review of 200 sources, including 48 primary studies and 52 meta-analyses encompassing over 15,000 critically ill patients, reveals several important findings regarding probiotic interventions and the gut-lung axis in patients with lung edema. Probiotic administration consistently reduces ventilator-associated pneumonia incidence, with risk ratios ranging from 0.52 to 0.75 across meta-analyses (1,2,3). This effect translates into modest but significant reductions in mechanical ventilation duration (1-2.5 days) and ICU length of stay (1-2 days) (4,6). However, mortality benefit remains inconsistent, with the largest and most rigorous trial showing no effect on survival (5).

The gut-lung axis mechanisms underlying these clinical effects are increasingly well-characterized. Probiotics improve intestinal barrier function, as demonstrated by reduced lactulose-mannitol excretion ratios (12) and enhanced tight junction protein expression (102,103). Systemic inflammation decreases significantly, with IL-6 reductions of approximately 140 pg/mL (14) and CRP reductions of 72.7% (15). Short-chain fatty acid production, particularly butyrate and acetate, increases following synbiotic administration (11,101), providing metabolic substrates that modulate pulmonary immune responses (16). Competitive exclusion of pathogenic organisms, including *Pseudomonas aeruginosa* and *Staphylococcus aureus*, reduces respiratory tract colonization (45,47).

Critically, these effects are population-specific rather than universal. Trauma patients consistently demonstrate substantial benefits (19,67), COVID-19 patients show accelerated symptom resolution and reduced inflammatory markers (55,100), and surgical populations experience fewer infectious complications (90). Conversely, general mixed ICU populations receiving contemporary care show minimal benefit, as demonstrated by the negative PROSPECT trial (5). This heterogeneity explains the apparent contradiction between early positive meta-analyses and recent negative trials, suggesting that probiotic efficacy depends critically on patient selection rather than representing a uniformly effective or ineffective intervention.

Context-Dependent Efficacy

The differential effects across populations provide important insights into the mechanisms and optimal application of probiotic therapy. Trauma patients experience acute, profound gut barrier disruption due to hemorrhagic shock, ischemia-reperfusion injury, and systemic inflammation (83,129). In this context, probiotics may restore barrier function and prevent secondary infections more effectively than in patients with chronic critical illness (19,67). Spindler-Vesel et al. demonstrated significant reductions in infections (5 vs combined totals, $p=0.003$) and pneumonias (4 vs combined totals, $p=0.03$) in trauma patients receiving synbiotics (12). Kotzampassi et al. found dramatic reductions in mechanical ventilation (15 vs 26 days, $p=0.001$) and ICU stay (25 vs 43 days) in multiple trauma patients (67). These effects likely reflect the ability of probiotics to mitigate the acute systemic inflammatory response following severe injury (74,85).

COVID-19 patients represent another population with specific susceptibility to gut-lung axis modulation. SARS-CoV-2 exhibits tropism for gastrointestinal tissue, with ACE2 receptor expression in intestinal epithelium facilitating viral entry and replication (41,155). This creates bidirectional gut-lung involvement, where intestinal inflammation perpetuates pulmonary pathology through cytokine release and microbial translocation (133,159). Probiotic interventions in COVID-19 consistently reduce inflammatory markers, accelerate symptom resolution, and decrease oxygen

requirements (15,22,55). Saviano et al. demonstrated 35% reduction in fecal calprotectin versus 16% in controls, with 72.7% CRP reduction and reduced need for high-flow oxygen (15). Tian et al.'s meta-analysis found probiotics increased complete symptom improvement (RR 1.62, 95% CI 1.10-2.38) and reduced CRP by 4.03 mg/L (23). These effects may reflect direct antiviral properties, immunomodulation through TLR signaling, and competitive exclusion of pathogens in the gastrointestinal tract (16,26).

In contrast, general mixed ICU populations show more variable and generally smaller effects. The PROSPECT trial, the largest and highest-quality study, found no difference in VAP (21.9% vs 21.3%) or other clinical outcomes despite adequate dosing and duration of *Lactobacillus rhamnosus* GG (5). Several factors may explain this discrepancy. First, contemporary ICU care has improved substantially since earlier positive trials, with VAP prevention bundles, reduced antibiotic duration, and enhanced infection control practices potentially diminishing the incremental benefit of probiotics (33,119). Second, the PROSPECT population included patients with diverse underlying conditions, many of whom may not have had the acute barrier disruption necessary for probiotic efficacy (116). Third, the use of a single-strain probiotic (*L. rhamnosus* GG) may be less effective than multi-strain or synbiotic formulations (17,18).

Intervention Characteristics and Optimal Formulation

The evidence strongly supports that synbiotic formulations outperform probiotics alone. Wang et al.'s meta-analysis directly comparing these approaches found synbiotics reduced VAP (RR 0.61, 95% CI 0.47-0.80) and sepsis (RR 0.41, 95% CI 0.22-0.72) while probiotics alone showed no significant effect (17). Similarly, Shimizu et al. demonstrated VAP incidence of 14.3% in the synbiotic group versus 48.6% in controls ($p<0.05$) in septic patients (11). The mechanistic basis for this enhanced efficacy likely involves prebiotic support for probiotic growth and metabolic activity, particularly short-chain fatty acid production (66,134). Synbiotic 2000 Forte, containing four probiotic strains (*Pediococcus pentosaceus*, *Leuconostoc mesenteroides*, *Lactobacillus*

paracasei, *Lactobacillus plantarum*) with fermentable fibers, has demonstrated consistent benefits across multiple trials in trauma and surgical populations (67,74).

Dosage and duration represent critical determinants of efficacy. Konsta et al. found that higher doses ($\geq 5 \times 10^9$ CFU/day) and longer treatment duration (≥ 14 days) were associated with greater improvement across outcomes (18). Successful interventions in trauma populations typically continued for 14-21 days (56,67), while the PROSPECT trial administered probiotics for a median of 9 days, which may have been insufficient for sustained gut microbiome modulation (5). The ROCIT trial, administering *L. plantarum* 299v for up to 60 days, demonstrated feasibility of prolonged therapy and ongoing recruitment (51,115). Whether extended duration would have altered the PROSPECT results remains speculative but warrants investigation.

Strain selection influences outcomes through species-specific mechanisms. *Lactobacillus rhamnosus* GG, the most extensively studied strain, demonstrates excellent safety profile and competitive exclusion properties but may have limited immunomodulatory effects compared to other strains (4,5). VSL#3, containing eight bacterial strains (four *Lactobacillus* species, three *Bifidobacterium* species, and *Streptococcus thermophilus*), has shown significant anti-inflammatory effects in multiple trials (10,14,46). *Lactobacillus plantarum* 299v exhibits strong mucosal adhesion and pathogen exclusion (57,63), while *Bifidobacterium longum* BB536 modulates septicemia markers in antibiotic-exposed patients (61). Multi-strain formulations may provide complementary mechanisms, explaining their apparent superiority over single strains in meta-analyses (17,28).

Mechanistic Insights into Gut-Lung Axis Modulation

The gut-lung axis encompasses multiple interconnected pathways through which probiotics exert pulmonary effects. Gut barrier dysfunction in critical illness involves disruption of tight junction proteins, increased intestinal permeability, and loss of mucus layer integrity (164,173). Probiotics restore barrier function through several mechanisms. Leng et al. demonstrated reduced FITC-dextran permeability following L92 treatment, associated with activation of microbiome-

mediated glutamate-glutamine biosynthesis (13). Spindler-Vesel et al. documented decreased lactulose-mannitol excretion ratio from 0.148 to 0.061 ($p<0.05$) in synbiotic-treated trauma patients (12). Preclinical studies consistently show upregulation of tight junction proteins ZO-1, occludin, and claudin following *Lactobacillus* administration (102,103).

Systemic inflammation, a hallmark of critical illness, is attenuated by probiotic therapy through multiple pathways. Sanaie et al. observed significant reductions in IL-6 (from 211.85 ± 112.76 to 71.80 ± 28.41 pg/mL, $p<0.001$) and procalcitonin (from 1.67 ± 1.27 to 0.47 ± 0.41 ng/mL, $p<0.001$) with VSL#3 administration (14). Similar reductions were noted in COVID-19 patients, with CRP decreasing by 72.7% in the probiotic group versus 62% in controls (15). These effects likely involve modulation of Toll-like receptor signaling, with Mitrou et al. demonstrating probiotics upregulated TLR2 while downregulating TLR4 in COVID-19 patients (26). The immunomodulatory effects extend to specific immune cell populations, including innate lymphoid cells (89), neutrophils (87), and T-cell subsets (85,199).

Short-chain fatty acids, particularly butyrate, acetate, and propionate, represent key metabolites linking gut microbiota to pulmonary outcomes. Produced through bacterial fermentation of dietary fiber, SCFAs enter the circulation via portal vein and lymphatic system, reaching the lungs where they modulate immune function (36,177). Shimizu et al. documented increased total organic acid concentration, particularly acetate, in synbiotic-treated septic patients (11). Horvath et al. observed increased butyrate after 6 months of probiotic intervention in post-COVID patients (101). The mechanisms linking SCFAs to lung protection involve G-protein-coupled receptor activation (FFAR2/3), histone deacetylase inhibition, and regulation of inflammatory gene expression (16,137). Pham et al. demonstrated that butyrate from *L. rhamnosus* downregulated PDE4B expression and IL-6 secretion through FFAR2 activation in SARS-CoV-2 membrane glycoprotein-stimulated cells (16).

Competitive exclusion of pathogenic organisms occurs through multiple mechanisms including production of antimicrobial substances, competition for adhesion sites and nutrients, and

modulation of the local microenvironment (40,69). Zeng et al. found 24% of probiotic-treated patients acquired gastric colonization with potentially pathogenic microorganisms versus 44% in controls ($p=0.004$) (21). Xu et al. reported lower microbial colonization rates in the oropharynx and stomach (51.6% vs 89.7%, $p<0.05$) (47). Specific pathogen reductions included *Pseudomonas aeruginosa*, with Siempos et al. showing reduced colonization (OR 0.35, 95% CI 0.13-0.93) (6) and Forestier et al. demonstrating significantly delayed acquisition (45). These effects reduce the pathogenic burden available for aspiration and subsequent VAP development.

Methodological Quality and Evidence Hierarchy

The substantial heterogeneity in study quality explains much of the apparent contradiction in the literature. The PROSPECT trial represents the highest-quality evidence, with concealed allocation, quadruple blinding, 99.9% follow-up completion, adequate power (2,653 patients), and prespecified statistical analysis plan (5,116). In contrast, many earlier positive trials had significant methodological limitations including lack of blinding (21,70), small sample sizes (57,75), high attrition (48), and inadequate allocation concealment (92). Sensitivity analyses excluding high-risk-of-bias studies frequently negate positive findings. Sharif et al. noted that excluding such studies eliminated effects on VAP, healthcare-associated pneumonia, and hospital length of stay (4).

Publication bias likely inflates early estimates of treatment effect. Small positive trials are more likely to be published and cited than negative studies, creating an impression of efficacy that larger, more rigorous trials may contradict (33,118). The PROSPECT trial's negative findings, while disappointing to proponents of probiotics, provide essential counterbalance to the published literature and suggest that the true effect size in unselected populations is smaller than meta-analyses of early trials suggest (5). However, it would be equally erroneous to conclude that probiotics are ineffective in all populations based on a single trial, given the consistent signal of benefit in specific subgroups (19,55,67).

Temporal trends in ICU care complicate comparisons across eras. Contemporary VAP prevention bundles include head-of-bed elevation, subglottic secretion drainage, oral care with chlorhexidine, and minimized sedation—interventions that were less consistently applied during earlier probiotic trials (119,127). Antibiotic stewardship programs have reduced unnecessary antibiotic exposure, potentially preserving gut microbiota diversity (157,158). Improved nutritional support and glycemic control may also modulate the gut-lung axis independently of probiotics (166,187). These advances may diminish the incremental benefit of probiotics, explaining why recent trials show smaller effects than historical controls.

Safety Considerations

The safety profile of probiotics in critically ill patients requires careful consideration. While most studies report no probiotic-related infections (10,20,21,45,76), large trials reveal important signals. The PROSPECT trial identified *L. rhamnosus* in sterile sites in 15 patients (1.1%) receiving probiotics versus 1 patient (0.1%) in controls (OR 14.02, 95% CI 1.79-109.58, $p < 0.001$) (5). Sharif et al. reported increased serious adverse events (RR 9.96, 95% CI 1.25-79.09) (4). These findings indicate that probiotic translocation and bacteremia, while rare, occur at higher rates than in controls and warrant clinical vigilance.

Specific populations may face elevated risk. Immunocompromised patients were typically excluded from trials (18,44), limiting safety data in this vulnerable group. Patients with severe acute pancreatitis receiving probiotics with postpyloric feeding showed increased mortality in the PROPATRIA trial, highlighting risks in severely compromised gut perfusion states (118,136). The mechanism may involve probiotic translocation across ischemic gut mucosa, exacerbating rather than ameliorating systemic inflammation. Patients with central venous catheters, particularly those receiving total parenteral nutrition, may have increased risk of line contamination and subsequent bacteremia (135).

Risk-benefit assessment must therefore be individualized. In trauma patients with acute barrier disruption and high infection risk, the substantial benefits demonstrated in multiple trials (19,67) likely outweigh the small risk of probiotic-related infection. In general ICU populations without specific risk factors, the absence of demonstrated benefit coupled with measurable risk argues against routine use (5). Careful patient selection, avoidance in severely immunocompromised or pancreatitis patients, and clinical vigilance for signs of probiotic translocation are essential components of safe practice (31,135).

Reconciling Contradictory Evidence

The evidence synthesized in this review can be reconciled through a framework of context-dependent efficacy rather than uniform effectiveness. Probiotics appear most beneficial when:

1. **Acute gut barrier disruption exists:** Trauma, surgical, and burn patients experience acute, severe barrier dysfunction that probiotics may ameliorate (19,67,79)
2. **Specific pathogen burden is high:** Populations with high rates of *Pseudomonas* or multidrug-resistant organism colonization may benefit from competitive exclusion (45,47)
3. **Synbiotic formulations are used:** Prebiotic support enhances probiotic survival and metabolic activity (17,18)
4. **Adequate dosing and duration are employed:** $\geq 5 \times 10^9$ CFU/day for ≥ 14 days optimizes outcomes (18,115)
5. **Baseline inflammation is severe:** Subgroup analyses suggest benefit in severe sepsis but not milder illness (52)

Conversely, probiotics appear ineffective when:

1. **General mixed ICU populations receive contemporary care:** Improved baseline standards diminish incremental benefit (5)
2. **Single-strain probiotics are used without prebiotics:** Limited metabolic support and strain diversity (4)
3. **Inadequate dosing or duration:** Insufficient for sustained microbiome modulation (92)
4. **Patients are immunocompromised or have pancreatitis:** Risk may outweigh benefit (118)

This framework explains why early meta-analyses including predominantly trauma and surgical populations showed large effects (1,6), while recent trials in mixed populations show minimal benefit (5). It also explains why COVID-19 studies, capturing patients with specific gut-lung pathophysiology, demonstrate consistent effects (55,100). The challenge for clinicians is identifying which patients in their specific ICU population fit the "responsive phenotype" and might therefore benefit from targeted probiotic therapy.

Implications for Clinical Practice

Based on this evidence synthesis, several practical recommendations emerge. First, routine probiotic administration to unselected mechanically ventilated ICU patients is not supported by current evidence and may expose patients to unnecessary risk (5). Second, targeted therapy in specific populations—particularly trauma patients, those undergoing major abdominal surgery, and COVID-19 patients with moderate-severe illness—may be considered given consistent benefit in these subgroups (19,55,67). Third, when probiotics are used, synbiotic formulations should be preferred over probiotics alone based on superior efficacy (17,18). Fourth, adequate dosing ($\geq 5 \times 10^9$ CFU/day) and duration (≥ 14 days or throughout ICU stay) should be ensured (18,115). Fifth, patients should be monitored for signs of probiotic-related infection, and therapy should be discontinued if translocation is suspected (31).

Clinicians must also consider local epidemiology and antibiotic resistance patterns. Units with high rates of multidrug-resistant organism colonization may derive greater benefit from competitive exclusion strategies (21,45). Conversely, units with excellent VAP prevention bundle compliance and low baseline infection rates may see minimal incremental benefit (5). Probiotic selection should consider strain-specific properties and the local formulary, with preference for strains with demonstrated efficacy in critical care populations (*L. rhamnosus* GG, *L. plantarum* 299v, VSL#3, Synbiotic 2000 Forte).

Future Research Directions

Future research should prioritize several areas. First, large pragmatic trials in specific responsive populations (trauma, COVID-19, surgical) are needed to confirm benefit with contemporary care standards. Second, mechanistic studies integrating serial microbiome, metabolomic, and immunological assessments with clinical outcomes would clarify pathways of effect and identify predictive biomarkers. Third, comparative effectiveness trials directly comparing different strains, doses, and formulations would inform optimal intervention design. Fourth, long-term follow-up studies are needed to assess sustained effects on quality of life, readmission, and late mortality. Fifth, implementation science research examining barriers and facilitators to probiotic use in ICUs would inform translation of evidence into practice. Sixth, cost-effectiveness analyses incorporating both benefits and rare adverse events would guide resource allocation. Seventh, investigation of probiotics in combination with other microbiome-targeted therapies (fecal microbiota transplantation, prebiotics, dietary interventions) may reveal synergistic effects (189).

CONCLUSION AND RECOMMENDATIONS

Summary of Evidence

This comprehensive systematic review of probiotic interventions and the gut-lung axis in critically ill patients with lung edema synthesizes evidence from 200 sources encompassing over 15,000 patients. The principal findings demonstrate that probiotics reduce ventilator-associated pneumonia incidence, shorten mechanical ventilation duration, and decrease ICU length of stay through multiple gut-lung axis mechanisms including improved intestinal barrier function, attenuated systemic inflammation, enhanced short-chain fatty acid production, and competitive exclusion of pathogens. These clinical benefits are most pronounced in specific populations—particularly trauma, surgical, and COVID-19 patients—who experience acute gut barrier disruption and high inflammatory burden. Synbiotic formulations combining probiotics with prebiotic fibers demonstrate superior efficacy to probiotics alone, with higher doses ($\geq 5 \times 10^9$ CFU/day) and longer duration (≥ 14 days) optimizing outcomes.

Reconciliation of Contradictory Evidence

The apparent contradiction between early positive meta-analyses and the negative PROSPECT trial is resolved through recognition of context-dependent efficacy rather than uniform effectiveness. Early trials predominantly enrolled trauma and surgical populations with substantial potential for benefit, while recent trials in general mixed ICU populations with contemporary care standards show minimal incremental effect. Methodological quality explains additional variance, with high-risk-of-bias studies inflating early estimates. This framework reconciles the literature and provides guidance for patient selection: probiotics benefit specific subgroups but are not indicated for routine use in unselected ICU populations.

Clinical Recommendations

For clinical practice, we recommend:

1. **Against routine use** of probiotics in unselected mechanically ventilated ICU patients, given absence of benefit and measurable risk in large rigorous trials
2. **Consider targeted therapy** in specific populations with demonstrated benefit:
 - Trauma patients with acute barrier disruption
 - Patients undergoing major abdominal surgery
 - COVID-19 patients with moderate-severe illness
 - Populations with high rates of multidrug-resistant organism colonization
3. **Prefer synbiotic formulations** combining probiotics with prebiotic fibers over probiotics alone
4. **Ensure adequate dosing** ($\geq 5 \times 10^9$ CFU/day) and duration (≥ 14 days or throughout ICU stay)
5. **Avoid probiotics** in severely immunocompromised patients and those with acute pancreatitis, where risk may outweigh benefit
6. **Monitor for signs of probiotic-related infection** and discontinue therapy if translocation is suspected

Research Priorities

Future research should prioritize identification of responsive phenotypes through biomarker discovery, comparative effectiveness trials of different strains and formulations, mechanistic studies integrating multi-omics approaches, and long-term outcome assessment. The gut-lung axis

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represents a promising therapeutic target in critical illness, and continued investigation may refine our ability to deploy probiotic interventions effectively and safely in selected populations.

Concluding Statement

The gut-lung axis is a critical determinant of pulmonary outcomes in critically ill patients with lung edema. Probiotic interventions modulate this axis through multiple mechanisms, reducing ventilator-associated pneumonia and ICU stay in selected populations. However, the era of routine probiotic administration to all mechanically ventilated patients should end. The future lies in precision medicine: identifying which patients, with which probiotic formulations, at what dose and duration, derive meaningful benefit without unacceptable risk. This review provides the evidence synthesis to guide that evolution toward targeted, mechanism-based probiotic therapy in critical illness.

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