Gut Microbiome as a Predictive Biomarker for Febrile Neutropenia in Pediatric Acute Lymphoblastic Leukemia: A Clinical Integrative Framework

Bijurica Chakraborty[1] Rajib De[1,2]

[1] Multi-Disciplinary Research Unit, Nil Ratan Sircar Medical College & Hospital, Kolkata, India
[2] Department of Haematology, Nil Ratan Sircar Medical College & Hospital, Kolkata, India

Address for correspondence Rajib De, MD, DM, Multi-Disciplinary Research Unit, Nil Ratan Sircar Medical College & Hospital, 138, A.J.C. Bose Road, Kolkata 700014, India
(e-mail: drrajibacademics@gmail.com).

Ind J Med Paediatr Oncol 2026;47:146–149.

Introduction

Febrile neutropenia (FN) is a common and potentially life-threatening complication mostly observed in pediatric patients undergoing chemotherapeutic regimen for the treatment of hematological malignancies, such as acute lymphoblastic leukemia (ALL).[1] It is characterized by a single oral temperature $\geq 38.3°C$ (101.0°F) or an oral temperature $\geq 38.0°C$ (100.4°F) sustained for over an hour or occurring twice within a 24-hour period. An absolute neutrophil count (ANC) $< 0.5 \times 10^9/L$ or ANC $< 1.0 \times 10^9/L$ is expected to decrease to $< 0.5 \times 10^9/L$ over the subsequent 48 hours, accompanied by fever.[2,3] Despite standardized chemotherapy protocols, FN risk in the pediatric population remains heterogeneous, with current risk stratification relying on post-onset clinical features, limiting early intervention.[4–6] Recent reports link baseline gut microbial dysbiosis, marked by reduced microbial diversity and elevated Proteobacteria, to FN complications, suggesting their prospective role as an anticipatory biomarker, providing a valuable window for early risk stratification and targeted supportive care.[7–14]

Predictive Value of Gut Microbial Signatures

The gut microbiome population comprises a highly dynamic ecosystem that gets profoundly disrupted by multiple interventions—including chemotherapy, mucositis, dietary alterations, and differential antibiotic exposures.[7,8,15] Dysbiosis—marked by reduced microbial diversity (such as intraspecific or α diversity) and expansion of opportunistic taxa—has strong associations with increased risk to infections.

Some key findings from pediatric ALL and hematopoietic stem cell transplantation (HSCT) cohorts include:

- Loss of gut microbial diversity often precedes neutropenia correlating with FN incidence and duration.[1,7,11]
- Expansion of specific microbial taxa, such as *Enterococcus*, is linked to prolonged FN episodes and adverse outcomes.[8,11,16]
- In pediatric HSCT recipients, low α diversity and an enriched antimicrobial resistome (pooled collection of microbiome resistance genes) predicts bloodstream infections, thereby underscoring a microbiome-based predictive potential in highly immunocompromised patients.[7,9,17]

These combined data indicate toward microbiome metrics as early biomarkers of infection risk in immunocompromised pediatric patients, such as those undergoing chemotherapy for ALL, enabling clinicians to predict and potentially prevent conditions such as sepsis and FN before the onset of clinical symptoms.[10,18]

Proposed Framework for Clinical Integration

To translate the above insights into future clinical practice, we hereby propose a three-tiered, evidence-based framework for integrating longitudinal gut microbial assessment into supportive care for pediatric ALL.

Tier 1: Baseline Microbial Profiling

- Collecting stool samples at diagnosis.
- Employing 16S rRNA sequencing to estimate α diversity and relative abundance of key gut microbial phyla.

article published online
January 6, 2026

DOI https://doi.org/10.1055/s-0045-1814748.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Private Limited, A-13A, Graphix Tower 1, 6th floor, Sector 62, Noida 201309, Uttar Pradesh, India

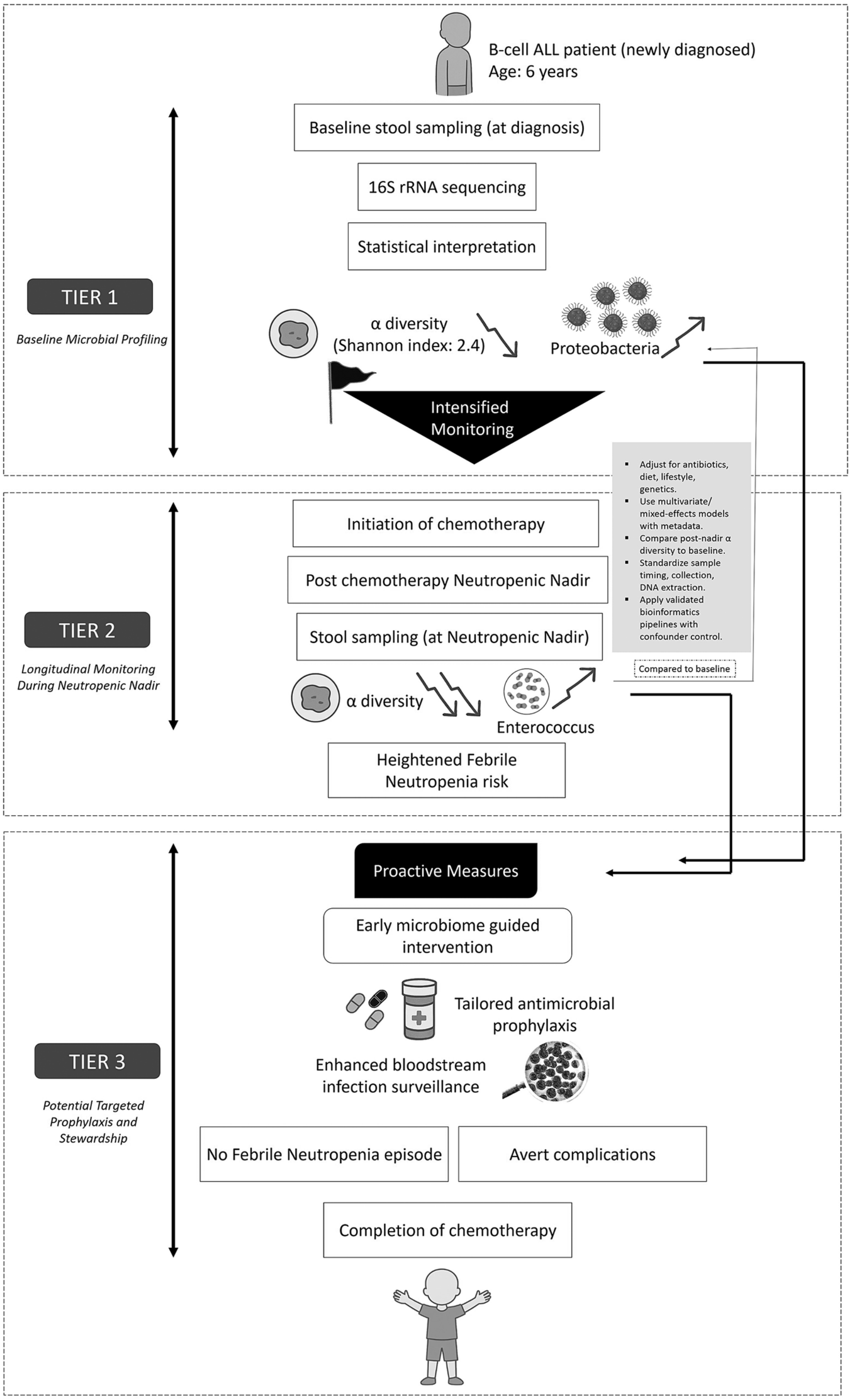

Fig. 1 Hypothetical application of the three-tiered gut microbiome framework in a pediatric ALL patient. A 6-year-old child with newly diagnosed B-cell ALL undergoes baseline stool sampling (Tier 1), revealing low α diversity (Shannon index 2.4) and increased Proteobacteria abundance, prompting flagging for intensified monitoring. During induction chemotherapy, stool analysis at neutropenic nadir (Tier 2) demonstrates further decline in microbial diversity and *Enterococcus* overgrowth. Based on these findings, Tier 3 interventions including tailored antimicrobial prophylaxis and enhanced surveillance for bloodstream infections are implemented. The patient completes chemotherapy without febrile neutropenia episodes, illustrating how early, microbiome-guided interventions may potentially prevent infectious complications. ALL, acute lymphoblastic leukemia.

- Linking alteration gut microbial diversity or relative abundance of potentially pathogenic taxa (e.g., Proteobacteria) to identify patients at elevated FN risk, thereby guiding intensified monitoring.[1,7]

Note: While Tier 1 enables early gut microbial risk stratification, it is critical to note that universally validated α diversity range or precise pathogenic taxa in pediatric ALL are not currently available. This lack of standardization stems from heterogeneity in sequencing platforms, analytical pipelines, and patient cohorts. Nevertheless, multiple studies, including Oldenburg et al (2021),[19] have consistently demonstrated that reduced microbial diversity and enrichment of taxa such as Proteobacteria or Enterococcaceae correlate with heightened infection risk. Specifically, a study by Hakim et al (2018) reported that a Proteobacteria relative abundance $\geq$ 0.01% or Enterococcaceae dominance $\geq$ 30% was associated with FN and infectious complications.[1] These findings further reinforce the clinical relevance of Tier 1 profiling, while emphasizing that such thresholds remain cohort-specific observations rather than validated diagnostic cutoffs.

Tier 2: Longitudinal Monitoring during Neutropenic Nadir (Lowest Count of Patient Neutrophil)

- Collecting stool samples at postchemotherapy neutropenic nadir using standardized timing and protocols to minimize preanalytical variability.
- Comparing postnadir α diversity alterations (if any) to baseline for predicting heightened FN risk, prompting earlier clinical interventions.[3,6]
- Ensuring reproducibility through consistent DNA extraction methods, centralized 16S rRNA sequencing pipelines, and validated bioinformatics workflows with stringent statistical adjustments for confounders.

Tier 3: Potential Targeted Prophylaxis and Stewardship

For identified high-risk FN patients from Tiers 1 and 2, potential proactive measures may include:

- Tailored antimicrobial prophylaxis preserving commensal bacteria.
- Targeted surveillance for bloodstream pathogens associated with dysbiosis.[9,10]

This approach can target antibiotic-driven gut dysbiosis, which contributes to infection susceptibility during neutropenic episodes, potentially mitigating FN and reducing hospitalization in pediatric patients.[15]

In developing the above three-tiered framework, it is essential to account for confounding variables such as antibiotic prophylaxis, geographical locations, dietary intake, genetic constitutions, lifestyle factors, and environmental exposures, which can substantially influence the gut microbial composition of patients.[20,21] Future analytic approaches should incorporate these metadata into statistical modeling or risk algorithms to ensure that predictions of FN risk reflect true microbial shifts rather than external modifiers. This strategy will enable more accurate, clinically meaningful interpretation of microbial profiling across diverse patient populations. A hypothetical application of the three-tiered system is provided in ►**Fig. 1**.

Translational Prospects and Future Implications

Although comprehensive metagenomic sequencing remains a cost-prohibitive approach for routine clinical practice, assessing simpler diversity indices or targeted resistome panels could offer practical and actionable insights.[7,11,22] Future prospective validation studies embedding longitudinal stool sampling with clinical outcomes are thus essential.[1,8,10]

As discussed earlier, it is important to recognize that gut microbial diversity and composition may vary profoundly across global populations due to multiple confounding factors.[20,21] Consequently, microbial signatures identified in one cohort may not be directly generalizable, underscoring the need for large multicentric validation across diverse populations before clinical implementation.

By standardizing and integrating gut microbiome assessment into clinical decision-making, FN management in pediatric ALL can shift from a reactive, clinical symptom–based approach to an anticipatory, biomarker-driven strategy; this in turn will potentially improve patient outcomes and reduce infection-related morbidity.[1–6,14,18,23]

Authors' Contributions

B.C. and R.D. collaboratively prepared and submitted the manuscript. B.C. has drafted the manuscript, and R.D. has proofread the manuscript and extensively helped by providing essential information.

Patient Consent

This is a Perspective article so patient consent is not required. No real patient, patient data or identifiable clinical information is involved. The illustrative case described is purely hypothetical and used for conceptual explanation only.

Conflict of Interest

None declared.

Acknowledgments

The authors would like to express their sincere gratitude to the Department of Haematology and the Multi-disciplinary Research Unit of Nil Ratan Sircar Medical College & Hospital for providing relevant infrastructure and information pertaining to this article.

References

1 Hakim H, Dallas R, Wolf J, et al. Gut microbiome composition predicts infection risk during chemotherapy in children with acute lymphoblastic leukemia. Clin Infect Dis 2018;67(04): 541–548

2 Freifeld AG, Bow EJ, Sepkowitz KA, et al; Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010

update by the Infectious Diseases Society of America. Clin Infect Dis 2011;52(04):e56

3 Febrile neutropenia. SciDirect Topics. Accessed August 24, 2025, at: https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/febrile-neutropenia

4 Santschi M, Ammann RA, Agyeman PKA, et al. Outcome prediction in pediatric fever in neutropenia: development of clinical decision rules and external validation of published rules based on data from the prospective multicenter SPOG 2015 FN definition study. PLoS One 2023;18(08):e0287233

5 Lehrnbecher T, Robinson P, Fisher B, et al. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. J Clin Oncol 2017;35(18):2082–2094

6 Lehrnbecher T, Robinson PD, Ammann RA, et al. Guideline for the management of fever and neutropenia in pediatric patients with cancer and hematopoietic cell transplantation recipients: 2023 update. J Clin Oncol 2023;41(09):1774–1785

7 Masetti R, D'Amico F, Zama D, et al. Febrile neutropenia duration is associated with the severity of gut microbiota dysbiosis in pediatric allogeneic hematopoietic stem cell transplantation recipients. Cancers (Basel) 2022;14(08):1932

8 Liu X, Zou Y, Zhang Y, et al. Characteristics in gut microbiome is associated with chemotherapy-induced pneumonia in pediatric acute lymphoblastic leukemia. BMC Cancer 2021;21(01):1190

9 Peled JU, Gomes ALC, Devlin SM, et al. Microbiota as predictor of mortality in allogeneic hematopoietic-cell transplantation recipients. N Engl J Med 2020;382(09):822–834

10 Galloway-Peña JR, Smith DP, Sahasrabhojane P, et al. The role of the gastrointestinal microbiome in infectious complications during induction chemotherapy for acute myeloid leukemia. Cancer 2016;122(14):2186–2196

11 Sørum ME, Boulund U, De Pietri S, et al. Changes in gut microbiota predict neutropenia after induction treatment in childhood acute lymphoblastic leukemia. Blood Adv 2025;9(07):1508–1521

12 Wang H, Zhang Y, Zhou Q, et al. Microbial metagenomic shifts in children with acute lymphoblastic leukaemia during induction therapy and predictive biomarkers for infection. Ann Clin Microbiol Antimicrob 2024;23(01):52

13 Le TT, Hoang TN, Do DH, et al. Current state of microbiota clinical applications in neonatal and pediatric bacterial infections. Gut Microbes 2025;17(01):2529400

14 Masetti R, Muratore E, Leardini D, et al. Gut microbiome in pediatric acute leukemia: from predisposition to cure. Blood Adv 2021;5(22):4619–4629

15 Schluter J, Peled JU, Taylor BP, et al. The gut microbiota is associated with immune cell dynamics in humans. Nature 2020;588(7837):303–307

16 Stein-Thoeringer CK, Nichols KB, Lazrak A, et al. Lactose drives *Enterococcus* expansion to promote graft-versus-host disease. Science 2019;366(6469):1143–1149

17 Taur Y, Jenq RR, Perales MA, et al. The effects of intestinal tract bacterial diversity on mortality following allogeneic hematopoietic stem cell transplantation. Blood 2014;124(07):1174–1182

18 Nycz BT, Dominguez SR, Friedman D, et al. Correction: evaluation of bloodstream infections, *Clostridium difficile* infections, and gut microbiota in pediatric oncology patients. PLoS One 2018;13(05):e0197530

19 Oldenburg M, Rüchel N, Janssen S, Borkhardt A, Gössling KL. The microbiome in childhood acute lymphoblastic leukemia. Cancers (Basel) 2021;13(19):4947

20 Parizadeh M, Arrieta MC. The global human gut microbiome: genes, lifestyles, and diet. Trends Mol Med 2023;29(10):789–801

21 Bai X, Sun Y, Li Y, et al. Landscape of the gut archaeome in association with geography, ethnicity, urbanization, and diet in the Chinese population. Microbiome 2022;10(01):147

22 McDonald D, Hyde E, Debelius JW, et al; American Gut Consortium. American gut: an open platform for citizen science microbiome research. mSystems 2018;3(03):e00031–e18

23 Knight R, Callewaert C, Marotz C, et al. The microbiome and human biology. Annu Rev Genomics Hum Genet 2017;18:65–86