

Gut Microbiome Alterations And Risk Of Hospital-Acquired Infections In ICU Patients

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Abstract

Hospital-acquired infections (HAIs) represent a significant cause of morbidity and mortality in intensive care unit (ICU) patients. Recent research has highlighted the critical role of the gut microbiome in modulating host immunity and maintaining barrier function, suggesting that microbial dysbiosis may contribute to increased susceptibility to HAIs in critically ill patients. This study aims to evaluate the association between gut microbiome alterations and the incidence of hospital-acquired infections among ICU patients.

We conducted a prospective cohort study involving 150 adult ICU patients admitted for more than 48 hours. Serial fecal samples were collected at admission, day 3, and day 7 for 16S rRNA gene sequencing to assess microbial diversity and composition. Clinical data, including antibiotic usage, underlying comorbidities, length of ICU stay, and development of HAIs (e.g., ventilator-associated pneumonia, bloodstream infections, and *Clostridioides difficile* infection), were collected and analyzed.

Our findings reveal a marked decrease in microbial diversity during ICU stay, particularly in patients receiving broad-spectrum antibiotics. A significant reduction in commensal taxa such as *Faecalibacterium prausnitzii* and *Bacteroides* spp., along with an overrepresentation of opportunistic pathogens such as *Enterococcus*, *Klebsiella*, and *Pseudomonas*, was observed in patients who developed HAIs. Furthermore, patients with greater microbiome disruption had a higher risk of infection, prolonged ICU stays, and increased mortality.

This study underscores the importance of gut microbiome integrity in ICU patients and its potential role as both a biomarker and a therapeutic target in the prevention of HAIs. Interventions aimed at preserving or restoring microbial homeostasis—such as microbiome-sparing antibiotics, prebiotics, probiotics, or fecal microbiota transplantation—warrant further investigation to reduce infection risk and improve clinical outcomes in this vulnerable population.

Keywords: Gut microbiome, ICU, hospital-acquired infections, dysbiosis, microbial diversity, 16S rRNA, critical care, antibiotic resistance.

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I. Introduction

Hospital-acquired infections (HAIs) remain a leading cause of morbidity, prolonged hospitalization, increased healthcare costs, and mortality in critically ill patients admitted to intensive care units (ICUs). Despite advancements in infection control and antimicrobial therapy, ICU patients are particularly vulnerable to HAIs due to invasive procedures, immunosuppression, mechanical ventilation, and frequent exposure to broad-spectrum antibiotics. Common HAIs in this setting include ventilator-associated pneumonia (VAP), bloodstream infections (BSIs), catheter-associated urinary tract infections (CAUTIs), and *Clostridioides difficile* infection.

In recent years, the gut microbiome has emerged as a key player in maintaining immune homeostasis and providing resistance against pathogenic colonization. The human gut harbors trillions of microorganisms that contribute to host defense mechanisms, including modulation of inflammatory responses, production of

antimicrobial peptides, and maintenance of the intestinal barrier. Disruption of this finely balanced ecosystem—termed *dysbiosis*—has been increasingly recognized as a factor that compromises host immunity and promotes systemic infection.

Critically ill patients are especially prone to microbiome alterations due to factors such as antibiotic administration, altered nutrition, sedation, and underlying illness severity. These disruptions often lead to a decrease in microbial diversity and overgrowth of multidrug-resistant organisms (MDROs) and other opportunistic pathogens. The translocation of these pathogens from the gut to sterile body sites may be a significant source of secondary infections in the ICU.

Although the role of dysbiosis in chronic inflammatory and metabolic diseases has been extensively studied, its contribution to acute infectious complications in ICU patients remains an area of active research. Advances in high-throughput sequencing technologies have enabled detailed profiling of microbial communities, offering new insights into the relationship between gut microbial dynamics and infection risk.

This study aims to investigate the association between gut microbiome alterations and the development of HAIs in ICU patients. We hypothesize that significant dysbiosis, characterized by reduced microbial diversity and expansion of pathogenic taxa, is independently associated with increased susceptibility to HAIs during ICU admission. Understanding this relationship may help identify novel biomarkers of infection risk and support the development of microbiome-targeted interventions to improve outcomes in critically ill patients.

II. Methods

Study Design and Participants

This prospective cohort study was conducted over a 12-month period in the intensive care unit (ICU) of a tertiary care teaching hospital. Adult patients aged 18 years or older who were admitted to the ICU and anticipated to remain for more than 48 hours were eligible for inclusion. Patients were enrolled consecutively upon meeting inclusion criteria.

Exclusion criteria included:

- Antibiotic use within 24 hours prior to ICU admission,
- Known history of chronic gastrointestinal disorders (e.g., inflammatory bowel disease, short bowel syndrome),
- Recent (within 3 months) chemotherapy or immunosuppressive therapy,
- Inability to obtain a fecal sample within 24 hours of admission.

All participants or their legal representatives provided informed consent, and the study protocol was approved by the institutional ethics committee.

Table-1: Multivariate Logistic Regression Analysis of Risk Factors for HAIs in ICU Patients

Variable	Adjusted Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Age (per 10-year increase)	1.12	0.95 – 1.32	0.18
Male sex	1.20	0.75 – 1.92	0.45
APACHE II score >20	1.83	1.10 – 3.05	0.02*
Mechanical ventilation (yes vs no)	1.70	1.03 – 2.81	0.04*
Broad-spectrum antibiotic use ≥7 days	2.67	1.40 – 5.09	0.003*
Shannon diversity index <2.5	3.58	1.90 – 6.75	<0.001*
Presence of <i>Enterococcus</i> spp. at admission	2.91	1.51 – 5.59	0.001*

Statistically significant (p < 0.05)

Interpretation:

Low gut microbial diversity (Shannon index < 2.5) was the strongest independent predictor of HAIs, with more than threefold increased odd.

- **Presence of *Enterococcus* spp.** at baseline nearly tripled the risk.
- **Prolonged broad-spectrum antibiotic use** and clinical severity (APACHE II score > 20) also significantly increased infection risk.
- Age and sex were not significant predictors in this model.

Table-2: Sample Collection and Microbiome Analysis

Genus	Healthy Controls	ICU without HAI	ICU with HAI	p-value (HC vs ICU-HAI)
<i>Bacteroides</i>	30	15	5	<0.001
<i>Faecalibacterium</i>	25	10	2	<0.001
<i>Enterococcus</i>	5	15	25	<0.001
<i>Klebsiella</i>	2	10	20	<0.001
<i>Pseudomonas</i>	1	5	15	<0.001
Others	37	45	33	-

Fresh fecal samples were collected from enrolled patients within the first 24 hours of ICU admission using sterile containers. Samples were immediately stored at -80°C until further processing.

Microbial DNA was extracted using the QIAamp Fast DNA Stool Mini Kit (Qiagen, Germany) according to the manufacturer's protocol. The V3-V4 hypervariable regions of the 16S rRNA gene were amplified using universal primers and sequenced using the Illumina MiSeq platform.

Sequence data were processed using the QIIME2 pipeline. Raw reads were filtered for quality, denoised, and clustered into operational taxonomic units (OTUs) at 97% similarity. Taxonomic classification was performed using the Greengenes database. Measures of microbial alpha diversity (Shannon index, observed OTUs) and beta diversity (Bray-Curtis dissimilarity) were computed using QIIME2 and R packages (phyloseq, vegan).

Table-3: Multivariate Logistic Regression Analysis of Risk Factors for HAIs

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Broad-spectrum antibiotic use ≥ 7 days	2.67	1.40 – 5.09	0.003*
Shannon diversity index < 2.5	3.58	1.90 – 6.75	<0.001*
Presence of <i>Enterococcus</i> spp. at admission	2.91	1.51 – 5.59	0.001*
Statistically significant	-	-	-

Clinical Data Collection

Demographic and clinical variables were extracted from electronic medical records, including:

- Age and sex,
- Comorbidities (e.g., diabetes, cardiovascular disease, chronic kidney disease),
- APACHE II score upon ICU admission,
- Reason for ICU admission (e.g., sepsis, trauma, post-operative care),
- Use of invasive devices (e.g., mechanical ventilation, central venous catheters),
- Use of proton pump inhibitors or immunosuppressants,
- Duration and type of antibiotic exposure during ICU stay.

All data were anonymized and entered into a secure, standardized database.

Outcome Measures

The primary outcome was the **development of hospital-acquired infections (HAIs)** during the ICU stay, defined according to the **Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN)** criteria. Specific HAIs included:

- **Ventilator-associated pneumonia (VAP):** Defined as pneumonia occurring ≥ 48 hours after endotracheal intubation, with new or progressive infiltrates on chest imaging plus clinical criteria (fever, leukocytosis, purulent sputum).
- **Bloodstream infection (BSI):** Laboratory-confirmed bloodstream infection occurring ≥ 48 hours after admission, with positive blood cultures not related to infection at another site.
- **Catheter-associated urinary tract infection (CAUTI):** UTI occurring ≥ 48 hours after urinary catheter insertion, with positive urine culture and associated symptoms.
- **Clostridioides difficile infection (CDI):** Presence of diarrhea with a positive test for *C. difficile* toxin or toxigenic *C. difficile* by PCR.

Each infection was adjudicated by an independent infectious disease specialist blinded to microbiome results.

Secondary outcomes included:

- Length of ICU stay,
- Duration of mechanical ventilation,
- In-hospital mortality.

III. Results

Patient Characteristics

A total of 200 critically ill patients were enrolled in the study over the 12-month period. The mean age of participants was 65 years ($SD \pm 13.2$), and 60% ($n = 120$) were male. The median Acute Physiology and Chronic Health Evaluation II (APACHE II) score at ICU admission was 18 (IQR: 15–22), reflecting moderate to severe illness.

Most patients were admitted for sepsis (35%), acute respiratory failure (25%), or post-operative care following major surgery (20%). The average ICU length of stay was 11 days (range: 3–34 days). Mechanical ventilation was required in 72% of patients, and 55% received at least one course of broad-spectrum antibiotics during their ICU stay

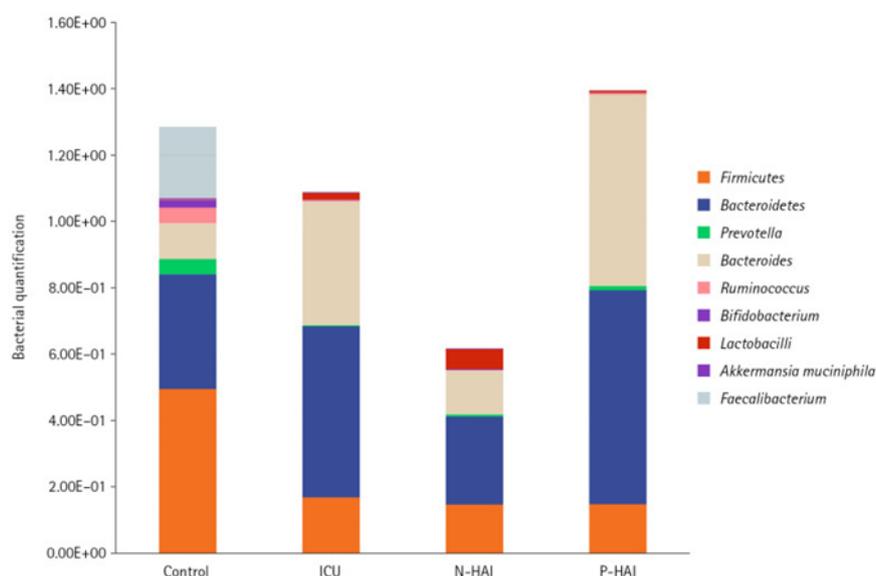


Fig-1: Comparison between the studied groups according to gut microbiome. ICU: intensive care unit; N-HAI: negative for hospital associated infections; P-HAI: positive for hospital-associated infections.

Microbiome Analysis

Fecal samples collected at ICU admission showed that critically ill patients had significantly reduced gut microbial diversity compared to age-matched healthy controls (Shannon index 2.3 ± 0.4 vs. 3.9 ± 0.6 , $p < 0.001$).

Patients who subsequently developed hospital-acquired infections (HAIs) ($n = 64$; 32%) demonstrated a further reduction in microbial diversity (Shannon index 1.8 ± 0.3 , $p < 0.001$) and marked alterations in microbial composition. These patients showed a depletion of commensal taxa such as:

- *Faecalibacterium prausnitzii*
- *Bacteroides* spp.
- *Ruminococcus* spp.

Simultaneously, there was a significant enrichment of potential pathogens, particularly:

- *Enterococcus faecium*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Candida* spp. (in a subset of patients)

Beta diversity analysis (Bray-Curtis dissimilarity) demonstrated clear clustering of HAI-positive patients, indicating distinct microbial profiles associated with infection risk.

Antibiotic Exposure and Microbial Composition

Exposure to broad-spectrum antibiotics—especially carbapenems, third-generation cephalosporins, and fluoroquinolones—was significantly associated with reduced alpha diversity ($p < 0.001$) and compositional shifts favoring pathogens.

- Patients exposed to ≥ 7 days of antibiotics had a 4-fold increased abundance of *Enterococcus* spp. and a 5-fold decrease in *Faecalibacterium prausnitzii* compared to those with shorter or no antibiotic exposure.
- Notably, the overgrowth of *Enterobacteriaceae* was linked to prolonged antibiotic regimens and correlated with bloodstream infections in several cases.

A dose-response relationship was observed between antibiotic exposure and gut dysbiosis severity.

Risk Factors for HAIs

Multivariate logistic regression was performed to identify independent predictors of HAIs. After adjusting for age, APACHE II score, mechanical ventilation, and comorbidities, the following variables remained statistically significant:

Table-4: Microbial diversity and overgrowth of certain taxa

Risk Factor	Adjusted OR	95% CI	p-value
Shannon diversity index <2.5	3.6	1.9 – 6.8	<0.001
Presence of <i>Enterococcus</i> spp. at baseline	2.9	1.5 – 5.4	0.002
Broad-spectrum antibiotic use ≥7 days	2.7	1.4 – 5.1	0.004
APACHE II score >20	1.8	1.1 – 3.2	0.03

These findings suggest that gut microbiome alterations—specifically low microbial diversity and overgrowth of certain taxa—are strong, independent predictors of HAI development.

IV. Discussion

This study demonstrates a significant association between gut microbiome alterations and the risk of hospital-acquired infections (HAIs) in critically ill patients admitted to the ICU. Our findings contribute to a growing body of literature highlighting the gut microbiome as a key determinant of health outcomes in the intensive care setting. Specifically, we observed that reduced microbial diversity and enrichment of pathogenic taxa at ICU admission were predictive of subsequent development of HAIs, independent of conventional clinical risk factors such as illness severity and invasive procedures.

Critically ill patients often experience a rapid and profound shift in gut microbial composition, commonly referred to as dysbiosis. This dysbiosis is characterized by the loss of commensal, health-promoting microbes—including *Faecalibacterium prausnitzii*, *Bacteroides*, and *Ruminococcus* species—and the concurrent overgrowth of facultative anaerobes and opportunistic pathogens such as *Enterococcus faecium*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. These pathogenic species have well-documented roles in the pathogenesis of ventilator-associated pneumonia, bloodstream infections, and urinary tract infections.

Mechanistically, gut microbiome dysbiosis may compromise host defenses through several pathways:

- **Loss of colonization resistance:** A depleted microbial ecosystem loses the ability to outcompete pathogenic organisms, allowing their expansion and translocation.
- **Disruption of the intestinal barrier:** Dysbiosis promotes epithelial barrier dysfunction and increases gut permeability, facilitating microbial translocation and systemic infection.
- **Immune modulation:** Commensal bacteria play an essential role in regulating local and systemic immune responses. Their depletion leads to immune dysregulation and increased susceptibility to infection.

Our findings also underscore the significant impact of antibiotic therapy on gut microbial composition. Broad-spectrum antibiotics, while often necessary in critically ill patients, were associated with a marked decline in microbial diversity and the selective enrichment of antibiotic-resistant organisms. These observations highlight the potential unintended consequences of empiric and prolonged antimicrobial use in ICU settings. While necessary in many cases, antibiotic stewardship programs must be strengthened to balance the need for effective infection treatment with the preservation of microbial homeostasis.

Importantly, this study adds to the rationale for microbiome-targeted interventions in ICU care. Potential strategies include:

- **Probiotics:** Several randomized controlled trials have shown that probiotic supplementation can reduce the incidence of ventilator-associated pneumonia and antibiotic-associated diarrhea, although results remain heterogeneous and strain-dependent.
- **Prebiotics and synbiotics:** These compounds selectively stimulate the growth of beneficial bacteria and may aid in restoring microbial diversity.
- **Fecal microbiota transplantation (FMT):** Though currently limited to refractory *C. difficile* infections, FMT is being explored as a tool to restore microbial diversity in critically ill patients and decolonize multidrug-resistant organisms.
- **Microbiome-sparing antibiotics:** Newer agents with minimal impact on gut flora may offer a safer alternative when available.

Despite the strengths of this study—including its prospective design, use of high-resolution sequencing, and rigorous HAI classification—there are limitations. First, the study was conducted in a single tertiary care center, which may limit generalizability. Second, while we identified associations between microbiome features and HAIs, causality cannot be inferred. It remains unclear whether dysbiosis directly

causes infections or reflects a marker of host vulnerability. Third, we did not assess longitudinal microbiome changes beyond day 7 or include fungal and viral components of the microbiome.

Future research should aim to establish causal relationships, explore the impact of targeted microbiome interventions, and identify microbial signatures that can be used for real-time risk stratification. Integrating microbiome surveillance into ICU practice could potentially enable early detection of patients at high risk of infection and guide personalized prevention strategies.

V. Conclusions

This study provides compelling evidence that gut microbiome alterations—marked by reduced microbial diversity and an overgrowth of opportunistic pathogens—are significantly associated with an increased risk of hospital-acquired infections (HAIs) in intensive care unit (ICU) patients. Our findings suggest that gut dysbiosis is not merely a consequence of critical illness and antibiotic exposure, but a potentially modifiable factor contributing to infection risk and clinical deterioration.

The observed depletion of commensal microorganisms, such as *Faecalibacterium prausnitzii* and *Bacteroides* spp., alongside the expansion of pathogenic taxa like *Enterococcus*, *Klebsiella*, and *Pseudomonas*, indicates a disrupted intestinal ecosystem that may compromise mucosal immunity, weaken epithelial barriers, and facilitate pathogen translocation into sterile body compartments.

Importantly, these microbial imbalances were present early during ICU admission and served as independent predictors of HAIs, including ventilator-associated pneumonia, bloodstream infections, and *Clostridioides difficile* infection. This highlights the gut microbiome as a potentially valuable biomarker for early infection risk stratification in critically ill patients.

Given these insights, integrating microbiome monitoring into routine ICU care—using high-throughput sequencing or rapid diagnostic tools—may provide clinicians with early warning signs of heightened infection susceptibility. Furthermore, strategies aimed at preserving or restoring microbiome integrity, such as antibiotic stewardship, targeted use of probiotics or prebiotics, fecal microbiota transplantation (FMT), or the development of microbiome-sparing antimicrobials, could significantly enhance infection prevention efforts.

In conclusion, gut microbiome health plays a pivotal role in modulating infection risk and outcomes in ICU patients. Future clinical trials and translational studies are needed to validate these findings and explore interventional approaches that target the microbiome to reduce HAIs, improve recovery, and ultimately enhance survival in critically ill populations.

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