Review

Glucocorticoid Receptor Signaling: Protective Effects on the Gut Barrier and Microbiome Interventions in Critically Ill Patients

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Review

Glucocorticoid Receptor Signaling: Protective Effects on the Gut Barrier and Microbiome Interventions in Critically Ill Patients

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Abstract: The glucocorticoid receptor (GR) signaling pathway is vital for gut barrier protection, particularly in critically ill patients, where the gut can act as a "motor" for systemic inflammation. This manuscript compiles evidence that GR signaling preserves gut barrier function, alleviates inflammation, and restores interactions between the microbiome and the gut barrier. It emphasizes the role of short-chain fatty acids (SCFAs) as essential mediators that synergize with GR signaling to stabilize the intestinal barrier, modulate immune responses, and reduce oxidative stress. This review explores a rationale for combining probiotics with glucocorticoid (GC) therapy as a synergistic strategy. Probiotics enhance epithelial barrier integrity, promote SCFA production, and stabilize the microbiome, amplifying the anti-inflammatory and protective effects of GR signaling. This dual approach could mitigate complications such as nosocomial infections, ventilator-associated pneumonia (VAP), and multi-organ dysfunction syndrome (MODS). Despite its potential, the combination of GC therapy and probiotics requires further validation through randomized controlled trials (RCTs) to establish its efficacy. Future research should explore this integrative strategy to improve patient outcomes, including restoring gut-lung axis integrity, modulation of systemic inflammation, and support for immune homeostasis in critically ill patients.

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Introduction

The gut barrier is critical for maintaining systemic homeostasis. It ensures selective permeability, allowing nutrient absorption while preventing harmful microbial translocation. In critically ill patients, gut barrier integrity is often compromised, leading to systemic inflammation and contributing to the development of multiple organ dysfunction syndrome (MODS). The GR signaling system offers significant protective effects by modulating gut barrier function and shaping the microbiome.

The gut barrier is a dynamic, multi-layered interface that regulates the selective absorption of nutrients while preventing the entry of harmful substances like pathogens, toxins, and antigens. It consists of a single layer of intestinal epithelial cells linked by tight and adherens junctions, covered by a mucus layer produced by goblet cells. This mucus traps pathogens, contains antimicrobial peptides, and includes secretory immunoglobulin A (IgA), which neutralizes toxins and microbes. The gut microbiota further enhances protection by competing with pathogens for adhesion and nutrients, while gastric acid, bile, and antimicrobial peptides secreted by Paneth cells contribute to pathogen neutralization.

The gut's immune component, centered on the gut-associated lymphoid tissue (GALT), includes immune cells such as dendritic cells, macrophages, T cells, and B cells that balance immune defense and tolerance. Cytokines and chemokines coordinate immune responses to maintain homeostasis. The enteric nervous system supports barrier integrity through motility and neurotransmitters like serotonin. Continuous epithelial renewal and gut motility clear pathogens and help maintain the barrier's integrity.

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The gut barrier protects against harmful agents, regulates immunity, facilitates nutrient absorption, and communicates with the microbiome and nervous system. However, its disruption, often called "leaky gut," can increase intestinal permeability and systemic inflammation, contributing to autoimmune diseases, allergies, and metabolic disorders. Critical illness frequently disturbs this delicate balance, triggering systemic inflammation and advancing the progression of MODS.

Emerging evidence underscores the gut microbiome's vital role in supporting GR signaling, primarily producing short-chain fatty acids (SCFAs). These microbiome-derived metabolites work synergistically with GR signaling to strengthen the gut barrier, modulate immune responses, and mitigate oxidative stress. Additionally, the gut-lung axis represents a critical point of interaction, where gut dysfunction exacerbates lung inflammation and complications such as acute respiratory distress syndrome (ARDS) or ventilator-associated pneumonia (VAP).

This manuscript explores the interplay between GR signaling, the gut barrier, and the microbiome in critically ill patients. It emphasizes the importance of SCFAs as mediators in gut health and systemic inflammation and highlights therapeutic strategies that integrate microbiome-targeted therapies with glucocorticoid (GC) treatment. These approaches offer potential benefits in restoring gut integrity, reducing complications, and improving patient outcomes.

Mechanisms of GR signaling play a critical role in gut barrier protection. One key mechanism involves strengthening tight junctions. GC-GR signaling preserves the structural integrity of tight junctions by regulating the expression of occludin, claudin-1, and ZO-1 proteins. This signaling counteracts cytokine-induced disruption of tight junctions by upregulating these proteins, as demonstrated in studies [1–3]. Experimental models of colitis further highlight GC-mediated protection of epithelial integrity under inflammatory stress [3].

Another important mechanism is the reduction of inflammation. GR signaling suppresses pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, while enhancing anti-inflammatory mediators, including IL-10 and Annexin A1. Evidence shows that GC treatment reduces intestinal inflammation by preventing neutrophil-driven epithelial damage and promoting macrophage polarization toward anti-inflammatory phenotypes. Annexin A1 is pivotal in resolving gut inflammation and maintaining epithelial integrity. GC-GR signaling also mitigates oxidative stress by increasing the expression of antioxidant enzymes, such as superoxide dismutase and catalase, to protect epithelial cells from reactive oxygen species (ROS)-induced apoptosis. Studies have shown that GC therapy reduces oxidative damage markers and prevents epithelial apoptosis in septic models [7,8]. Additionally, GCs enhance mitochondrial antioxidant defenses, thereby preserving epithelial viability during oxidative stress [8].

Finally, GR signaling contributes to restoring microbiome-barrier interactions. Healthy microbiota produces metabolites like short-chain fatty acids (SCFAs), which synergize with GR signaling to stabilize the intestinal barrier. SCFAs, particularly butyrate, promote GR nuclear translocation, enhancing anti-inflammatory transcription and epithelial integrity [9,10]. Dysbiosis exacerbates barrier dysfunction in critically ill patients, but microbiome-targeted therapies have been shown to mitigate these effects [11].

Short-chain fatty acids (SCFAs) are fatty acids with fewer than six carbon atoms, primarily produced through the fermentation of dietary fibers by anaerobic bacteria in the gut microbiome. SCFAs, such as butyrate, are critical in regulating gut health. They promote the GR nuclear translocation, amplifying anti-inflammatory transcription [9]. Additionally, SCFAs enhance epithelial energy metabolism and the production of tight junction proteins, contributing to the maintenance of gut barrier integrity [10]. SCFAs also act as histone deacetylase (HDAC) inhibitors, modulating immune cell activity and cytokine production, further supporting immune balance and gut health [8,11].

Preventing Gut-Origin Sepsis

Critically ill patients are highly susceptible to gut-origin sepsis, which arises from bacterial translocation and the release of danger-associated molecular patterns (DAMPs). GR signaling is pivotal in mitigating these risks. It downregulates pro-inflammatory pathways by suppressing Toll-

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like receptor-4 (TLR4)-mediated inflammation. Additionally, GR signaling curtails DAMP release by reducing epithelial apoptosis and limiting DAMP production, thereby preventing systemic inflammation and the progression to multiple organ dysfunction syndrome (MODS) [3,4].

The Gut-Lung Axis in Critically Ill Patients

The gut-lung axis represents a critical pathway for interaction in critically ill patients, where the gut and lungs influence each other through microbial metabolites, immune signaling, and barrier integrity. Microbial metabolites like short-chain fatty acids (SCFAs), such as butyrate, exert systemic anti-inflammatory effects that modulate lung immune responses. Tryptophan metabolites produced by gut bacteria interact with the aryl hydrocarbon receptor (AhR) in lung epithelial and immune cells, promoting epithelial repair and reducing inflammation. Systemic immune signaling also plays a significant role, as dysbiosis leads to elevated pro-inflammatory cytokines, such as IL-6 and TNF-α, and danger-associated molecular patterns (DAMPs), which exacerbate lung injuries, including acute respiratory distress syndrome (ARDS) and ventilator-associated pneumonia (VAP). Regulatory T cells (Tregs) supported by a healthy gut microbiota help suppress excessive lung inflammation, maintaining immune balance. However, gut barrier dysfunction allows microbial translocation, introducing endotoxins into the systemic circulation, which triggers pulmonary inflammation. GC therapy profoundly impacts the gut-lung axis by suppressing inflammatory cascades through GR signaling, which dampens systemic pro-inflammatory cytokines and mitigates lung inflammation caused by gut-derived endotoxemia. GCs also maintain barrier integrity in the gut and lungs, reducing microbial translocation and secondary infections. Furthermore, SCFAs enhanced by probiotics synergize with GC effects, amplifying their anti-inflammatory and barrier-stabilizing properties, thereby improving gut and lung outcomes. [14]

Microbiome-Targeted Interventions

Probiotics

Probiotics, which are live microorganisms, are key in restoring microbial diversity, reducing inflammation, and promoting short-chain fatty acid (SCFA) production. These benefits contribute to strengthening the gut barrier and supporting immune modulation. Specific strains such as *Lactobacillus rhamnosus GG* and *Saccharomyces boulardii* have been shown to improve gut permeability and amplify GR mediated anti-inflammatory effects, particularly in critically ill ICU patients. Beyond their local gut effects, probiotics influence systemic inflammation and enhance resilience against stress-induced gut dysfunction, promoting homeostasis and reducing complications such as sepsis [15,16].

Prebiotics

Prebiotics are non-digestible substrates that selectively nourish beneficial gut bacteria, increasing their growth and activity. By enhancing SCFA production, particularly butyrate, prebiotics stabilize the intestinal barrier and reduce gut permeability, which is crucial for preventing systemic inflammation. Elevated butyrate levels support intestinal health and enhance GR signaling, helping to balance immune responses and maintain epithelial integrity. Familiar sources of prebiotics include inulin and fructooligosaccharides (FOS), which are integral to modulating the gut environment and improving outcomes in critical illness by supporting GR-mediated pathways [17].

Postbiotics

Postbiotics are bioactive microbial metabolites or compounds, such as butyrate, produced during the fermentation of prebiotic substrates by probiotics. Unlike live microorganisms, Postbiotics offer safety for critically ill patients, where live probiotics may pose risks. These compounds directly interact with GR pathways, amplifying anti-inflammatory responses and enhancing the barrier-protective effects of the intestinal lining. Administration of butyrate, a key postbiotic, has been shown

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to restore tight junction integrity, reducing gut permeability and systemic inflammation. Also, postbiotics increase GR-mediated Annexin A1 expression, pivotal in resolving inflammation and supporting homeostatic corrections [18,19].

Nutritional Support

Nutritional strategies targeting the microbiome complement probiotics, prebiotics, and postbiotics. Nutrients such as omega-3 fatty acids and polyphenols profoundly affect the modulation of gut microbiota, reduce oxidative stress, and enhance GR sensitivity. Omega-3 fatty acids improve GR activity and reduce inflammation in critically ill patients, promoting systemic homeostasis. Polyphenols from dietary sources such as berries, tea, and dark chocolate further contribute to enriching beneficial gut microbes and providing antioxidant effects that support GR signaling. These interventions synergize with microbiome-targeted therapies, offering a holistic approach to managing critical illness [20].

Clinical Applications in Critically Ill Patients

Microbiome-targeted interventions, including probiotics, prebiotics, and postbiotics, restore gut homeostasis, enhance GR actions, and reduce complications such as nosocomial infections. These strategies are detailed in Tables 1 and 2 [8,9,15]. Optimizing GC therapy with low-to-moderate doses helps preserve microbiome integrity and gut barrier function. At the same time, dynamic tapering minimizes adverse effects during GC withdrawal [8]. Monitoring and early intervention are crucial; biomarkers such as short-chain fatty acid (SCFA) levels, zonulin, and inflammatory cytokines should be assessed [8,9].

Table 1. Key Probiotic Strains for Critically Ill Patients.

Probiotic Strain	Mechanism of Action	Evidence
Lactobacillus rhamnosus GG	*Enhances tight junction proteins, reduces inflammation*	Improves gut permeability in ICU patients [15].
Saccharomyces boulardii	Restores microbial diversity, increases SCFA production	Shown to prevent antibiotic-associated diarrhea and nosocomial infections [16].
Bifidobacterium longum	Anti-inflammatory cytokine production, SCFA generation	Protects epithelial integrity and reduces pro-inflammatory cytokines [9].
Lactobacillus plantarum	Mitigates oxidative stress, enhances epithelial defense	Reduces oxidative markers and promotes tight junction repair in septic models [17].
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Table 1 Legend: Key Probiotic Strains for Critically Ill Patients. This table provides an overview of essential probiotic strains used in critically ill patients, highlighting their primary mechanisms of action and the clinical evidence supporting their use. Probiotics work through various pathways, including enhancing the expression of tight junction proteins, reducing inflammation, promoting the production of short-chain fatty acids (SCFAs), and mitigating oxidative stress. These mechanisms contribute to restoring gut integrity and reducing systemic complications, ultimately improving patient outcomes.

Table 2. Microbiome-Targeted Interventions in Critically Ill Patients.

Intervention	Mechanism	Clinical Relevance
Probiotics	Restore microbial diversity, reduce inflammation, produce SCFAs	Improve gut barrier integrity, reduce systemic inflammation, and lower infection risks.
Prebiotics	Serve as substrates for beneficial bacteria, boost SCFA levels	Enhance gut healing and stabilize microbiota.
Postbiotics	Directly modulate GR signaling, amplify anti-inflammatory effects	Restore gut barrier function and reduce inflammation in critical illness.

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Nutritional Support	Modulate microbiota through polyphenols, omega-3s	Reduce oxidative stress and enhance the efficacy of GR signaling.

Table 2 Legend: This table outlines various microbiome-targeted therapeutic strategies, detailing their mechanisms of action and clinical relevance for critically ill patients. These interventions, including probiotics, prebiotics, and postbiotics, aim to restore gut homeostasis, stabilize microbiota composition, enhance GC-GR signaling, and suppress inflammation. These therapies support recovery and improve clinical outcomes by addressing gut barrier dysfunction and systemic inflammatory responses.

Conclusions

The combination of probiotic therapy and GC treatment represents a theoretically synergistic strategy for managing critically ill patients. Probiotics enhance epithelial barrier integrity, increase the expression of tight junction proteins, and stabilize the microbiome, which is often disrupted during critical illness. Additionally, their ability to promote the production of short-chain fatty acids (SCFAs) can amplify these benefits by supporting gut barrier function, modulating immune responses, and enhancing the anti-inflammatory effects of GR signaling. This interaction could strengthen the protective mechanisms of GC therapy, potentially reducing epithelial apoptosis, systemic inflammation, and oxidative stress.

This dual approach has the potential to mitigate complications such as nosocomial infections, ventilator-associated pneumonia (VAP), and multi-organ dysfunction syndrome (MODS) by addressing key factors like microbial translocation, danger-associated molecular patterns (DAMPs), and cytokine-induced inflammation. Furthermore, probiotics may help preserve microbiome diversity, which is critical for maintaining immune homeostasis and reducing the risk of gut-origin sepsis. The dynamic tapering of GC therapy and sustained probiotic use could offer long-term benefits while minimizing adverse effects such as dysbiosis or immune suppression.

However, the combination of GC therapy and probiotics has yet to be proven in randomized controlled trials (RCTs), and additional research is essential to validate this approach. Future studies should investigate the clinical outcomes of this synergistic therapy, focusing on its ability to address gut-lung axis integrity, systemic inflammation, and overall patient recovery. With further evidence, this integrative strategy may pave the way for improved protocols in the care of critically ill patients.

Conflicts of Interest: the author declares no conflict of interest.

References

1. van der Heijden C, et al. Glucocorticoid receptor signaling in the intestinal epithelium reduces immune-mediated colitis. *Proc Natl Acad Sci U S A.* 2015;112(40):12472-12477. doi:10.1073/pnas.1515022112.
2. Ferrier L, et al. Impairment of the intestinal barrier by ethanol involves oxidative stress in the rat and human intestine. *Gastroenterology.* 2006;131(1):130-139. doi:10.1053/j.gastro.2006.04.001.
3. Al-Sadi R, Ma T. IL-1β causes an increase in intestinal epithelial tight junction permeability. *J Immunol.*2007;178(7):4641-4649.
4. Assimakopoulos SF, et al. The role of the gut barrier function in health and disease. *Gastroenterol Res.*2018;11(5):261-268. doi:10.14740/gr1063w.
5. Bailey MA, et al. Corticosteroids enhance bacterial clearance and modulate the gut-lung axis in a model of Pseudomonas aeruginosa pneumonia. *Infect Immun.* 2017;85(2):e00920-16. doi:10.1128/IAI.00920-16.
6. Leoni G, et al. Annexin A1, formyl peptide receptor, and NOX1 orchestrate epithelial repair. *J Clin Invest.*2013;123(1):443-454. doi:10.1172/JCI65410.
7. Flowers SA, et al. Antidepressant-induced modification of the gut microbiota and intestinal permeability. *J Psychiatr Res.* 2019;112:1-10. doi:10.1016/j.jpsychires.2019.02.003.
8. Tan J, et al. The role of short-chain fatty acids in health and disease. *Adv Immunol.* 2014;121:91-119. doi:10.1016/B978-0-12-800100-4.00003-9.
9. Kelly CJ, et al. Crosstalk between microbiota-derived short-chain fatty acids and intestinal epithelial HIF augments tissue barrier function. *Cell Host Microbe.* 2015;17(5):662-671. doi:10.1016/j.chom.2015.03.005.
10. Fukuda S, et al. Bifidobacteria can protect from enteropathogenic infection through production of acetate. *Nature.*2011;469(7331):543-547. doi:10.1038/nature09646.
11. Zhuang X, et al. The spatial temporal dynamics of the human gut microbiome and resistome revealed by a longitudinal childbirth cohort study. *Microbiome.* 2020;8(1):161. doi:10.1186/s40168-020-00940-1.

12. Tan J, McKenzie C, Potamitis M, et al. The role of short-chain fatty acids in health and disease. *Adv Immunol.*2014;121:91-119. doi:10.1016/B978-0-12-800100-4.00003-9.
13. Kelly CJ, Zheng L, Campbell EL, et al. Crosstalk between microbiota-derived short-chain fatty acids and intestinal epithelial HIF augments tissue barrier function. *Cell Host Microbe.* 2015;17(5):662-671. doi:10.1016/j.chom.2015.03.005.
14. Ouwehand AC, Salminen S, Isolauri E. Probiotics: mechanisms and established effects. *Int Dairy J.* 2002;12(5):403-414. doi:10.1016/S0958-6946(02)00089-3.
15. Ouwehand AC, et al. Probiotics: mechanisms and established effects. *Int Dairy J.* 2002;12(5):403-414. doi:10.1016/S0958-6946(02)00089-3.
16. Thomas CM, Versalovic J. Probiotics-host communication: Modulation of signaling pathways in the intestine. *Gut Microbes.* 2010;1(3):148-163. doi:10.4161/gmic.1.3.11712.
17. Roberfroid M. Prebiotics: the concept revisited. *J Nutr.* 2007;137(3 Suppl 2):830S-837S. doi:10.1093/jn/137.3.830S.
18. Leonel AJ, et al. Butyrate modulates intestinal inflammation in chemically induced colitis model. *J Nutr Biochem.*2013;24(9):1609-1616. doi:10.1016/j.jnutbio.2013.01.002.
19. Hidalgo-Cantabrana C, et al. Bacteria-host interactions: bacterial surface molecules and their role in probiotic effect. Microbiol Spectr. 2017;5(3):10.1128/microbiolspec.BAD-0018-2016. doi:10.1128/microbiolspec.BAD-0018-2016.
20. Singer P, et al. Omega-3 fatty acids and the immune response. World Rev Nutr Diet. 2001;88:116-131. doi:10.1159/000059715.