ISSN(O): 3107-7889

Jana Nexus: Journal of Health and Medicine

Publisher's Name: Jana Publication and Research LLP

https://www.jananexushm.com

REVIEWER'S REPORT

Manuscript No.: JNHM 105

Title: The Hidden Microbe-Pharmacokinetic Axis: Navigating Erratic Drug Absorption in Critically Ill Patients,

Recommendation:
Accept after minor revision.....

Rating	Excel.	Good	Fair	Poor
Originality			✔	
Techn. Quality			✔	
Clarity		✔		
Significance	✔			

Reviewer's ID: JPR- Bilqees Hamza

Detailed Reviewer's Report

The manuscript titled "The Hidden Microbe-Pharmacokinetic Axis: Navigating Erratic Drug Absorption in Critically Ill Patients" provides a comprehensive narrative review that explores the intersection of critical care medicine, gastrointestinal physiology, and clinical pharmacology. The work evaluates how acute, severe dysbiosis in the intensive care unit (ICU)—traditionally examined as a source of systemic inflammation or immune dysfunction—functions as a major, unmonitored covariate in drug disposition. The scope of the review focuses specifically on "pharmacomicrobiomics," mapping out how the enzymatic machinery of the disrupted gut microbiome alters the presystemic fate, bioavailability, and plasma concentration-time curves of enterally administered therapeutic compounds.

The authors conducted a narrative synthesis structured in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines, incorporating selective reporting principles from the PRISMA framework.

- **Search Strategy and Execution:** The data infrastructure is built upon a literature search across primary academic databases, including PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library. The search was temporally restricted to articles published between January 2020 and May 2026, targeting international clinical trials, mechanistic studies, and clinical protocols from the FDA and NCCN.
- **Inclusion/Exclusion Logic:** The literature selection strategy prioritized adult human data and highly relevant *in vivo* mammalian models demonstrating direct microbial biotransformation of

ISSN(O): 3107-7889
Jana Nexus: Journal of Health and Medicine
Publisher's Name: Jana Publication and Research LLP
https://www.jananexushm.com

REVIEWER'S REPORT

xenobiotics, explicitly excluding unreviewed literature and non-pharmacological nutritional studies lacking clear pharmacokinetic (PK) endpoints.

The central thesis asserts that standard, fixed-dose enteral regimens in critical care are fundamentally flawed because they rely on pharmacokinetic data derived from healthy populations, ignoring the complex "presystemic microbial gauntlet" present in the critically ill gut.

The narrative outlines three primary pillars:

1. **The Pathophysiology of the "Critical Care Gut":** The review establishes that localized ischemia, hypoperfusion, vasopressor use, and broad-spectrum antibiotics decimate protective anaerobic commensals. The resulting ecological collapse triggers altered luminal pH, delayed transit times, and "leaky gut" mucosal permeability via tight-junction disruption, which fundamentally compromises passive and active drug transport mechanics.
2. **Mechanisms of Enzymatic Hijacking:** The paper describes how microbial exoenzymes directly execute oxidation, reduction, hydrolysis, condensation, and decarboxylation of drug molecules prior to host absorption. Specific examples highlight how microbial alterations of host bile acids disrupt the solubility of lipophilic agents, modify host nuclear receptors (like FXR), and shift hepatic cytochrome P450 expression.
3. **Class-Specific Pharmacokinetic Disruption:** The authors categorize these erratic biotransformations across key ICU drugs:
    - *Antimicrobials:* Localized beta-lactamases and thick microbial biofilms physically sequester and inactivate enterally administered antibiotics (such as linezolid or vancomycin), driving sub-therapeutic plasma concentrations and expanding the host resistome.
    - *Cardiovascular Agents:* Gut bacteria alter the enterohepatic circulation of antiarrhythmics like amiodarone through premature deconjugation, while short-chain fatty acid (SCFA) fluctuations modify enteric blood flow gradients.
    - *Analgesics and Sedatives:* Severe dysbiosis coupled with proton pump inhibitor (PPI)-driven gastric pH elevation allows colonic bacteria to migrate proximally into the duodenum. These misplaced microbes directly glucuronidate and inactivate sedatives (e.g., methadone or benzodiazepines), triggering erratic sedation depths and prolonged mechanical ventilation.

The scholarly contribution of this work lies in its cohesive synthesis of microbiomic variability data into a functional clinical blueprint for modern therapeutic drug monitoring (TDM).

ISSN(O): 3107-7889
Jana Nexus: Journal of Health and Medicine
Publisher's Name: Jana Publication and Research LLP
https://www.jananexushm.com

REVIEWER'S REPORT

Technical Suggestions for Improvement

Formulate a Structured Clinical Dosing and Monitoring Matrix

While the manuscript provides an excellent mechanistic description of microbial biotransformation, the transition from molecular pathways to bedside recommendations requires greater structural clarity. The authors should synthesize these findings into a comprehensive reference matrix positioned at the conclusion of the drug-specific sections. This matrix must explicitly correlate each therapeutic class with its corresponding microbial mechanism of action, the subsequent pharmacokinetic aberration, and a precise, prescriptive therapeutic drug monitoring strategy to guide intensivists in adjusting regimens for patients with severe dysbiosis.

Integrate a Flow Schematization of the Microbe-Pharmacokinetic Axis

To enhance the conceptual accessibility of the multi-step pathophysiological cascades described in the text, the manuscript would benefit from a formal structural flowchart. This schematic should visually map the causal pipeline, beginning with common intensive care stressors such as systemic hypoperfusion, heavy antimicrobial selective pressure, and proton pump inhibitor therapy. It should then trace how these factors lead to epithelial barrier degradation and proximal bacterial overgrowth, detail the specific enzymatic transformations that occur, and culminate in the systemic pharmacokinetic failures observed in clinical practice.

Delineate the Methodological Bottlenecks of Bedside Metagenomics

In discussing future diagnostic strategies, the authors advocate for real-time microbiome profiling to tailor patient-specific dosing. However, the paper understates the significant logistical and technical constraints currently preventing this technology from being implemented in acute care units. The manuscript should be expanded to include a dedicated analysis of these operational barriers, explicitly addressing the prolonged turnaround times of next-generation sequencing platforms, the high capital costs of equipment, the lack of standardized validation protocols, and the bioinformatic complexity of translating raw metagenomic data into immediate clinical decisions at the patient's bedside.

Refine the Scope and Causal Claims of the Fecal Microbiota Transplantation Data

The section evaluating therapeutic interventions highlights fecal microbiota transplantation as a promising modality for restoring regular drug absorption profiles. To ensure scientific precision, the authors must clarify the primary endpoints of the clinical trials cited to support this claim. The text should clearly state whether these investigations were specifically designed to stabilize drug pharmacokinetics, or if the normalization of drug absorption was merely an observed secondary outcome during trials aimed at eradicating recurrent infections caused by opportunistic pathogens.

Standardize Reference Metadata and Complete Bibliographic Details

ISSN(O): 3107-7889
Jana Nexus: Journal of Health and Medicine
Publisher's Name: Jana Publication and Research LLP
https://www.jananexushm.com

REVIEWER'S REPORT

A meticulous audit of the concluding reference bibliography reveals formatting omissions among the most recent citations. Several entries from the 2025 and 2026 literature cohorts are missing essential metadata components, including specific journal volume numbers, issue designations, and definitive page ranges. The entire bibliography must undergo a rigorous technical review to ensure every citation conforms perfectly to a singular, standardized academic style manual.

Eradicate Typographical Anomalies and Structural Layout Artifacts

The manuscript contains several minor typographical remnants and layout artifacts generated during document processing. Notable examples include an unanchored, isolated two-letter character string on page 1, compressed line spacing across major transition zones, and inconsistent capitalization within the subsection headings. Manually resolving these formatting issues is necessary to ensure the manuscript possesses the professional appearance required for formal peer-reviewed publication.

Editorial Recommendation

This manuscript is recommended for publication with minor revisions. The authors have delivered a highly sophisticated, original, and clinically relevant narrative review that addresses an overlooked frontier in critical care pharmacology. By establishing the gut microbiome as an active, metabolically volatile organ capable of directly modifying drug bioavailability, this work provides a valuable framework for understanding therapeutic failure in the critically ill.

The scientific reasoning is sound, the application of narrative review guidelines is rigorous, and the pharmacological mechanics are detailed accurately. Once the visual formatting anomalies are eliminated, the incomplete 2026 bibliographic metadata is resolved, and a structured clinical monitoring matrix is integrated into the text, the manuscript will be fully prepared for publication.