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Microbiome-Targeted Opportunities in Thalassemia: A Systematic Scoping Review of Human Studies

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 September 2025 and was last updated on 23 September 2025.

INTRODUCTION

Review question / Objective The review will address the following questions: 1) What are the key characteristics of human studies investigating the microbiome in thalassemia? 2) What microbial alterations and functional/metabolic changes have been reported? 3) How do iron supplementation, transfusion-related iron overload, and iron chelation therapy influence microbiome profiles? 4) What methodological approaches have been used to study the microbiome in this population? 5) What knowledge gaps exist, and what are the opportunities for microbiome-targeted interventions?

Background Thalassemia is a group of inherited hemoglobinopathies characterized by ineffective erythropoiesis, chronic anemia, and a clinical dependency on regular blood transfusions. Patients with transfusion-dependent thalassemia (TDT) commonly develop secondary complications including iron overload, endocrinopathies, cardiomyopathy, and chronic liver disease. In addition, long-term exposure to oral iron supplementation, iron chelation therapy, and recurrent antibiotic use creates a unique internal environment that may significantly affect the human microbiome.

Emerging evidence suggests that individuals with thalassemia experience gut microbial dysbiosis, with reports of reduced microbial diversity, depletion of beneficial commensals (e.g., Faecalibacterium), and overrepresentation of pro-inflammatory taxa. These microbial alterations may contribute to systemic inflammation, immune dysregulation, metabolic complications, and progression of comorbidities. Nevertheless, the evidence base remains fragmented, with variability in study design, population characteristics, sequencing technologies, and analytic methods, limiting the ability to draw firm conclusions.Thalassemia, a group of inherited hemoglobinopathies, is characterised by chronic anemia, frequent blood transfusions, and iron

overload in transfusion-dependent patients. These clinical features—together with oral iron supplementation, iron chelation therapy, and frequent antibiotic use—create a unique internal environment that may influence the human microbiome. Preliminary evidence suggests that individuals with thalassemia exhibit gut microbial dysbiosis, including reduced microbial diversity, an increased abundance of pro-inflammatory taxa, and depletion of beneficial species, potentially contributing to inflammation, immune dysregulation, metabolic complications, and comorbidities such as liver disease. However, the scope, depth, and methodological quality of microbiome research in thalassemia remain unclear.

Rationale Despite growing recognition of the microbiome's role in hematological and metabolic diseases, there has been no comprehensive synthesis of human microbiome research in thalassemia. Mapping the available evidence through a systematic scoping review will:
1) Clarify the extent, characteristics, and quality of microbiome studies in thalassemia.
2) Identify consistent patterns of microbial alterations across patient populations.
3) Highlight knowledge gaps in methodology, study design, and outcomes.
4) Provide a foundation for developing microbiome-targeted interventions (e.g., probiotics, prebiotics, dietary modulation, or fecal microbiota transplantation) to improve patient care and mitigate complications.
This review will therefore offer timely insights for researchers, clinicians, and policymakers, while guiding future clinical and translational studies that explore microbiome-based strategies in thalassemia.

METHODS

Strategy of data synthesis - Data from eligible studies will be synthesized descriptively and narratively, in accordance with the objectives of a scoping review. Study characteristics (e.g., year, country, design, population, thalassemia subtype, transfusion and chelation status, microbiome sample source, sequencing platform, and analytic methods) will be extracted and summarized in tabular form.
- Findings will be categorized according to population characteristics (children, adults, transfusion-dependent vs. non-dependent), methodological approaches (e.g., 16S rRNA vs. metagenomics), and clinical variables (iron overload, comorbidities, liver disease). Reported microbial alterations will be grouped into broad domains, including changes in diversity indices, enrichment of pro-inflammatory taxa, depletion of beneficial commensals, and predicted functional pathway shifts.
- A narrative synthesis will be conducted to identify consistent patterns and discrepancies across studies, and findings will be contextualized in relation to clinical outcomes such as inflammation, immune dysregulation, metabolic complications, and organ comorbidities. Methodological quality and limitations of included studies will be discussed to assess the strength of the evidence base.
Finally, evidence gaps and potential microbiome-targeted therapeutic opportunities (e.g., probiotics, prebiotics, dietary modulation, fecal microbiota transplantation) will be highlighted to guide future research and clinical applications.

Eligibility criteria
Population:
- Human participants of any age or sex diagnosed with thalassemia (transfusion-dependent or non-transfusion-dependent).
- Both pediatric and adult populations will be considered.
- Studies including healthy or non-thalassemic comparison groups will also be eligible.
Concept:
- Studies that assess the human microbiome (gut, oral, skin, or other body sites) using culture-independent methods (e.g., 16S rRNA sequencing, shotgun metagenomics, metatranscriptomics, metabolomics).
- Outcomes of interest include microbial diversity indices (alpha, beta), taxonomic composition, functional/metabolic pathway profiles, and associations with clinical or biochemical outcomes (e.g., iron overload, inflammation, organ complications).
Context:
- No restriction on geographic region, healthcare setting, or publication year.
- Studies published in English will be included.
Study Types:
- Original human research: observational (cross-sectional, case–control, cohort), interventional studies, and clinical trials.
- Case series with more than 5 participants will be considered.
- Reviews, editorials, animal studies, in vitro studies, and single case reports will be excluded.

Source of evidence screening and selection
This scoping review will follow the methodological framework proposed by Arksey and O'Malley, with refinements by Levac et al., and will be reported in accordance with the PRISMA Extension for

Scoping Reviews (PRISMA-ScR) checklist. A comprehensive search will be conducted in PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library, from database inception to the present, to identify human studies examining the microbiome in patients with thalassemia. Eligible studies will include observational and interventional research reporting microbial composition, diversity indices, or functional/metabolic profiles, assessed using sequencing or culture-based methods. All records will be imported into a reference management software, and duplicates will be removed. Two reviewers will independently screen titles and abstracts, followed by full-text assessment against the predefined eligibility criteria. Disagreements will be resolved through discussion or consultation with a third reviewer. Data from included studies will be charted independently by two reviewers using a standardized extraction form, with iterative refinement as necessary. Findings will be synthesized descriptively and grouped by study design, microbiome compartment (gut, oral, skin, etc.), and analytic methodology.

Data management All search results will be imported into reference management software EndNote for organization and removal of duplicates. Screening (title/abstract and full text) will be performed using a systematic review management platform Covidence to ensure transparency and reproducibility. A standardized data extraction (charting) form will be developed in Microsoft Excel or Google Sheets, piloted on a subset of studies, and refined iteratively. Extracted variables will include: study identifiers (author, year, country), design, population characteristics (age, sex, thalassemia subtype, transfusion/chelation status), sample source (gut, oral, skin, etc.), microbiome assessment methods, sequencing platform, outcomes (diversity, taxa abundance, functional/metabolic pathways), and relevant clinical correlates (e.g., iron overload, liver disease, inflammation markers). Two reviewers will independently extract and cross-check all data. Any discrepancies will be resolved through discussion or by a third reviewer. A secure backup of all files will be maintained on institutional storage, with version control to track updates.

Reporting results / Analysis of the evidence The results of this scoping review will be reported in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist. A PRISMA flow diagram will be used to document the study selection process, including the number of records identified, screened, included, and excluded, with reasons for exclusion at the full-text stage. Findings will be summarized using both narrative synthesis and descriptive statistics. Extracted data will be presented in tabular and graphical formats, including: Characteristics of included studies (population, setting, design, methods). Microbiome assessment approaches (sample type, sequencing technology, analytic tools). Reported outcomes (diversity indices, taxonomic shifts, functional/metabolic pathways). Associations with clinical features (iron overload, inflammation, organ comorbidities). Results will be grouped by study design, microbiome compartment (gut, oral, skin, etc.), and analytic methodology, to highlight consistencies and discrepancies across the evidence base. No quantitative meta-analysis is planned. Instead, findings will be analyzed thematically to identify recurring patterns of dysbiosis, knowledge gaps, and opportunities for microbiome-targeted interventions.

Presentation of the results The results will be presented in accordance with the PRISMA-ScR framework. A PRISMA flow diagram will illustrate the study selection process. Descriptive data will be summarized in tables, charts, and narrative text.

Language restriction The search will be limited to studies published in English due to feasibility constraints and the likelihood that the vast majority of microbiome and thalassemia research is disseminated in English-language.

Country(ies) involved Thailand.

Keywords Thalassemia, Microbiome, Scoping review.

Contributions of each author

Author 1 - Najun Wanumkarng - Conceived and designed the study, developed the research question, supervised the protocol development.
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Author 2 - Oranut Chatsirisakul - Designed and refined the search strategy, will conduct database searches, manage reference screening (title/abstract and full text), and contribute to data charting.
Email: oranutchatsiri@gmail.com
Author 3 - Natasha Leenabanchong - Will coordinate data extraction, develop and pilot the data charting form, lead the descriptive and thematic synthesis of findings, and prepare draft tables and figures.
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Author 4 - Krit Pongpirul - Provided overall supervision, critical guidance on study design and

methodology, and will oversee quality assurance at all stages. Will contribute to interpretation of findings, ensure adherence to PRISMA-ScR standards, and provide final approval of the manuscript.
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