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APGHN

Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Volume 4 / No. 4

November 2025



www.apghn.com



Published by
Indonesian Society of Pediatric Gastroenterology, Hepatology, and Nutrition

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TABLE OF CONTENT

The Role of Gut Microbiota in Pediatric Obesity: A Systematic Review and Meta Analysis of Microbiota Profiles in Obese versus Normal Weight Children.....158

Karina Fitria Alhaq, Fayyaza Faiz Adams, Athifah Nur Azizah Arif, Pricilia Laurenza Salsabila, Filla Reviyani Suryaningrat

Aerobic Exercise as a Therapeutic Strategy in Children and Adolescents with Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD) and Obesity: A Systematic Review174

Neerissa Arviana Fuad, Annisa Alifianti, Nabila Annisa Harum, William Cheng

Pediatric Hepatic Abscess in a Resource-Limited Setting: A Case Report.....189

Adinda Paramitha Sukma Damayanti, Khalisah Nurjihany Salsabila, Bethseba Brontang Pulinggomang

Treatment of Severe Unconjugated Hyperbilirubinemia with Phenobarbitone in Two First-Degree Siblings with Crigler-Najjar Syndrome (CNS) Type 2: A Success Story.....201

Sachin Kumar, Siddhavatam Rahul Karthik, Gandharav Pahuja, Sarthak Chakrabarti, Prateek Kumar Panda, Indar Kumar Sharawat

Nutritional Formula Selection in Pediatric High-Output Stoma with Acute Kidney Injury: A Review Article208

Gisheila Ruth Anggitha, Ariani Dewi Widodo, Adrian Himawan Singgih

Original Article

The Role of Gut Microbiota in Pediatric Obesity: A Systematic Review and Meta Analysis of Microbiota Profiles in Obese versus Normal Weight Children

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e-ISSN: 2830-5442

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Published:

30st November 2025

DOI:

<https://doi.org/10.58427/apghn.4.4.2025.158-173>

Citation:

Alhaq KF, Adams FF, Arif ANA, Salsabila PL, Suryaningrat FR. The role of gut microbiota in pediatric obesity: a systematic review and meta analysis of microbiota profiles in obese versus normal weight children. *Arch Pediatr Gastr Hepatol Nutr*. 2025;4(4). 158-173

Abstract:

Background: Pediatric obesity is increasingly acknowledged as a significant public health issue with the gut microbiome identified as a potential contributing factor. Increasing evidence indicated that the gut microbiome is integral to metabolic health and the etiology of obesity. Nonetheless, data pertaining specifically to pediatric populations is still limited and underexplored. This study compared the composition of gut microbiota between obese and normal-weight children and to identify microbial patterns associated with pediatric obesity.

Methods: This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A thorough literature search was performed across various databases. We looked at eligible studies and then rated their quality and analyzed them with Newcastle–Ottawa Scale (NOS) and Review Manager (RevMan) 5.4.

Result: This systematic review and meta-analysis included ten studies involving 562 children, utilizing cross-sectional and case-control methodologies. The meta-analysis, which included two studies with 124 participants (64 obese and 60 normal-weight), showed that the Firmicutes to Bacteroidetes (F/B) ratio was much higher in obese children than in normal-weight (mean difference = 5.15; $p < 0.00001$). Taxonomic analysis showed obese children had more members of the phylum Firmicutes, such as *Lactobacillus*, *Clostridium*, and *Megamonas*. On the other hand, Bacteroidetes, especially *Prevotella* and *Bacteroides*, were usually less abundant.

Conclusion: The results indicate that dysbiosis in gut microbiota may contribute to pediatric obesity. These results underscore the potential of gut microbiota modulation as a treatment for childhood obesity. Research is necessary to clarify causal mechanisms and investigate microbiota-based-interventions.

Keyword: gut microbiota, normal weight, obese, pediatric

Introduction

Obesity in children has become a major health problem around the world. The World Health Organization says that the number of overweight kids between the ages of 5 and 19 has gone up by 6.3 percent in 2022.¹ Childhood obesity is when a child stores too much fat, which can lead to serious long-term health problems like a higher risk of diabetes, early death, and heart disease.^{2,3} A child's socioeconomic status, the place they live, their behavior, and their genetic profile can all lead to obesity.⁴

Recent evidence indicates that gut microbiota significantly influences the onset and advancement of obesity. The gut microbiota significantly influences critical metabolic processes, including metabolic health, energy balance, and inflammation.⁵ Advanced gene sequencing technologies, such as 16S rRNA, have produced numerous findings from case-control and cross-sectional studies of children, demonstrating that compositional alterations in the gut microbiota (dysbiosis) are associated with the onset of obesity.⁶

Although the precise compositional variations contributing to pediatric obesity are not consistently defined, the ratio of the phylum Firmicutes to Bacteroidetes (F/B) has been suggested as a potential indicator of dysbiosis. Additionally, changes in the gut microbiome, such as a rise in Firmicutes and a decrease in Bacteroidetes, have been associated in children with subsequent metabolic disorders, including impaired insulin signaling, and non-alcoholic fatty liver disease (NAFLD).^{7,8} For instance, an increased F/B ratio has been noted in obese individuals with hepatic steatosis, indicating that microbial dysbiosis may serve as a mechanistic target for intervention in the metabolic consequences of childhood obesity.^{8,9}

This review sought to compare the gut microbiota composition between obese and normal-weight children, identifying microbial patterns linked to pediatric obesity.

Method

Data Source and Search Strategy

We conducted the study in accordance with PRISMA flow diagrams. Four investigators independently searched studies from EBSCO, Epistemonikos, PubMed, and Science Direct. The search was limited to English-language, peer-reviewed studies published up to May 11th, 2025. The following indicated databases performed the search strategy: (Pediatric OR Child* OR Infant) AND (Obese OR Obesity OR Childhood Obesity) AND (Normal Weight AND Gut Microbiota OR Microbiota OR Microbiome OR Biological Community OR Biotic Community).

Inclusion and Exclusion Criteria

The inclusion criteria included: (1) Children under 18 years as the study population, (2) Children with obesity, (3) Studies reporting gut microbiota composition related to

obesity, including but not limited to the (F/B) ratio, or other relevant bacteria taxa, and (4) Cross-sectional and case-control studies. The exclusion criteria included: (1) Irrelevant title/abstract, (2) Non-english literature, (3) Inaccurate PICO's component, and (4) Irretrievable full text.

Eligibility Criteria

The identified studies were uploaded to Rayyan.id, and any duplicate records were eliminated before screening. Four reviewers independently assessed the titles, abstracts, and full texts. If disagreements arose, a fifth reviewer (FRS) was involved to resolve discrepancies and finalize study selection.

Data Extraction

The extracted data were arranged in a Google Spreadsheet, with the first step being to record study details like the names of the authors, the year of publication, the design of the study, the population (criteria and amount), the exposure, the comparison, the outcome, the diversity (methods and result), the abundance of bacterial species (methods and result), the ratio of Bacteroidetes (methods and result), the differences between bacterial taxa (methods and result), the exposure to define obese, the control to define non-obese, the result, and the conclusion. The next step was to collect data that was specific to the outcome, such as the number of samples, the means, and the standard deviations for the exposure and control groups. All results were shown as odds ratios (OR) with their 95% confidence intervals (CI).

Quality Assessment

We implemented the Newcastle–Ottawa Scale (NOS) tools to assess the risk of bias for the included cross-sectional and case-control study.

Statistical Analysis

A random-effects model was used to combine study results for continuous variables like the F/B ratio. This model took into account the fact that study results might not be the same across studies. The results were reported as mean differences (MD) along with the corresponding 95% confidence interval (CI). The I² statistic was used to measure heterogeneity, and an I² value over 50% was seen as a sign of significant heterogeneity. In addition to the meta-analysis, outcomes unsuitable for quantitative pooling, such as variations in the relative abundance of particular bacterial taxa, were analyzed via a descriptive narrative synthesis. This method involved combining and comparing data from multiple studies to identify comparable trends or discrepancies in gut microbial alterations associated with obesity.

Result

Study Selection

A total of 602 records were identified. After removing 17 duplicates using Rayyan software, 585 records remained. Screening of titles and abstracts resulted in the exclusion of 536 irrelevant studies. Twenty-seven full-text articles were unavailable. Following full-text assessment based on the inclusion and exclusion criteria, 10 studies were included in the final analysis. The study selection process is presented in **Figure 1**.

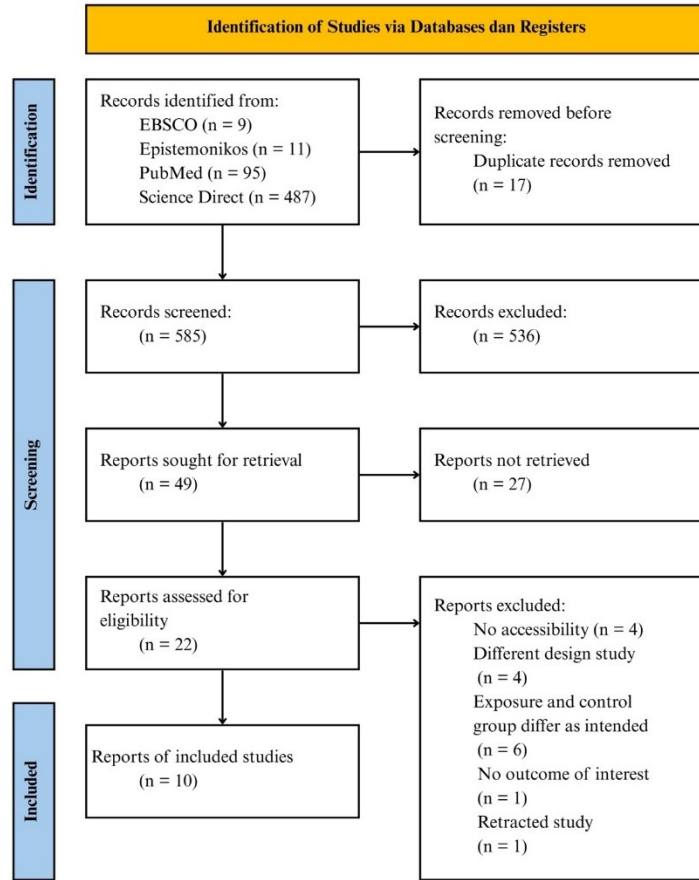


Figure 1. PRISMA Flowchart

Quality Assessment

NOS was used to assess and classify the methodological quality of the included studies, as summarized in **Table 1** for cross-sectional studies and **Table 2** for case-control studies. Based on the NOS, 3 of the 10 studies (30%) were rated as “good quality,” while 7 (70%) were rated as “fair quality.” The scores ranged from a minimum of 6 to a maximum of 8. The lower NOS scores of the case-control study by Borgo et al. were mainly due to limitations in case and control selection and exposure ascertainment.

Table 1. Newcastle-Ottawa Scale Risk of Bias for Cross-Sectional Study

Study Cross-sectional	Selection	Comparability	Outcome	Score NOS	Standard AHRQ
Da Silva et al., 2020 ¹⁰	★★★	★★	★★★	8	Fair quality
Riva et al., 2017 ¹¹	★★★★	★★	★★	8	Good quality
Maya-Lucas et al., 2018 ¹²	★★★	★★	★★	7	Fair quality
Chen et al., 2020 ¹³	★★★	★★	★★★	8	Fair quality
Shin et al., 2020 ¹⁴	★★★	★★	★★★	8	Fair quality
Barczynska et.al., 2018 ¹⁵	★★★	★★	★★	7	Fair quality
Ma et al., 2023 ¹⁶	★★★★	★★	★★	8	Good quality

Table 2. Newcastle-Ottawa Scale Risk of Bias for Case-Control Study

Study Case Control	Selection	Comparability	Exposure	Score NOS	Standard AHRQ
Wang et al., 2024 ¹⁷	★★★★	★★	★★	8	Good quality
Borgo et al., 2016 ¹⁸	★★	★★	★★	6	Fair quality
Li et al., 2025 ³	★★	★★	★★★	7	Fair quality

Study Characteristics

Seven cross-sectional studies and three case-control studies were included, originating from China, Korea, Italy, Poland, Mexico, and Republic of Trinidad and Tobago. In total, 562 children were enrolled, comprising 287 obese children and 275 with normal weight. The definitions of obesity and normal weight varied across studies and are summarized in **Table 3**. Most studies measured bacterial outcomes analysis.

Table 3. Characteristics of Included Studies

Author, Year	Country	Study Design	Population		Exposure	Comparison	Outcome
			Age (years)	N			
Wang et al., 2024 ¹⁷	China	Case-control study	6–16	66 children; 47 obese and 19 normal-weight	Chinese Society of Pediatric Endocrinology and Metabolism (2022) and WHO growth-reference standards	WHO growth-reference standards	Obese children had a higher abundance of Firmicutes and Actinobacteriota and a lower abundance of Bacteroidota, leading to an increased Firmicutes/Bacteroidota ratio. Significant differences in gut microbial composition and predicted metabolic pathways were observed, suggesting microbial dysbiosis associated with obesity.
Borgo et al., 2016 ¹⁸	Italy	Case-control study	8–12	61 children; 28 obese and 33 normal-weight	WHO criteria (BMI z-score; obesity defined by WHO growth standards)	Age- and sex-matched children within WHO normal range	Obese children exhibited lower levels of <i>Akkermansia muciniphila</i> , <i>Faecalibacterium prausnitzii</i> , <i>Bacteroides/Prevotella</i> group, <i>Candida</i> spp., and <i>Saccharomyces</i> spp. compared to normal-weight children, indicating reduced bacterial and fungal diversity and a potential microbial imbalance related to obesity.
Barczyńska et al., 2018 ¹⁵	Poland	Case-control study	6–15	40 children; 10 overweight, 10 obese, and 20 normal-weight	International Obesity Task Force (IOTF) criteria (Cole et al., 2012)	IOTF reference range (BMI 18.5–22.38)	Obese children showed a predominance of Firmicutes (<i>Clostridium</i> , <i>Lactobacillus</i>) and a reduction in Bacteroidetes (<i>Bacteroides</i> , <i>Prevotella</i>) compared with normal-weight children. Fecal samples from obese children also contained lower levels of short-chain fatty acids (SCFAs), indicating altered microbial metabolism associated with obesity.
Chen et al., 2020 ¹³	China	Case-control study	6–11	51 children; 28 obese and 23 normal-weight	BMI cutoffs for overweight and obesity in Chinese children and adolescents (Li et al., 2010)	BMI within normal range per Li et al., 2010	Obese children exhibited significantly lower gut microbial diversity and richness than normal-weight children. The relative abundance of Bacteroidetes was reduced, while Firmicutes and Actinobacteria were more abundant. <i>Faecalibacterium</i> , <i>Phascolarctobacterium</i> , <i>Lachnospira</i> , <i>Megamonas</i> , and <i>Haemophilus</i> were elevated in obese children, whereas <i>Oscillospira</i> and <i>Dialister</i> were reduced, indicating gut microbiota dysbiosis associated with obesity.

Author, Year	Country	Study Design	Population		Exposure	Comparison	Outcome
			Age (years)	N			
Ma et al., 2023 ¹⁶	China	Cross-sectional case-control study	3–5	60 preschool children; 30 obese and 30 normal-weight	Centers for Disease Control and Prevention (CDC) criteria (BMI \geq 95th percentile)	BMI between 5th and 85th percentile (CDC reference)	Children with obesity had significant alterations in both oral and gut microbiota composition, with higher Firmicutes/Bacteroidetes ratios than controls. <i>Faecalibacterium</i> , <i>Tyzzelerella</i> , and <i>Klebsiella</i> were more abundant in obese children's fecal samples, while <i>Filifactor</i> and <i>Butyrivibrio</i> were enriched in oral samples. A total of 148 bacterial pathways differed significantly, mainly in biosynthetic functions, suggesting functional and compositional dysbiosis linked to obesity.
Shin and Cho, 2020 ¹⁴	South Korea	Cross-sectional observational study	5–13	46 children; 22 obese and 24 normal-weight	Korean National Growth Chart 2017 (BMI \geq 95th percentile)	BMI 5th–85th percentile (Korean Growth Chart)	Obese children showed a significant decrease in Bacteroidetes abundance, which correlated negatively with BMI z-score, while Firmicutes and Actinobacteria proportions increased. Beta diversity differed significantly between groups. Predicted microbial functions related to carbohydrate and lipid metabolism were enriched in normal-weight children, while obese children exhibited distinct clustering of genera associated with inflammation and metabolic risk.
Riva et al., 2017 ¹¹	Italy	Case-control study	6–16	78 children; 42 obese and 36 normal-weight	BMI z-score \geq 2 SD (WHO criteria)	BMI z-score between -2 SD and $+1$ SD (WHO criteria)	Obese children exhibited a distinct gut microbiota composition, characterized by increased Firmicutes (72.1%) and decreased Bacteroidetes (16.6%), resulting in a significantly higher Firmicutes/Bacteroidetes ratio (7.7 vs. 2.6; $p < 0.0001$). SCFA concentrations (acetate, propionate, butyrate) were significantly higher in obese children ($p < 0.05$), and BMI z-scores positively correlated with SCFA levels and Firmicutes abundance, indicating that microbial shifts and elevated fermentation activity are associated with pediatric

Author, Year	Country	Study Design	Population		Exposure	Comparison	Outcome
			Age (years)	N			
Maya-Lucas et al., 2018 ¹²	Mexico	Case-control metagenomic study	5–11	20 children; 10 obese and 10 normal-weight	BMI percentile \geq 95th (WHO criteria)	BMI percentile 5th–85th	obesity. Obese Mexican children had altered gut microbiome composition, with a <i>Prevotella</i> -dominated enterotype (Enterotype 2) in 50% of obese children, while normal-weight children mainly exhibited a <i>Ruminococcus</i> -dominated enterotype (Enterotype 3). <i>Megamonas</i> spp. were significantly enriched, and Oscillospiraceae members were depleted in obese children, correlating negatively with serum cholesterol. Functional pathway analysis revealed that glycolysis pathways (Glycolysis I & II) were overrepresented in normal-weight children, while obese children showed enrichment of catabolic genes (α -amylase) related to starch metabolism, indicating functional and compositional dysbiosis linked to lipid metabolism and obesity.
Da Silva et al., 2020 ¹⁰	Brazil	Cross-sectional case-control study	6–14	51 children; 21 obese/overweight and 30 normal-weight	BMI \geq 97th percentile (WHO criteria)	BMI 15th–85th percentile	Obese children presented reduced microbial diversity and higher abundance of Firmicutes and Actinobacteria, with lower Bacteroidetes compared to controls. Lachnospiraceae and Ruminococcaceae were predominant in obese subjects, while <i>Bacteroides</i> and <i>Prevotella</i> were enriched in normal-weight children. Functional prediction indicated increased carbohydrate metabolism pathways in obese children, suggesting that gut microbiota composition contributes to enhanced energy harvest and obesity risk.
Li et al., 2025 ³	China	Cross-sectional case-control study	7–14	99 children; 49 obese and 50 normal-weight	Chinese BMI-for-age reference \geq 95th percentile	5th–85th percentile (Chinese standard)	Obese children exhibited decreased microbial richness and diversity, with a significant increase in Firmicutes and Proteobacteria, and reduction in Bacteroidetes and Verrucomicrobia. The Firmicutes/Bacteroidetes ratio

Author, Year	Country	Study Design	Population		Exposure	Comparison	Outcome
			Age (years)	N			
							correlated positively with BMI and waist circumference. <i>Faecalibacterium</i> , <i>Blautia</i> , and <i>Clostridium</i> were enriched in obese children, whereas <i>Bacteroides</i> and <i>Akkermansia</i> were more abundant in normal-weight peers, indicating gut microbiota dysbiosis strongly associated with metabolic indicators of childhood obesity.

Microbiota Composition in Obese Children

Shown in **Table 4**, obese children exhibited modifications in gut microbiota, marked by an increase in Firmicutes and Proteobacteria, coupled with a decrease in Bacteroidetes. Multiple studies have also shown a lower diversity of microbes and a higher F/B ratio.

Phylum-level changes

Wang et al. and Riva et al. reported a predominance of Firmicutes, with Riva et al. documenting a significantly higher F/B ratio.^{11, 17} Furthermore, Shin et al. noted a negative correlation between Bacteroidetes abundance and BMI z-scores, whereas Li et al. (2025) reported an enrichment of Proteobacteria, including *Enterobacter*, *Haemophilus*, and *Sutterella*.^{3, 14}

Genus- and species-level changes

Barczyńska et al. observed elevated levels of *Clostridium* and *Lactobacillus*, accompanied by decreases in *Prevotella* and *Bacteroides*.¹⁵ Similarly, Da Silva et al. identified increased *Lactobacillus* and decreased *Bifidobacterium*.¹⁰ Ma et al. also found that *Fusobacterium*, *Butyrivibrio*, *Faecalibacterium*, *Tyzzerella*, and *Klebsiella* were important groups of bacteria linked to obesity.¹⁶ Maya-Lucas et al. described higher abundances of *Megamonas*, *Ruminococcus*, *Clostridium citroniae*, *Streptococcus thermophilus*, and *Oscillibacter*, with reductions in *Bacteroides* and *Desulfovibrionaceae*.¹² In addition, Borgo et al. emphasized the depletion of *A. muciniphila* and *F. prausnitzii* as notable in obese children.¹⁸

Diversity and community structure

Da Silva et al. noted diminished overall microbial diversity, whereas Chen et al. validated a general reduction in gut microbiota, with no substantial alterations in Firmicutes.^{10, 13}

Table 4. Result of Microbiota Profile in Obese Children

Author, year	↑ Microbiota in Obesity	↓ Microbiota in Obesity	Significance of Findings
Wang et al., 2024 ¹⁷	Firmicutes (63.5%)	Bacteroidota (37.7%)	-
Borgo et al., 2016 ¹⁸	<i>Bifidobacterium</i> spp, <i>Lactobacillus</i> spp, Enterobacteriaceae, <i>Saccharomyces</i> spp, <i>Candida</i> spp	-	Significant: <i>A. muciniphila</i> , <i>F. prausnitzii</i> , <i>Bacteroides/Prevotella</i> group
Barczynska et.al., 2018 ¹⁵	Firmicutes (<i>Clostridium</i> , <i>Lactobacillus</i>)	Bacteroidetes (<i>Prevotella</i> , <i>Bacteroides</i>)	<i>Bifidobacterium</i> (p = 0.036), <i>Bacteroides</i> (p < 0.01)
Ma, et.al, 2023 ¹⁶	<i>Fusobacterium</i> , <i>Butyrivibrio</i> , <i>Faecalibacterium</i> , <i>Typhloferella</i> , <i>Klebsiella</i>	-	Significant based on LEfSe
Chen et al., 2020 ¹³	-	Overall gut microbiota decreased	No significant change in Firmicutes
Shin et al., 2020	-	Bacteroidetes	Negative correlation with BMI z-score
Li et al., 2025 ³	Proteobacteria (<i>Enterobacter</i> , <i>Haemophilus</i> , <i>Sutterella</i>)	<i>Oscillibacter</i> , <i>Alistipes</i>	Proteobacteria (p = 0.018)
Da Silva et al., 2020 ¹⁰	Firmicutes, <i>Lactobacillus</i>	<i>Bifidobacterium</i>	Firmicutes (p = 0.001), <i>Lactobacillus</i> (p = 0.049), <i>Bifido</i> (p = 0.039), reduced diversity (p = 0.009)
Riva et al., 2017 ¹¹	Firmicutes, Ruminococcaceae	Bacteroidaceae, Bacteroidetes	Firmicutes/Bacteroidetes ratio increased (p < 0.00001)
Maya-Lucas et al., 2018 ¹²	<i>Megamonas</i> spp, <i>Ruminococcus</i> spp, <i>Clostridium citroniae</i> , <i>Streptococcus thermophilus</i> , <i>Oscillibacter</i> spp	<i>Bacteroides</i> spp, Desulfovibrionaceae	Higher Human herpesvirus 4 in obese children (p = 0.017)

Quantitative Assessment

The forest plot shown in **Figure 2.** summarized a meta-analysis that compared a continuous outcome between children with obesity and those with normal weight across two studies (Riva et al. and Shin et al.). The pooled mean difference was 5.15 (95% CI: 3.07-7.22, p<0.00001), which means that the measured variable was much higher in the obesity group. The study by Riva et al. demonstrated a significant difference (MD = 5.10, 95% CI: 2.88-7.32), whereas the study by Shin et al. indicated a similar directional effect, albeit not statistically significant (MD = 5.46, 95% CI: -0.39-11.31).^{11, 14}

There was no heterogeneity among studies (I² = 0%, p = 0.91), indicating consistent findings across datasets. The overall effect, represented by the diamond to the right

of the line of no effect, indicated that the analyzed variable was significantly higher in children with obesity compared to their normal-weight counterparts.

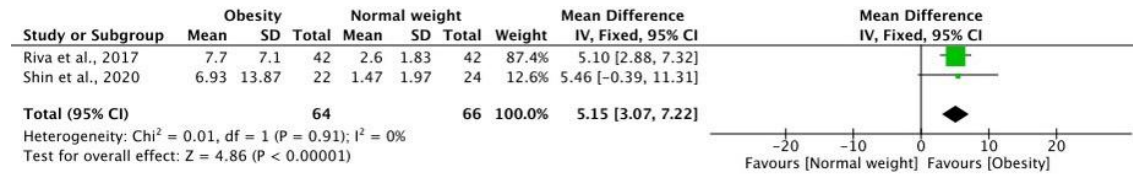


Figure 2. Meta-Analysis using Review Manager 5.4

Discussion

This systematic review and meta-analysis included ten studies that varied by demographic, study type, and country. The majority were cross-sectional, with populations ranging from 20 to 99 and children ages 3 to 16 years old.^{3, 10-18} Exposures included children with obesity based on body mass index (BMI z-score) compared with children of normal weight. The risk of bias using NOS in **Table 1** and **Table 2** resulted in three studies with good quality and seven with fair quality. A forest plot showed that the obese group had a much higher F/B ratio than the normal-weight group.^{11, 14} These findings reveal differences in the gut microbiome composition between obese and normal-weight children. Obese children exhibited a greater relative prevalence of Firmicutes bacteria compared to Bacteroidetes, leading to an elevated F/B ratio. This suggests that an imbalance in gut flora may elevate the risk of obesity.

Figure 3 illustrates the complex interplay between gut microbiota composition and the host's energy metabolism. It shows how the balance of microbes affects the processing of nutrients, the extraction of energy, and metabolic health. The gut microbiota plays a crucial role in regulating nutrition, energy metabolism, and the pathogenesis of diseases, including obesity.¹⁹ The bacterial phylum Firmicutes has been associated with an increased ability to harvest energy among its members. More Firmicutes in the body helps the body get more calories from food, which leads to more energy intake and fat storage.²⁰ In the left pathway, gut bacteria break down carbohydrates that can't be digested through fermentation, which makes short-chain fatty acids (SCFAs). These SCFAs act as signaling molecules that affect the release of the satiety hormones Glucagon-Like Peptide-1 (GLP-1) and Peptide YY (PYY) which enhance fat metabolism, reduce hunger, and suppress inflammation. This biochemical signaling not only promotes efficient energy use but also maintains metabolic and immune balance.²¹ Whereas, in the right pathway, gut bacteria contain genes that code for carbohydrate-active enzymes (CAZymes), which are essential for breaking down complex carbohydrates into simpler, absorbable components. This enzymatic breakdown made it easier for Firmicutes to get energy, which could have led to more calories being taken in and more fat being stored.¹⁷

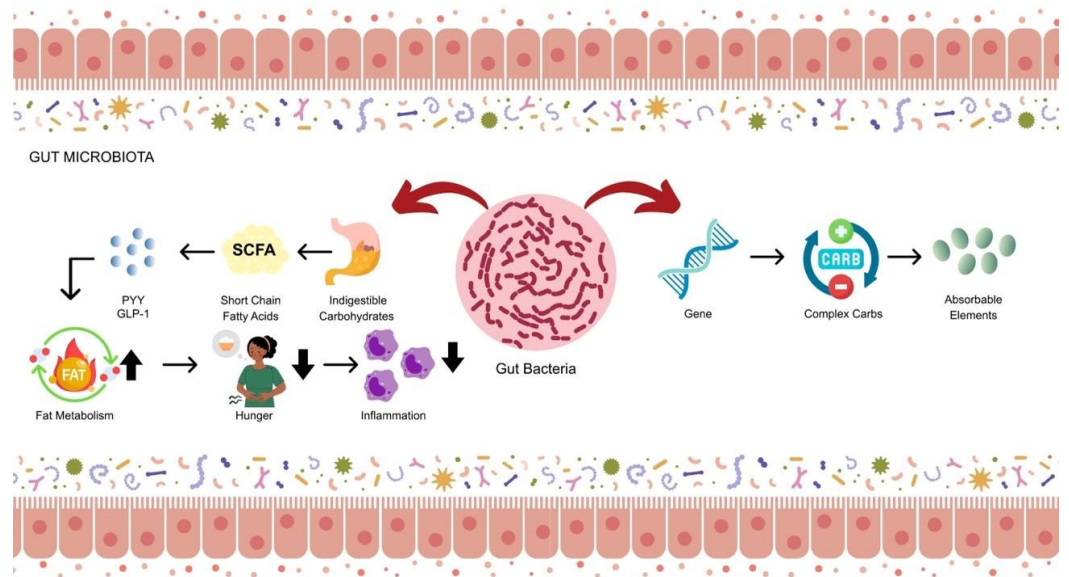


Figure 3. The Role of Gut Microbiota in Energy Metabolism

A decrease in the Bacteroidetes population is linked to continued high-fat food consumption, which may contribute to obesity.²² In contrast, Bacteroidetes have anti-obesity properties by enhancing insulin sensitivity, raising serum GLP-1, and promoting amino acid catabolism.²³ This finding is consistent with the observed higher F/B ratio in the intestines of obese children. Therefore, the abundance of Bacteroidetes and Firmicutes can be utilized as a biomarker to distinguish between obese children and those of normal weight.

In addition to the phylum-level changes in Firmicutes and Bacteroidetes, some of the studies included found that important beneficial taxa like *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* were less common. *F. prausnitzii* is a crucial butyrate-producing strain vital for gastrointestinal and metabolic health. *A. muciniphila*, on the other hand, is not a butyrate producer, but it is important for keeping the intestinal mucous layer intact, making acetate and propionate, controlling lipid metabolism, and making the intestines less permeable. Both taxa have been identified in markedly reduced abundance in obese or overweight children, indicating their protective functions against metabolic dysregulation.²⁴

This review has several limitations that should be acknowledged. First, the majority of the studies included were cross-sectional, limiting the capacity to establish causal inferences or ascertain temporal relationships. It is still not clear if changes in the gut microbiota happen before obesity and growth problems happen, or if they happen because of changes in diet and metabolism. Longitudinal studies examining dietary and physiological factors, alongside comprehensive functional analyses of the metabolic activity of the gut microbiota, are essential to elucidate this directionality.

Since all the studies included came from China, Korea, and Italy, and there were also studies from Poland, Mexico, and the Republic of Trinidad and Tobago, there is a big gap in data from Southeast Asia, such as Indonesia. Future prospective cohort studies in this region are necessary to examine regional dietary patterns, genetic backgrounds, and environmental exposures that may affect gut microbiota composition and its association with pediatric obesity. Such research would augment the applicability and generalizability of findings across varied populations.

Second, the studies that were included had problems with the way they collected samples. Stool samples, although frequently utilized, may not adequately reflect the microbial environment along the intestinal wall where host–microbiome interactions take place. This method provides limited information on microbial dynamics in the small intestine, the primary site of nutrient absorption. Third, the outcome parameters across studies were heterogeneous. The F/B ratio was the most consistently reported and widely used measure of gut health, but other results were very different, making it hard to compare and combine them. Only two studies (Riva et al. and Shin et al.) were suitable for quantitative synthesis regarding the F/B ratio, involving 124 participants (64 obese and 60 of normal weight), with one assessed as good quality and the other as fair quality. Although the pooled analysis demonstrated high homogeneity ($I^2 = 0\%$), the exclusion of the fair-quality study would leave insufficient data for meaningful pooling, a sensitivity analysis could not be performed.^{11, 14} This represents the limitations of the present review, and future meta-analysis including a greater number of high quality studies are needed to confirm the robustness of these findings.

The literature search in this review was limited to four databases and English-language studies that the reviewer could fully access, which also created limitations. While major databases such as Scopus and Web of Science, as well as grey literature sources, were not included, this approach was chosen to maintain methodological consistency. Consequently, some relevant studies may have been missed. Furthermore, the review predominantly contrasted obese or overweight children with their healthy peers, lacking a comprehensive examination of underlying biological mechanisms or broader determinants, such as metabolic parameters. These limitations highlight the necessity for forthcoming studies utilizing longitudinal designs and integrative multi-omics methodologies to more effectively clarify the intricate interactions among gut microbiota, nutrition, and child growth across various populations.

The existing evidence highlights the necessity for longitudinal and mechanistic studies to determine whether alterations in gut microbiota are a cause or a consequence of pediatric obesity. Standardized methodologies and the integration of multi-omics approaches are crucial for enhancing comparability and yielding more profound

insights into host-microbe interactions. Investigating contextual factors such as diet, antibiotic exposure, genetics, and regional variations will enhance the applicability of findings across diverse populations. Along with their therapeutic potential, the persistent patterns of microbial imbalance also create possibilities for gut microbiota profiles to function as screening instruments for the early detection of children predisposed to obesity.

From a clinical standpoint, these insights underscore the potential to explore microbiota-targeted approaches, including dietary interventions, prebiotics, probiotics, or synbiotics, as viable instruments for prevention and treatment. *Lactobacillus rhamnosus*, *Lactobacillus gasseri* SBT2055, and *Bifidobacterium breve* B-3 are some of the probiotic strains that have shown promise in changing gut dysbiosis related to obesity. *L. rhamnosus* demonstrates anti-obesogenic properties, in part by generating SCFAs that can influence hunger and satiety pathways at both peripheral and central levels. While the majority of studies did not directly isolate SCFAs from this species, it possesses the ability to produce them under diverse conditions, thereby contributing to anti-inflammatory, antimicrobial, and immunomodulatory effects that maintain intestinal integrity and permeability.²⁵ Randomized trials have shown that *L. gasseri* SBT2055 can help people lose weight by lowering their body mass index, waist circumference, abdominal visceral fat, and hip circumference after 12 weeks of supplementation. These effects are probably due to changes in lipid metabolism and the body's energy balance.²⁶ Likewise, supplementation with *Bifidobacterium breve* B-3 (BB-3) in double-blind, placebo-controlled trials resulted in substantial reductions in body weight, waist circumference, and hip circumference, demonstrating its safety and effectiveness in decreasing body fat.²⁷ Moreover, *A. muciniphila* supplementation has shown potential in enhancing metabolic parameters and preserving intestinal barrier integrity, whereas *F. prausnitzii* exhibits anti-inflammatory properties that promote metabolic health.^{28, 29}

To put these ideas into action, we need to do strict tests to see how well they work and how safe they are for kids. Advancing this line of research may ultimately contribute to precision medicine, in which interventions can be customized based on individual microbial and metabolic profiles, thereby improving the efficacy of obesity management in children.

Conclusion

In conclusion, our findings indicate that an imbalance in gut microbiota may contribute to pediatric obesity. The analysis shows that obese children have less microbial diversity overall and a higher F/B ratio. The increase in Firmicutes may lead to greater production of short-chain fatty acids, which in excess provide more energy. Meanwhile, the decrease in Bacteroidetes is linked to lower microbial diversity, which continued high-fat food consumption, and may contribute to obesity. Together, these

mechanism may explain how microbial imbalance contribute to metabolic disruption and fat accumulation in pediatric obesity. Nevertheless, further research is needed to clarify causal mechanisms and explore microbiota-based interventions in children

Acknowledgement

The authors gratefully acknowledge all those who contributed to this work. The graphic elements used in the figures were designed using Canva resources (www.canva.com).

Conflict of Interest

There is no conflict of interest.

Funding Statement

This systematic review and meta-analysis article receive no specific grants by any external funding.

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Original Article

Aerobic Exercise as a Therapeutic Strategy in Children and Adolescents with Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD) and Obesity: A Systematic Review

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e-ISSN: 2830-5442
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Published:
30th November 2025

DOI:
<https://doi.org/10.58427/apghn.4.4.2025.174-188>

Citation:
Fuad NA, Alifianti A, Harum NA, Cheng W. Aerobic exercise as a therapeutic strategy in children and adolescents with metabolic dysfunction associated steatotic liver disease (masld) and obesity: a systematic review. *Arch Pediatr Gastr Hepatol Nutr.* 2025;4(4). 174-188

Abstract:

Background: Metabolic dysfunction-associated Steatotic Liver Disease (MASLD) is the most prevalent chronic liver disease in children and adolescents, particularly those with obesity. MASLD often progresses to serious hepatic and metabolic complications. Although aerobic exercise (AE) is widely recommended as a first-line lifestyle intervention, its therapeutic efficacy remains unclear. This study evaluates the effects of AE on body composition, liver enzyme, lipid profile, metabolic markers, and liver imaging.

Methods: A comprehensive literature search was conducted across PubMed, Cochrane Library, Scopus, and EBSCOhost. Clinical studies involving AE in pediatric patients (≤ 18 years) with MASLD and BMI ≥ 85 th percentile were independently screened.

Result: From 141 records, five studies (3 RCT, 2 Interventional Study) involving 97 children (mean age 13.22 ± 2.24 years) met the inclusion criteria. AE protocols typically consisted of 30-60 minutes sessions, thrice weekly, over 1-12 months. AE intervention had significantly decreased BMI in 2 of 3 studies, and visceral fat in 1 of 2, with no change in lean mass. Significant improvements of AST and ALT ($\Delta -1.0$ to -34.0 and -1.0 to -27.17) were reported in 3 of 5 studies. However, lipid profiles showed inconsistent effects, and most metabolic markers (glucose, insulin, HOMA-IR, adiponectin, leptin) showed no significant changes. Liver imaging from 3 studies reported resolution or reduced MASLD severity.

Conclusion: AE provides selective benefits in MASLD-obese children and adolescents. Improvements were observed in BMI, liver enzymes, and liver imaging, while the effects on lipid and metabolic markers remain inconsistent.

Keyword: aerobic exercise, liver biomarker, liver imaging, masld, obesity

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a significant health concern among children and adolescents, particularly in the context of rising obesity rates.¹ The nomenclature for this condition has evolved considerably over recent years. Initially, the term non-alcoholic fatty liver disease (NAFLD) was widely adopted to describe hepatic steatosis in the absence of significant alcohol consumption. However, in 2020, the scientific community shifted to the term metabolic dysfunction-associated fatty liver disease (MAFLD), which better reflects the underlying metabolic factors contributing to the condition.² This evolution continued in 2023 with the introduction of the term metabolic dysfunction-associated steatotic liver disease (MASLD).³ MASLD is characterized by the pathological accumulation of fat in the liver, which can subsequently progress to inflammation, fibrosis, and ultimately liver failure if left untreated.⁴

The prevalence of pediatric MASLD demonstrates considerable variation across different studies, influenced by factors such as geographic location, study population characteristics, and diagnostic methodologies. A comprehensive meta-analysis conducted from 1997-2023 demonstrated that the prevalence of MASLD in children was 13% in the general population and 47% in obese children, with a notably higher prevalence observed among males. Geographic variations are particularly striking, with the prevalence of MASDL being highest in studies conducted in the Asian region, affecting 15% of the general pediatric population and 53% of obese children.⁵ Another study revealed the prevalence of MASDL in the pediatric population to be 7.4% in the general pediatric population and up to 52.5% in obese children, with the highest rates documented in North America (8.53%), followed by Asia (7.01%), and the lowest prevalence in Europe (1.65%).⁶

The etiology of pediatric MASLD appears to differ from adult presentations, with maternal and perinatal risk factors potentially exerting greater influence on MASLD development compared to environmental factors.⁷ The strong correlation between MASLD prevalence and increased body mass index (BMI) underscores the critical role of metabolic dysfunction in disease pathogenesis.⁸ The natural history of pediatric MASLD reveals a highly variable clinical course with outcomes ranging from spontaneous resolution to life-threatening complications. Among children with MASLD who have undergone liver biopsy, 16% demonstrated significant fibrosis and 0-1% had developed cirrhosis.^{9,10} Long-term follow-up studies demonstrate that while some children experience improvement in hepatic steatosis and fibrosis with standard lifestyle interventions, others progress to advanced liver disease requiring transplantation or resulting in mortality.¹¹

Current clinical guidelines recommend lifestyle modifications as the primary treatment for MASLD, with aerobic exercise (AE) widely advocated as a first-line intervention. However, despite its widespread recommendation, the therapeutic efficacy of aerobic exercise in pediatric MASLD remains unclear. This systematic review aims to evaluate the effectiveness of aerobic exercise interventions in pediatric MASLD and provide clarity on its therapeutic potential as a treatment modality for this increasingly prevalent condition.

Method

Search Strategy

A comprehensive literature search was performed across PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and EBSCOhost. Our search terms included various combinations of “Metabolic dysfunction-associated steatotic liver disease”, “MASLD”, “Pediatric” “Children”, “Obesity”, “Aerobic exercise”. We utilized Boolean operators (AND, OR) to effectively combine these terms. The search was restricted to articles published in English, with no limitations on publication date.

Study Selection and Eligibility Criteria

We included a wide range of study designs in our review. The target population consisted of published studies involving children and adolescents aged 0-18 years who had confirmed diagnosis of MASLD alongside obesity, investigating the impact of aerobic exercise on improving biomarkers related to MASLD. Aerobic exercise was defined as any structured physical activity program aimed at enhancing cardiovascular fitness, characterized by sustained, rhythmic movement involving large muscle groups.

Outcomes

Our primary outcomes focused on improvements in biochemical markers of liver function, specifically serum glutamic-oxaloacetic transaminase (SGOT/AST), serum glutamic-pyruvic transaminase (SGPT/ALT), and lipid profile parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides. Secondary outcomes included biomarkers of metabolic dysfunction, such as homeostatic model assessment for insulin resistance (HOMA-IR), fasting insulin levels, and fasting blood glucose concentrations.

Data Extraction

The study selection process was carried out by two independent reviewers. Initially, we screened titles and abstracts against our eligibility criteria, followed by a full-text assessment of potentially relevant articles. Any disagreements between reviewers were resolved through discussion. The extracted data included study characteristics (author, publication year, study design), participant demographics (age, sex, BMI), intervention details (type, intensity, frequency, duration of aerobic exercise), and outcome measures (baseline and post-intervention values for all relevant biomarkers).

Quality Assessment and Risk of Bias

To evaluate the methodological quality and risk of bias of included studies, we employed appropriate tools based on study design. For randomized controlled trials (RCTs), we utilised the Revised Cochrane Risk of Bias tool (RoB 2), which assesses various domains, including randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. For non-randomized studies, the Risk of Bias in Non-randomized Studies of Intervention (ROBINS-I) tool was applied, which evaluates bias related to confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and selection of reported results. All quality assessments were conducted by two independent reviewers, with any disagreements resolved through discussion.

Data synthesis

We presented a narrative synthesis of the findings in a tabular format to facilitate comparison across the studies included in our review. This approach allows for a clearer understanding of the impact of aerobic exercise on MASLD-related biomarkers in the pediatric population.

Result

Population and Study Characteristics

A total of 153 studies were identified in the initial comprehensive search of 4 databases. Twelve duplicate records were removed before screening, resulting in a total of 141 studies. Another 84 studies were disqualified because they were irrelevant records identified by automated screening tools. Fifty-seven studies were assessed through title and abstract, of which 14 had an incompatible study design, 15 involved deviant interventions, 12 had incompatible outcome measures, and 11 did not meet the inclusion criteria. At last, five studies were identified that fulfilled the prespecified inclusion criteria. A visual representation of our search process is provided through a PRISMA flow diagram (**Figure 1**).

The quality of each study was assessed using various tools, including the Cochrane Risk of Bias tool for RCT study designs, the Risk of Bias in Non-randomized Studies of Intervention (ROBINS-I) tool for prospective observational study designs, and the Newcastle-Ottawa Scale (NOS) tool for prospective observational studies. All the studies indicated a low risk of bias, suggesting that the findings are likely to be minimally affected by error.

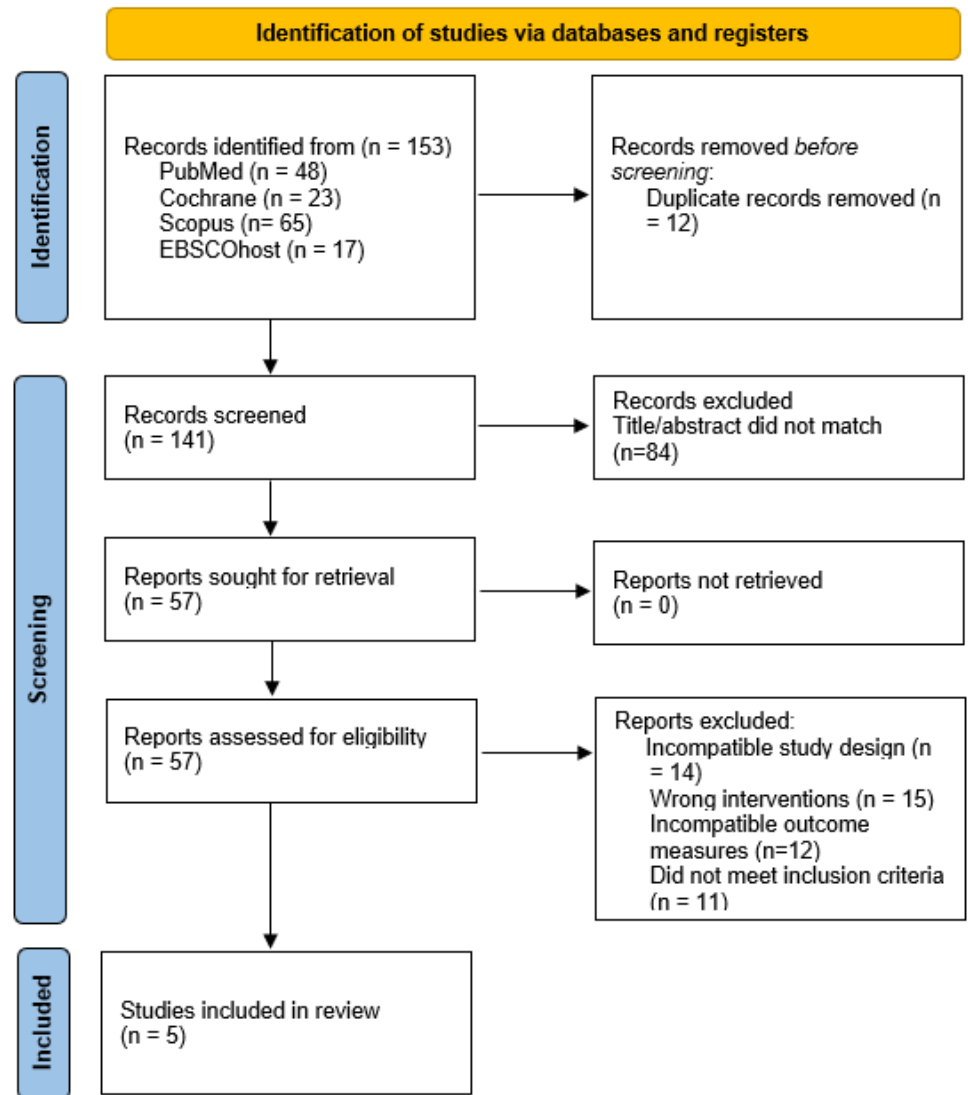


Figure 1. PRISMA flowchart

The characteristics of all eligible studies are summarized in **Table 1**. This review included 203 study participants who met the inclusion criteria for this study, which were children and adolescents aged 1-19 years, obesity as defined by their BMI, and the presence or at risk for MASLD based on their laboratory and imaging results. One study reported a 71.1% prevalence of liver steatosis during ultrasonography screening. However, this study still met the inclusion criteria, considering liver steatosis remained predominant within the study population, and they also had elevated liver enzymes, which may indicate that stress or inflammation had occurred in their liver.

Table 1. Study Characteristics

Author, Year	Study Design	Study Population		Intervention	Control	Duration	Follow up	Outcomes
		n	Obesity					
Santomauro et al. (2012) ¹²	Non-RCT	24 Children and adolescents	BMI > 97th percentile (P97) for age and sex	Confirmed by ultrasonography	Baseline (before intervention)	12 months	12 months	<ul style="list-style-type: none"> Weight (kg) Height (cm) BMI (kg/m²) BMI Z-Score Abdominal circ. (cm) Waist/hip ratio Fatty area (mm²) Muscular area (mm²) Blood Pressure (mmHg) Calories(kcal/day) Carbohydrates (g) Fat (g) Protein (g) Physical Activity (h/week) Exercise : yes/no (%) Steps/day Hours/day TV and video
Malecki et al. (2021) ¹³	Prospective Observational cohort	49 Children and adolescents	BMI greater than 1-2 SD above the WHO Growth reference	Confirmed MASLD based on medical history, physical examination and increased aminotransferase levels and hepatic steatosis in abdominal ultrasonography	Baseline (before intervention)	2.45±1.45 years	Every 3 months during the first year and every 6 months afterwards during outpatient visits.	<ul style="list-style-type: none"> Weight (kg) Height (cm) BMI (kg/m²) ALT (IU/L) AST (IU/L) GGT (IU/L) PLT (G/L) APRI
Lefere et al. (2022) ¹⁴	Uncontrolled prospective cohort	79 Children and adolescents	Median BMI was 36.0 kg/m ²	Liver steatosis on ultrasound was present in 71.1% of patients	Baseline (before intervention)	11–12 months	5-6 and 11-12 months	<ul style="list-style-type: none"> CAP (dB/m) TE (kPa) Weight (z-score) BMI Z-Score Waist circumference (cm) Hip circumference (cm) Body fat (%) Body weight loss (%) BMI loss (%) ALT (U/L)

Author, Year	Study Design	Study Population			Intervention	Control	Duration	Follow up	Outcomes
		n	Obesity	MASLD					
					ogical support			<ul style="list-style-type: none"> • AST (U/L) • Total cholesterol (mg/dL) • HDL cholesterol (mg/dL) • LDL cholesterol (mg/dL) • Triglycerides (mg/dL) • Glucose (mg/dL) • Insulin (mIU/L) • HOMA-IR • hs-CRP (mg/dL) 	
de Piano et al. (2012) ¹⁵	RCT	14 adolescents	BMI was 36.55±4.6 kg/m ²	MASLD according to ultrasonography	Aerobic vs aerobic + resistance training and dietary modification (60-min session three times a week)	Baseline (before intervention)	12 months	12 months	<ul style="list-style-type: none"> • Weight (kg) • BMI (kg/m²) • Fat mass (%) • Fat mass (kg) • Lean mass (kg) • Visceral (cm) • Sub (cm) • Glycemia • Insulin • HOMA-IR • Total cholesterol (mg/dL) • LDL cholesterol (mg/dL) • VLDL • HDL cholesterol (mg/dL) • Triglycerides (mg/dL) • AST • ALT • GGT
Tas et al. (2023) ¹⁶	RCT	37 adolescents	BMI ≥ 95th percentile for age and sex	High risk for MASLD, defined as VCTE-CAP ≥ 241 dB/m	4-week supervised HIIT program (60 minutes, 3 times a week)	No exercise	1 month	1 month	<ul style="list-style-type: none"> • Weight (kg) • BMI z-score • Body fat percent (%) • LBM (kg) • Visceral fat area (cm²) • IHTG (%) • CAP score (dB/m) • LSM Score (Kpa) • VO₂ peak (ml.min/kg per • LBM • Fasting glucose (mg/dL) • 2h-glucose (mg/dL) • Fasting insulin (uIU/mL) • 2h-Insulin (uIU/mL) • HOMA-IR

Author, Year	Study Design	Study Population		Intervention	Control	Duration	Follow up	Outcomes
		n	Obesity MASLD					
								<ul style="list-style-type: none"> • TC (mg/dL) • HDL-c (mg/dL) • LDL (mg/dL) • TG (mg/dL) • ALT (IU/L) • AST (IU/L) • Adiponectin ng/ml) • Leptin (pg/mL) • FGF-21 (pg/mL)

ALT: Alanine Aminotransferase; APRI: AST-to-Platelet Ratio Index; AST: Aspartate Aminotransferase; BMI: Body Mass Index; CAP: Controlled Attenuation Parameter; FGF-21: Fibroblast Growth Factor-21; GGT: Gamma-Glutamyl Transferase; HDL: High-Density Lipoprotein Cholesterol; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; IHTG: Intrahepatic Triglyceride Content; LDL: Low-Density Lipoprotein Cholesterol; LSM: Liver Stiffness Measurement; PLT: Platelet Count; RCT: Randomized Controlled Trial; TC: Total Cholesterol; TE: Transient Elastography; TG: Triglycerides; VCTE: Vibration-Controlled Transient Elastography; VLDL: Very Low-Density Lipoprotein; VO2 peak: Peak Oxygen Consumption; hs-CRP: High-Sensitivity C-Reactive Protein

All the studies utilized aerobic exercise as their initial intervention. One of the studies included a HIIT exercise program as an intervention, but since HIIT also involves cycles of intense aerobic exercise, we consider it still suitable.¹⁶ Four of the five studies included an intervention on their daily diets, and one of them also provided psychological support as an additional intervention.¹⁴ The intensity of aerobic exercise was varied, ranging from 30 minutes to 60 minutes per training session, with 3 to 5 training sessions per week. This aerobic exercise was observed over a period ranging from 1 month to 2.5 years, with a comparative group before and after the intervention. However, one of five studies compared exercise with no exercise. The outcomes of the studies are summarized in terms of body composition, liver enzymes, lipid profile, laboratory metabolic markers, and liver imaging, using various indicators.

Body Composition

Elevated BMI is consistently associated with a higher incidence and greater severity of MASLD, particularly when accompanied by increased visceral fat distribution.¹⁷ Aerobic exercise is reported to reduce fat mass and lead to a decrease in body weight.¹⁸ This study demonstrated a significant improvement in BMI for age Z-score and BMI (kg/m²) among pediatric patients with or at high risk of MASLD and obesity in 2 of 3 studies following aerobic exercise training.^{12, 14} Another study also reported an improvement, although it was not statistically significant.¹⁶ Changes in BMI for age Z-score and BMI (kg/m²) were calculated based on the study results and reported as a

delta (Δ) value, showing a reduction ranging from $\Delta -0.27$ to -1.00 and $\Delta -0.03$ to -1.00 , respectively.

Divergent findings were found in Lean body mass (kg) and visceral fat area (cm^2). Two studies on lean body mass showed an increase (52.02 to 52.04) and a decrease (63.42 ± 7.39 to 3.69 ± 1.37), although the changes were not statistically significant.^{12,16} While 2 studies reported a significant loss (6.31 ± 1.33 to 62.45 ± 7.58) and insignificant gain (95.78 to 95.85) of visceral fat area (cm^2).^{15,16} These findings suggest that while BMI-related indicators consistently improved with aerobic exercise, the effects on lean body mass and visceral fat area remain inconclusive.

Liver Enzyme

Liver enzymes had an essential role in early detection, monitoring therapy and assessing the progression of MASLD. Alanine Aminotransferase (ALT) is commonly used as a marker of improvement in the histology of MASLD, as ALT is mainly found in hepatocytes.¹⁹ All of the reviewed studies included Aspartate Aminotransferase (AST) and ALT as their outcomes and observed a reduction following aerobic exercise training. A significant reduction was reported in 3 of 5 studies with delta values of AST ranging from $\Delta -1.00$ to -34.00 , and also ALT ranging from $\Delta -1.00$ to -27.17 IU/L.¹²⁻¹⁴ The other 2 of 5 studies also showed a reduction in levels of AST and ALT, with delta values ranging from $\Delta -0.86$ to -5.50 and $\Delta -0.53$ to -7.0 , although these differences were not statistically significant.^{15,16} These findings suggest that aerobic exercise may contribute to improvements in hepatic inflammation and liver enzyme profiles in pediatric patients with or at risk of MASLD, even when statistical significance is not consistently achieved.

Lipid Profile

Circulating lipids, such as Free Fatty Acids, Very Low-Density Lipoprotein, Low-Density Lipoprotein, and high-density lipoprotein, play an essential role in the development of MASLD.²⁰ Aerobic exercise intervention showed mixed effects on lipid profile. Total cholesterol was reported to significantly decrease in 2 of 4 studies, with delta values ranging from $\Delta -32.00$ to $+1.00$ mg/dL.^{14,16} As seen in total cholesterol, LDL levels also showed a significant decrease in 3 of 4 studies, with delta values ranging from $\Delta -11.55$ to $+2.38$ mg/dL.^{12,14,16} HDL levels exhibited mixed responses across studies, with 2 reporting increases^{12,15} and 2 reporting decreases following aerobic exercise training intervention.^{14,16} HDL was reported to have a significant increase in 1 of 2 studies (36.95 ± 9.58 to 44.08 ± 12.95) mg/dL, while the other one reported an insignificant increase of HDL (45.07 ± 9.35 to 47.23 ± 12.2) mg/dL. Triglyceride levels were mentioned with no significant change in 3 of 4 studies reviewed.^{12,14,16} Overall, aerobic exercise demonstrated a favourable effect on total cholesterol and LDL levels in pediatric patients with or at risk of MASLD. At the

same time, its impact on HDL and triglycerides appeared more variable and less consistent across studies.

Metabolic Dysfunction Markers

MASLD often coincides with other metabolic disease, especially with diabetes mellitus.²⁰ These studies conclude that aerobic exercise does not significantly affect metabolic dysfunction markers. It reported that 3 of 4 studies showed no significant change in fasting glucose, although 2 studies reported a decrease in fasting glucose with delta values ranging from Δ -0.35 to -4.00 mg/dL.^{12,15,16} 1 of 2 studies showed a significant change in 2-hour glucose level of 11.54mg/dL.¹⁶ Fasting insulin on the contrary, revealed a reduction in 4 studies with 2 studies having significant delta values ranging from Δ -2.84 to -8.90 mIU/L.^{12,14} Similarly with fasting insulin, 2 hour insulin also revealed a reduction in 2 of 2 studies with delta values ranging from Δ -9.39 to -4.75 mIU/L.^{12,16} However, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) reported a significant decrease in 2 of 4 studies with delta values ranging from Δ -0.58 to -2.40.^{12,14} Another hormone, adiponectin level, showed an insignificant decrease in 2 of 2 studies with delta values ranging from Δ -1.38 to -0.32 ng/mL.^{15,16} Last, the leptin hormone showed divergent insignificant results in 2 of 2 studies with delta values ranging from Δ -1.77 to +5.03 pg/mL.^{15,16} A minority of studies reported limited effectiveness in improving metabolic markers in patients with MASLD.

Liver Imaging

Radiology examinations are included in 3 of 5 studies using ultrasonography (USG), FibroScan and Magnetic Resonance Imaging (MRI) as examination tools.^{12,14,16} A study reported that the Intrahepatic Triglyceride Content (IHTG) measured by MRI Proton Density Fat Fraction (MRI-PDFF) was significantly decreased from 8.81% to 7.76% after HIIT training, while the control group reported a non-significant decrease (Δ = -1.12 pp, p = 0.182). The Controlled Attenuation Parameter (CAP) score after HIIT training also decreases significantly from 279 dB/m to 252 dB/m, while in the control group, the CAP also decreased (Δ = -16 dB/m, p = 0.359), but it is insignificant.¹⁶

Another study reported that after 6 months of aerobic exercise intervention, the resolution of steatosis occurred in 47.1% patients with steatosis baseline. Regression of fibrosis was observed in 75% of patients with fibrosis at baseline, while resolution of fibrosis (TE < 7 kPa) was achieved in 62.5% of patients. After 11-12 months, this study reported a 94.5% improvement and a 78.2% resolution of patients with MASLD at baseline (p < 0.001), based on USG and CAP scores.¹⁴

The third study performed liver USG at baseline and after intervention. The results were classified into mild, moderate, and severe MASLD. After intervention, the MASLD conditions disappeared in 37.5% patients. A significant improvement (P =

0.03) was observed after the intervention, where 30.6% of those with mild MASLD reduced to 22.2%, 27.8% of those with moderate MASLD reduced to 13.9%, and 8.3% of those with severe MASLD reduced to 5.6%. Collectively, radiological assessments across the included studies consistently demonstrated significant improvements in hepatic steatosis and fibrosis following aerobic exercise interventions, as evidenced by reductions in MRI-PDFF, CAP scores, and FibroScan values, as well as resolution rates observed on ultrasonography.¹²

Discussion

The systematic review evaluated the therapeutic role of aerobic exercise in obese children and adolescents with or at high risk of MASLD. Overall, the 5 included studies revealed differences in study design, but the population and interventions were uniform. Most studies employed RCTs with sample sizes ranging from 14 to 79 participants, aged from 3 years to 18 years old. All the studies included aerobic exercise as their initial intervention, with training sessions lasting 30 to 60 minutes and occurring 3 to 5 times per week over 1 to 12 months. These studies primarily compare outcomes before and after an intervention, including body composition, liver enzymes, lipid profile, laboratory metabolic markers, and liver imaging. All studies have a low risk of bias.

Exercise is widely accepted as a beneficial treatment for MASLD, as a sedentary lifestyle, poor aerobic fitness, and low muscle mass are all recognized risk factors for the condition.²¹ In this review, aerobic exercise led to clinically meaningful reductions in BMI-related indicators consistently, an effect that has similarly been demonstrated in prior pediatric studies on obesity and MASLD risk. These findings align with a study a study from Regaieg et al. where 28 obese children participated an aerobic exercise over 16-week, with four 60-min sessions per week at 70-85% of maximum heart rate showed significant reduction in BMI and waist circumference compared with the baseline values ($p < 0.001$).²² However another study revealed an inconsistent results where an aerobic training program with 60 minutes session per week over 24 months in children induced no significant differences in BMI ratio and z-score ($p > 0.9$) in the measured variables compared to controls at the final follow up, consistent with BMI, study also demonstrated no significant changes in the fat-free mass index ($p > 0.07$).²³ BMI does not accurately represent body composition and is less effective than waist circumference in predicting metabolic dysregulation, the hepatic manifestation of which is MASLD.²⁴ It has also been shown to overlook more than a quarter of children with excess body fat.²⁵

The effects of aerobic exercise on lean body mass and visceral fat area in children with MASLD remain inconclusive, likely due to variations in body composition responses that depend on other factors such as exercise modality, duration, and intensity.²⁶ Nevertheless, aerobic training is commonly prioritized in the development of fat loss

programs, as it incorporates strategies designed to optimize fat oxidation intensity and includes high-intensity interval training.²⁷ This approach is well-supported by substantial evidence highlighting its effectiveness in reducing visceral fat and improving metabolic health.²⁸ However, in a study where energy expenditure was standardized, no consistent differences were found between moderate continuous aerobic exercise and high-intensity interval training. These findings imply that total energy expenditure, which is determined by the duration and intensity of the exercise, may be a more crucial factor in fat reduction than the specific training modality itself.²⁹

Even though statistically inconsistent, liver enzymes, particularly ALT and AST, showed improvements after aerobic exercise interventions in obese children and adolescent patients with or at risk of MASLD, indicating decreased hepatocellular injury and inflammation. Likewise, a study by Malecki et al. studied 49 children and adolescents, ages 3 to 16, diagnosed with NAFLD through ultrasound. They were prescribed a Mediterranean diet and moderate-intensity aerobic exercise lasting at least 60 minutes five days per week. The participants were followed for an average of 2.45 ± 1.45 years. The study revealed a decrease in aspartate aminotransferase AST and alanine aminotransferase ALT levels in all patients, even those who did not show a reduction in BMI.¹³ Increased transaminase levels are recognized as an independent predictor of advanced fibrosis and have been shown to have a significant correlation with nonalcoholic steatohepatitis.³⁰

Aerobic exercise also demonstrated favourable reductions in total cholesterol and LDL levels. However, its impact on HDL and triglycerides appeared more variable and less consistent across studies. This effect is likely due to its ability to improve mitochondrial fatty-acid oxidation in the liver, up-regulating the expression of genes such as PPAR α and CPT1a. At the same time, aerobic exercise down-regulates lipogenesis by suppressing lipogenic factors like SREBP-1c and FAS, a pattern that is associated with a reduction in hepatic triglyceride accumulation.³¹ In contrast, markers of glucose metabolism, including fasting glucose, fasting insulin, and HOMA-IR, showed limited improvements. These studies conclude that aerobic exercise does not significantly affect markers of metabolic dysfunction in these limited studies. This may be due to the relatively short duration of the exercise interventions, which may not be long enough to induce significant changes in glucose metabolism. Additionally, the absence of dietary interventions in several of these studies could also limit the impact of aerobic exercise on insulin sensitivity and glucose regulation.³²

The results from the studies demonstrate the positive impact of aerobic exercise interventions on hepatic steatosis and fibrosis in pediatric patients with MASLD, as assessed through various radiological methods including USG, FibroScan, and MRI. Notably, aerobic exercise led to clinically significant improvements in MRI-measured liver fat, independent of substantial weight loss.³³ Moreover, more than 30% relative

reduction in MRI-measured liver fat was observed in patients with MASLD who were prescribed with 150 min/week of moderate-intensity aerobic exercise, which is similar to outcomes reported in early-phase MASLD drug trials primarily focused on antisteatogenic medications.³⁴ The significant improvements observed across multiple imaging modalities underscore the importance of these findings, further supporting the integration of aerobic exercise into clinical practice for the management of MASLD in children.

This review has several limitations. The number of eligible studies was small, and most had limited sample sizes, reducing statistical power. Additionally, the interventions varied across studies, and a meta-analysis could not be conducted. Nonetheless, this systematic review provides valuable insight into the potential effects of aerobic exercise on MASLD.

Conclusion

This systematic review revealed that aerobic exercise showed selective benefits to pediatric and adolescent with MASLD and obesity. Significant improvements were found in BMI and liver enzymes in several studies. Radiology examination also showed improvement in the resolution of liver steatosis. However, the effect on lipid profile and metabolic markers showed inconsistent improvement. The overall findings support aerobic exercise as a safe and effective non-pharmacologic intervention. Integration of structured aerobic exercise into standard management strategies for pediatric MASLD may enhance clinical outcomes, though further high-quality RCT are needed to define optimal exercise protocols and long-term effects.

Acknowledgement

The authors would like to acknowledge the authors from included studies who have done the research

Conflict of Interest

There is no conflict of interest.

Funding Statement

The authors received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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Case Report

Pediatric Hepatic Abscess in a Resource-Limited Setting: A Case Report

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e-ISSN: 2830-5442

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Published:

30th November 2025

DOI:

<https://doi.org/10.58427/apghn.4.4.2025.189-200>

Citation:

Damayanti APS, Salsabila KN, Pulinggomang BB. Pediatric hepatic abscess in a resource-limited setting: a case report. *Arch Pediatr Gastr Hepatol Nutr.* 2025;4(4): 189-200

Abstract:

Background: Liver abscess is a rare but serious pediatric infection, more common in developing regions where malnutrition, poor sanitation, and limited healthcare access increase risk. It is broadly classified into pyogenic and amoebic types, with the latter more prevalent in tropical areas. Symptoms such as fever, abdominal pain, and hepatomegaly are often nonspecific, making diagnosis difficult in low-resource settings. Ultrasound plays a crucial role when advanced diagnostics are unavailable. This case illustrates these challenges in a remote hospital in Eastern Indonesia.

Case: A 13-year-old boy presented with right upper quadrant pain, intermittent fever, and hepatomegaly. Ultrasound revealed a 7 × 6 cm hepatic abscess. He received empiric intravenous antibiotics, but due to limited facilities for image-guided drainage, exploratory laparotomy with abscess evacuation was performed. The patient showed steady postoperative improvement, was discharged in good condition, and achieved full recovery on follow-up.

Discussion: This case illustrates how resource availability influences diagnostic and therapeutic decisions for pediatric liver abscess. Although ultrasound-guided drainage is the preferred minimally invasive approach, the absence of interventional radiology services required surgical management. The patient's improvement with empiric antibiotics and intraoperative findings supported a pyogenic etiology, underscoring the value of clinical judgment when microbiological testing is unavailable. In settings such as Eastern Indonesia, early imaging and timely empiric treatment remain crucial to guide care despite limited diagnostic resources.

Conclusion: Pediatric liver abscess can still be effectively managed in low-resource settings through prompt diagnosis, empiric therapy, and timely surgical intervention.

Keywords: pediatric hepatic abscess, pyogenic liver abscess, resource-limited setting, ultrasonography

Introduction

Liver abscess is an uncommon but potentially life-threatening infection in children. Although its incidence is low in developed countries, it remains a significant cause of morbidity in developing regions, particularly where poor sanitation, malnutrition, and limited access to healthcare persist. Timely diagnosis and prompt intervention are essential to prevent severe complications such as rupture, sepsis, or peritonitis.^{1,2}

Two major types of hepatic abscess are recognized: pyogenic and amoebic. Pyogenic liver abscess (PLA) is more common in children and usually results from bacterial infection, while amoebic liver abscess (ALA) is caused by *Entamoeba histolytica*, prevalent in tropical regions. Infections may spread through the portal vein from intra-abdominal sources or via hematogenous dissemination, and risk factors such as immunodeficiency, malnutrition, and biliary abnormalities further increase susceptibility.^{3,4}

Clinical manifestations are often nonspecific, with fever, right upper quadrant pain, and hepatomegaly being the most common features. Laboratory findings typically reveal leukocytosis and elevated inflammatory markers but are not diagnostic. Imaging, particularly ultrasonography, remains the cornerstone for early detection, showing hypoechoic or mixed-echoic hepatic lesions. However, early abscesses can mimic cysts or hepatic tumors, posing diagnostic challenges, especially in resource-limited settings where CT or MRI is unavailable.^{1,2}

This case report presents a pediatric hepatic abscess initially suspected as a cystic or neoplastic lesion in a child from a remote hospital in Alor, Indonesia, highlighting the importance of clinical suspicion and ultrasound-based diagnosis in resource-constrained environments.

Case

A 13-year-old boy was brought to the Emergency Department of Kalabahi Hospital, Alor, East Nusa Tenggara, Indonesia, with a primary complaint of right upper quadrant abdominal pain for the past six days, which had worsened within the last five hours before admission. The pain was described as a constant, pressing discomfort localized to the right upper abdomen, not radiating, and aggravated by movement or palpation. The pain was associated with intermittent high-grade fever, particularly occurring at night, that responded poorly to over-the-counter analgesics. The patient's mother reported that he appeared weak and had reduced appetite since the onset of symptoms. Two episodes of vomiting occurred before hospital admission, consisting of non-bilious, non-bloody content. He denied abdominal distension, yellowish discoloration of the eyes or skin, diarrhea, bloody stools, or any history of trauma.

The patient had no significant past medical history and had never been hospitalized before. There was no history of chronic illness, previous abdominal infection, or trauma. His only medication prior to admission was ibuprofen, taken occasionally for fever. There was also no known family history of liver disease, jaundice, malignancy, or similar illness among close relatives. He was the second of three siblings, born at home and reportedly cried immediately after birth, with no complications during delivery. Growth and development were appropriate until the onset of the current illness. The patient's immunization history was incomplete, as his mother could not recall which vaccines had been administered. Nutritional assessment showed malnutrition. His diet mainly consisted of rice with fish or chicken and occasional vegetables. He lived with his parents and two siblings in a rural area of Alor, where sanitation and hygiene were poor. The family used refillable water for drinking and well water for bathing, with an outdoor bathroom and open waste burning.

Upon arrival at the emergency department, the patient appeared alert but febrile, with a temperature of 38.4°C. His blood pressure was 114/57 mmHg, pulse rate 85 beats per minute, respiratory rate 22 per minute, and oxygen saturation 97% on room air. Anthropometric measurements showed a body weight of 30.5 kg and height of 155 cm, corresponding to below the 5th percentile for both weight-for-age and height-for-age. The percentage of ideal body weight was 53%, consistent with a diagnosis of severe malnutrition.

On physical examination, the abdomen appeared flat and symmetrical overall, with slight fullness of the right upper quadrant compared to the left, suggesting hepatomegaly. Palpation revealed marked tenderness over the right upper quadrant with the liver palpable 4 cm below the right costal margin. The liver edge was smooth, with a firm consistency and mild tenderness. There was no splenomegaly, ascites, or shifting dullness. Bowel sounds were normal. Cardiopulmonary and neurological examinations were within normal limits.

Based on the presence of hepatomegaly with localized tenderness and the absence of jaundice or generalized abdominal distension, initial differential diagnoses included hepatic cyst, hepatoma, and hepatic abscess. Further investigations were performed to differentiate between cystic, neoplastic, and infectious causes of hepatic enlargement. Initial laboratory testing was obtained to support this diagnostic evaluation, and the findings are summarized in **Table 1**.

Table 1. Initial laboratory results of the patient at admission.

Parameter	Result	Reference Range	Interpretation
Complete Blood Count			
Leukocytes	$17.6 \times 10^3/\mu\text{L}$	$4.0\text{--}11.0 \times 10^3/\mu\text{L}$	High (leukocytosis)
Neutrophils	86%	40–70%	High (neutrophil predominance)
Hemoglobin	13 g/dL	12–16 g/dL	Normal
Hematocrit	37.8%	36–46%	Normal
Platelets	$303 \times 10^3/\mu\text{L}$	$150\text{--}450 \times 10^3/\mu\text{L}$	Normal
Liver Function Tests			
SGOT (AST)	27 U/L	< 40 U/L	Normal
SGPT (ALT)	10 U/L	< 41 U/L	Normal
Total Bilirubin	1.24 mg/dL	0.3–1.2 mg/dL	Slightly elevated
Direct Bilirubin	0.25 mg/dL	< 0.3 mg/dL	Normal
Indirect Bilirubin	0.99 mg/dL	< 1.0 mg/dL	Normal (upper limit)
Renal Function Tests			
Urea	27 mg/dL	10–50 mg/dL	Normal
Creatinine	1.0 mg/dL	0.6–1.2 mg/dL	Normal
Urinalysis			
Protein	+2	Negative	Proteinuria
Leukocytes	+2	Negative	Pyuria
Erythrocytes	+3	Negative	Hematuria
Other Tests			
Random Blood Glucose	139 mg/dL	< 140 mg/dL	Normal–High (pre-prandial borderline)

Abdominal ultrasonography revealed a well-circumscribed hyperechoic lesion in the right hepatic lobe, measuring 7×6 cm, with smooth borders, no nodularity, and absence of internal or peripheral vascularization on color Doppler. No intrahepatic or extrahepatic bile duct dilatation was noted. The sonographic impression was consistent with a hepatic abscess (**Figure 1 and Figure 2**). A plain abdominal radiograph (BNO) revealed a well-defined opacity projected over the right 10th posterior intercostal space, suggestive of hepatomegaly with no evidence of air-fluid levels or bowel obstruction (**Figure 3**).



Figure 1. Abdominal ultrasonography showing a well-defined hyperechoic lesion in the right hepatic lobe, measuring approximately 7×6 cm.



Figure 2. The lesion appears with smooth margins and no internal vascularization



Figure 3. Plain abdominal radiograph showing a well-defined opacity over the right upper quadrant, consistent with hepatomegaly and suggestive of a hepatic lesion.

The patient was admitted to the pediatric ward with a working diagnosis of hepatic abscess. Initial management included intravenous fluid therapy for rehydration and maintenance. On hospital day 2, empiric parenteral antibiotics—ceftriaxone and

metronidazole—were initiated to cover both pyogenic and amoebic etiologies, in accordance with local practice in settings without microbiological diagnostic support. Supportive therapy consisted of ketorolac for pain control, ranitidine for gastric protection, and ondansetron for antiemetic support.

Due to the large abscess size (7×6 cm) and the absence of facilities for percutaneous drainage, the surgical team decided to perform an exploratory laparotomy with abscess drainage. Intraoperatively, a well-formed abscess cavity was identified in the right hepatic lobe, containing thick yellowish purulent fluid with a mild reddish tinge, containing thick yellowish purulent fluid with a mild reddish tinge, consistent with purulent material mixed with a small amount of blood. Approximately 70 mL of pus was evacuated. The cavity was thoroughly irrigated with warm normal saline until the effluent became clear, and a surgical drain was placed for postoperative monitoring. Surrounding structures revealed inflammatory changes involving the pancreas with edema of adjacent tissue and a periduodenal–retropancreatic hematoma, suggesting local inflammatory extension. The gallbladder and bile ducts appeared intact, with no bile leakage or perforation. Hemostasis was achieved, and the abdomen was closed in layers after drain placement. The patient tolerated the procedure well and was transferred to the pediatric ward for further management.

On postoperative day 1, the drain site was clean and covered with a sterile dressing. No pus or wound leakage was noted, and the drain produced approximately 200 mL of serosanguinous fluid within 24 hours. By postoperative day 2, the drain output had decreased to about 80 mL/24 hours, and there was no evidence of bleeding or recurrent collection. On postoperative day 3, the surgical drain was removed after output further declined and the wound remained dry and intact. The patient showed progressive clinical improvement, was afebrile, tolerated oral feeding well, and ambulated independently. On postoperative day 4, the patient was discharged home in good condition with oral antibiotics and scheduled follow-up.

However, on postoperative day 10, the patient returned to the emergency department with complaints of purulent discharge and partial wound dehiscence at the laparotomy site. On physical examination, localized erythema and purulent drainage were noted at the incision site, without evidence of systemic sepsis. Laboratory investigations revealed a white blood cell count (WBC) of $12.6 \times 10^3/\mu\text{L}$, hemoglobin 8.1 g/dL, hematocrit 24.0%, and platelet count $340 \times 10^3/\mu\text{L}$.

These findings were consistent with a resolving infection accompanied by mild microcytic anemia, likely secondary to chronic inflammation and recent surgical blood loss. The patient remained hemodynamically stable but febrile, although clinically in good condition. He was readmitted for further management, including wound care and optimization of antibiotic therapy. Daily wound dressing and close monitoring

were performed throughout hospitalization, with progressive clinical improvement observed within 48 hours. The patient was discharged after two days of inpatient treatment with continued oral antibiotics and wound care instructions. Follow-up on postoperative days 16 and 20 revealed complete wound healing, satisfactory nutritional progress, and no residual pain or infection.

Discussion

The liver is a vital organ with a dual blood supply, predisposing it to an increased risk of infection. While the incidence of pyogenic liver abscess (PLA) has declined in developed countries, it remains relatively common in developing regions. The two major types of liver abscess are pyogenic and amebic, with PLA arising from biliary, portal, arterial, traumatic, or cryptogenic origins.^{3,5,6}

Liver abscess develops as a result of infection of the liver parenchyma via several routes, including ascending infection through the bile duct (acute cholangitis), spread through the portal vein or hepatic artery, and direct invasion following gastrointestinal tract trauma (such as perforation from fish or chicken bones). Predisposing factors for liver abscess include advanced age, male sex, history of malignancy, chronic alcohol consumption, diabetes mellitus, inflammatory bowel disease, liver cirrhosis, prior endoscopic sphincterotomy, immunocompromised states, and the use of proton pump inhibitors.^{3,5}

Pyogenic liver abscess (PLA) is the most common hepatic abscess in children, accounting for most reported cases. Meanwhile, the incidence of amebic liver abscess (ALA) has decreased due to improved sanitation and antiparasitic use. Pediatric PLA is commonly linked to bacteremia from gastrointestinal or biliary infections. Studies in Asia report *Klebsiella pneumoniae* and *Staphylococcus aureus* as the leading pathogens, highlighting the need for early detection, especially where microbiological testing is limited.⁴

In differentiating pyogenic from amebic liver abscess in resource-limited settings, macroscopic characteristics of the drained material can provide valuable diagnostic clues when microbiological confirmation is unavailable. Pyogenic liver abscesses typically contain thick, yellowish purulent pus, reflecting the accumulation of neutrophils, bacteria, and necrotic debris within the cavity. In some cases, the pus may appear tinged with small amounts of blood, especially when inflammation causes fragile surrounding tissues to bleed slightly during drainage. This macroscopic appearance contrasts with amoebic liver abscesses, which classically contain brownish, odorless, “anchovy sauce–like” fluid due to liquefactive necrosis of hepatocytes rather than true purulence. These distinctions are widely recognized in hepatology and infectious disease literature and are particularly helpful in settings where microbiological or serologic confirmation is unavailable.^{7, 8} Recognizing these

distinguishing features is essential for guiding appropriate management, especially when laboratory testing and serologic assays are not accessible.

In Indonesia, there remains a scarcity of large-scale studies focusing on pediatric liver abscess, with most available literature limited to single case reports or small case series. However, data from other ASEAN countries provide additional insights that may help contextualize our findings. A ten-year review from the Philippines, for example, analyzed pediatric hepatic abscess cases and emphasized the predominance of right lobe involvement and generally favorable outcomes with timely intervention.^{9, 10} Similarly, reports from Malaysia have described both typical and atypical presentations, including cases associated with melioidosis, underscoring the role of imaging in early detection and the challenges of diagnosis in endemic areas.¹¹ These regional studies highlight that while pediatric liver abscess remains relatively uncommon, its presentation and management may vary depending on local epidemiology, healthcare resources, and underlying comorbidities.

A case report from Indonesia described a young patient with a giant amoebic liver abscess associated with poor food hygiene and unsafe water consumption, further supporting the role of amoebic etiology in endemic regions such as Eastern Indonesia.¹⁰ This case underlines that, although pyogenic liver abscess accounts for the majority of pediatric cases globally, amoebic liver abscess should still be considered an important differential diagnosis in tropical and resource-limited areas. Environmental and socioeconomic factors such as poor sanitation, lack of access to clean water, and dietary practices involving undercooked food contribute to this risk. Clinicians working in endemic regions must therefore maintain a high index of suspicion for both pyogenic and amoebic etiologies when evaluating pediatric patients with hepatomegaly or liver lesions.^{1, 12, 13}

The most prevalent symptoms of fever and abdominal pain were similar to most previous reports. Prolonged fever commonly developed, as the median febrile duration before diagnosis exceeded 7 days. The location of pain was diverse, although the right upper quadrant was the most common. Pleural effusion, respiratory tract symptoms, and shortness of breath developed in a considerable percentage of patients, which could possibly be explained by subdiaphragmatic irritation or pleuropulmonary spread of the liver abscess.¹¹

A pediatric case report described an amoebic liver abscess initially misdiagnosed as a hepatic tumor because of its clinical and radiological presentation. The child presented with hepatomegaly and abdominal pain, while imaging demonstrated a large hepatic lesion with features that closely resembled neoplasia. Only after further evaluation and clinical correlation was the diagnosis of liver abscess confirmed. This highlights the diagnostic dilemma in pediatric hepatomegaly, as hepatic abscesses may mimic cystic

lesions or malignant tumors both clinically and radiologically. Such cases emphasize the importance of integrating clinical features, imaging findings, and therapeutic response to avoid misdiagnosis and ensure appropriate management in resource-limited settings.¹⁴

In our case, the patient presented with hepatomegaly, which raised initial suspicion of a cystic lesion or hepatoma. Hepatic cysts are often considered when a well-defined hypoechoic lesion is suspected, while hepatoma or hepatoblastoma may be suspected in pediatric patients presenting with hepatomegaly, abdominal mass, or constitutional symptoms such as weight loss and anorexia. However, ultrasonography revealed features consistent with a hepatic abscess, shifting the diagnosis away from cystic or neoplastic pathology.

Imaging systems, including ultrasonography and computed tomography scanning are valuable implements to validate an area occupying lesion and corroborate the occurrence or non-existence of a liver abscess. Computed tomography has a superior sensitivity compared to ultrasound for the detection of liver abscess; however, this possibility cannot permanently be available in low-middle income countries.^{6, 15} The diagnosis of liver abscess in children relies heavily on clinical suspicion supported by imaging studies. Ultrasonography (USG) remains the mainstay of initial evaluation due to its availability, safety, and high sensitivity for detecting hepatic lesions.⁶ However, in resource-limited settings such as Alor, several challenges arise. Limited access to advanced imaging modalities like CT or MRI may hinder accurate characterization of lesions, particularly when differentiating pyogenic abscesses from other hepatic pathologies such as tumors or cysts.^{6, 13} Furthermore, microbiological confirmation through blood or pus cultures is often not feasible due to laboratory constraints, leading to reliance on empirical antibiotic therapy. Delays in diagnosis may occur because early clinical features—such as fever, abdominal pain, and hepatomegaly—are nonspecific and may overlap with other common tropical diseases like malaria, typhoid fever, or dengue.⁴ These diagnostic limitations underscore the importance of maintaining a high index of suspicion, optimizing the use of available resources, and strengthening referral systems for timely intervention.

In addition to imaging, laboratory investigations play a complementary role in diagnosis. Laboratory findings in liver abscess are often nonspecific but can support clinical and imaging assessment. Leukocytosis with neutrophil predominance, elevated inflammatory markers such as C-reactive protein (CRP), and mild alterations in liver function tests are commonly observed. However, normal transaminase or bilirubin levels do not exclude hepatic abscess, especially in early or localized infections.^{1, 4} In resource-limited settings, where culture facilities are often unavailable, these laboratory clues—combined with ultrasonographic findings—remain crucial for early diagnosis and management.

Multiple studies have shown a clear shift in the management of liver abscesses toward nonsurgical, minimally invasive approaches. Ultrasound-guided percutaneous interventions, including percutaneous needle aspiration (PNA) and percutaneous catheter drainage (PCD), have largely replaced open surgical drainage as the preferred treatment due to their high success rates and lower morbidity.¹⁶ PNA has demonstrated high effectiveness, with reported success rates of 60–100% and minimal complications, while PCD offers comparable efficacy (up to 92%) but usually requires a longer drainage period and carries catheter-related risks. Although PCD is often recommended for very large abscesses (>10 cm), increasing evidence supports PNA as a safe, simple, and effective first-line option for abscesses >5 cm, and even larger lesions when performed under ultrasound guidance.¹⁷

In well-resourced settings, ultrasound-guided percutaneous drainage—either through needle aspiration or catheter placement—is considered the preferred initial treatment for liver abscesses because it is minimally invasive, safe, and associated with high success rates and shorter hospital stays.¹⁷ However, in resource-limited environments, where interventional radiology expertise or equipment may not be available, surgical drainage remains an important alternative for definitive management. This demonstrates that treatment decisions may depend as much on resource availability as on clinical factors. In our case, although the abscess size (7 × 6 cm) would typically be amenable to ultrasound-guided aspiration, the absence of percutaneous drainage facilities necessitated exploratory laparotomy, illustrating the practical challenges faced in low-resource settings despite strong evidence supporting minimally invasive approaches.

Aside from procedural considerations, appropriate antimicrobial therapy remains a key component of liver abscess management. In the management of liver abscesses, prompt initiation of empiric antibiotics is essential to prevent sepsis, and treatment should ideally begin after obtaining blood cultures. Small abscesses (<3–4 cm) may respond to medical therapy alone, but larger lesions generally require both antimicrobial therapy and drainage. Empiric regimens should provide broad coverage for gram-negative bacilli, gram-positive cocci, anaerobes, and *Entamoeba histolytica*, making combinations such as ceftriaxone plus metronidazole appropriate choices.¹⁸ For this patient, intravenous ceftriaxone and metronidazole were selected to cover both pyogenic and amoebic etiologies, which is consistent with recommended empiric management in settings lacking microbiological diagnostic capacity. In the absence of culture and serologic testing, the macroscopic appearance of the aspirated fluid and the patient's clinical improvement served as key indicators in determining the likely etiology. Such reliance on clinical response and intraoperative findings reflects the realities of resource-limited environments, where differentiating between pyogenic and amoebic liver abscess often depends on empirical assessment rather than laboratory confirmation.

This case underscores the importance of integrating clinical, laboratory, and imaging findings when evaluating pediatric hepatomegaly in endemic and resource-limited regions. Enhancing awareness among primary care providers and improving access to basic imaging and laboratory diagnostics can facilitate earlier recognition, timely intervention, and better outcomes for children with hepatic abscess.

Studies have shown that early antibiotic therapy combined with drainage, whether percutaneous or surgical, leads to excellent prognosis in most pediatric cases, even in limited-resource hospitals when managed promptly.^{1,4}

Conclusion

This case highlights the challenges of diagnosing and managing pediatric hepatic abscess in resource-limited settings, where advanced imaging and microbiological testing may not be available. Reliance on clinical assessment, basic laboratory findings, and ultrasonography remains essential for early detection. Timely empiric antibiotic therapy and appropriate drainage—whether percutaneous or surgical—can still provide excellent outcomes when minimally invasive options are not accessible. Strengthening early recognition, improving access to essential imaging, and enhancing referral pathways are key to optimizing the management of hepatic abscess in remote regions such as Eastern Indonesia.

Acknowledgement

The author would like to express sincere gratitude to dr. Bethseba Pulinggomang, Sp.A, Pediatrician at RSD Kalabahi, Alor, East Nusa Tenggara, Indonesia, for her valuable guidance, supervision, and support in the management of this patient and the preparation of this case report. The author also thanks the medical and surgical teams of RSD Kalabahi for their collaboration in providing patient care. We are also grateful to the patient and his family for their kind cooperation and consent to share this case for educational and scientific purposes. Written informed consent was obtained from the patient's parents for publication of this case report. A copy of the written consent is available for review by the editorial board of this journal.

Conflict of Interest

The authors declare no conflict of interest.

Funding Statement

This case report received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Case Report

Treatment of Severe Unconjugated Hyperbilirubinemia with Phenobarbitone in Two First-Degree Siblings with Crigler-Najjar Syndrome (CNS) Type 2: A Success Story

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e-ISSN: 2830-5442

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Published:

30th November 2025

DOI:

<https://doi.org/10.58427/apghn.4.4.2025.201-207>

Citation:

Kumar S, Karthik SR, Pahuja G, Chakrabarti S, Panda PK, Sharawat IK. Treatment of severe unconjugated hyperbilirubinemia with phenobarbitone in two first-degree siblings with crigler-najjar syndrome (cns) type 2: a success story. *Arch Pediatr Gastr Hepatol Nutr.* 2025;4(4): 201-207

Abstract:

Background: Crigler–Najjar syndrome (CNS) type 2 is a rare autosomal recessive disorder of bilirubin conjugation caused by mutations in the *UGT1A1* gene. It presents in infancy with unconjugated hyperbilirubinemia that does not respond to phototherapy but improves with phenobarbitone, which enhances residual enzyme activity. Although phenobarbitone remains the cornerstone of treatment, familial recurrence of CNS type 2 is rarely reported in pediatric literature.

Case: We report two siblings born to consanguineous parents who presented with progressive jaundice during early infancy. The first child, a 2-month-old boy, had multiple hospitalisations for phototherapy without benefit. Laboratory evaluation revealed total bilirubin of 31 mg/dL with normal liver function and no evidence of hemolysis. Genetic testing confirmed a homozygous *UGT1A1* (c.1456T>G; p.Tyr486Asp) mutation. He was treated with phenobarbitone (5–8 mg/kg/day) and calcium phosphate, achieving a bilirubin level <10 mg/dL within 4 weeks. Three years later, his younger sister developed similar unconjugated jaundice from day 4 of life and harboured the same mutation; she responded well to phenobarbitone alone. Both siblings remain well on long-term follow-up.

Discussion: This case highlights the genetic basis and favorable response of CNS type 2 to phenobarbitone, which induces hepatic *UGT1A1* expression. Familial clustering of CNS 2, though reported in few global studies, is seldom documented from India.

Conclusion: Early genetic diagnosis, timely institution of phenobarbitone, and family counselling are critical for successful management of CNS type 2. These cases reaffirm the long-term safety and efficacy of phenobarbitone in familial presentations of this rare disorder.

Keywords: crigler-najjar syndrome type 2, gene therapy, neonatal jaundice, phenobarbitone

Introduction

Crigler-Najjar syndrome (CNS) is a rare genetic disorder that affects the metabolism of bilirubin. It arises from mutations in the *UGT1A1* gene, which produces the enzyme uridine diphosphate glucuronosyltransferase (*UGT1A1*). When this enzyme is deficient, bilirubin cannot be conjugated properly, resulting in unconjugated hyperbilirubinemia from early infancy. There are two recognised types of CNS: type 1 has a complete enzyme deficiency and causes severe neonatal jaundice, which can progress to kernicterus without liver transplantation (LT). Type 2 has partial enzyme activity, allowing individuals to survive into adulthood, but with significant morbidity.^{1,2}

Clinically, infants with CNS present with persistent jaundice that does not respond to standard phototherapy. Type 1 typically shows serum bilirubin levels greater than 20–45 mg/dL and does not respond to phenobarbitone. In contrast, type 2 patients have bilirubin levels between 6–20 mg/dL and show a decrease in levels with phenobarbitone therapy.³ Phenobarbitone, a barbiturate that helps induce the enzyme activity of the *UGT1A1* enzyme, remains the mainstay of treatment in CNS type 2. It increases the transcription of *UGT1A1*, which boosts the body's ability to process bilirubin and lowers serum bilirubin by 30–60%.^{4,5} The use of phenobarbitone in pediatric type 2 CNS has been well-documented, showing long-term safety and effectiveness.⁶

Other treatments, like calcium phosphate, may also help reduce bilirubin by binding it in the gut and lowering enterohepatic circulation. Additional options include intensive phototherapy, plasmapheresis, exchange transfusions during emergencies, and liver transplantation for severe cases.⁷ In this report, we describe a unique case of two consecutive children in the same family with genetically confirmed CNS type 2 who responded well to phenobarbitone without any long-term adverse effects.

Case

The proband, a 2-month-old first-born male child of a third-degree consanguineous marriage, was brought by his parents to the pediatric outpatient clinic of All India Institute of Medical Sciences in Rishikesh (India) with the chief complaint of progressive yellowish discolouration of the skin and sclera noted since day 12 of life. There was no history of high-coloured urine or pale stools after birth. Birth and perinatal history were uneventful without the presence of cephalohematoma. He had multiple hospitalisations for phototherapy, with only transient and partial improvement. There was no history of poor feeding, lethargy, seizures, blood transfusions, or bleeding tendencies. There was an absence of Rh-incompatibility between the mother and the baby (the child's blood group was A positive, and the mother's blood group was B positive).

On examination, he was alert and consolable, deeply icteric, and moderately nourished, without organomegaly or dysmorphic features. Laboratory evaluation showed: total serum bilirubin 31 mg/dL (n: 0.3–1.2 mg/dl), direct bilirubin 0.9 mg/dL (n: <1 mg/dl), hemoglobin 11.5 g/dL (n: 10.5–13.5 g/dl), WBC 8,200/uL (n: 6,000–17,000/uL), platelets $310 \times 10^9/L$ (n:150–450), reticulocyte count 1.1% (n: 0.5–1.5%), LDH 190 U/L (n:140–280 U/L). There was no evidence of haemolysis on peripheral smear. Thyroid function tests were normal. Quantitative G6PD level in blood was normal. Liver synthetic function tests, too, were within normal limits with a normal prothrombin time. Ultrasound whole abdomen depicted a normal hepato-biliary system.

The patient was started on oral phenobarbitone at 5 mg/kg/day, which gradually had to be hiked to 7 mg/kg/day, and oral calcium phosphate at 75 mg/kg/day of elemental calcium. Over 4 weeks, his indirect bilirubin fell to <10 mg/dL, with excellent clinical response in the form of marked reduction of jaundice. No side effects were noted during treatment or follow-up due to phenobarbitone. Genetic testing (whole exome sequencing, WES) confirmed a homozygous missense mutation in exon 5 of the *UGT1A1* gene (c.1456T>G; p.Y486D), classified as pathogenic. Mother was counselled for genetic counselling during the next pregnancy, which she missed.

Three years later, his younger sister presented to our centre, in week 2 of life, with progressive jaundice from day 4 of life, without high-coloured urine or acholic stools, requiring NICU admission and multiple phototherapy sessions without significant improvement. Total serum bilirubin was 16 mg/dl (n:0.3-1 mg/dl), direct bilirubin 0.7 mg/dL (n: <1 mg/dl), hemoglobin 14.1 g/dL (n: 10.5–13.5 g/dl), WBC 8,800/uL (n: 6,000–17,000/uL), platelets $270 \times 10^9/L$ (n:150–450), reticulocyte count 1.4% (n: 0.5–1.5%), LDH 234 U/L (n:140–280 U/L). Genetic analysis revealed the same pathogenic missense *UGT1A1* mutation (c.1456T>G; p.Y486D) in her as in the elder sibling. She was started on phenobarbitone alone at 5 mg/kg/day, with sustained bilirubin reduction and good growth on follow-up. Both siblings continue to remain clinically stable on phenobarbitone, without neurotoxicity or adverse drug reactions.

Discussion

Indirect hyperbilirubinemia (IH) is the most common cause of neonatal admission. Despite most newborns with IH having a good prognosis, approximately 10% of cases do not have spontaneous lowering of bilirubin levels, which may lead to severe complications, including growth retardation, encephalopathy, autism, and hearing impairment.⁸ Crigler-Najjar syndrome (CNS), first described by John F. Crigler and Victor A. Najjar in 7 cases with congenital and familial non-hemolytic IH, is a rare autosomal recessive disorder due to mutations mostly in the coding regions of exons 2-5 of the uridine diphosphate glucuronosyltransferase (*UGT1A1*) gene cloned in

1991 on chromosome 2q37, leading to variable levels of UGT enzyme deficiency.^{9, 10} Whereas CNS type 1 (absence of *UGT1A1* activity) infants are effectively managed only by intensive phototherapy (up to 7 hours daily) and liver transplantation, and most of them die in infancy due to kernicterus, CNS type 2 (4-10 % of residual *UGT1A1* activity) infants have a more favourable outcome.¹¹ They are less likely to develop bilirubin-induced neurological dysfunction (BIND), and most of them have a smooth transition to adult life.¹⁰ The global incidence of CNS is estimated to be fewer than 1 in a million live births.¹¹ However, certain populations in Tunisian, Croatian, and Kuwaiti Bedouin families exhibit a higher prevalence of up to 6.1 cases per 1,000,000 live births, attributed to founder mutations.^{11, 12} The clinical hallmark of CNS type 2 is persistent jaundice with risk of kernicterus during intercurrent illness. A similar benign disease called Gilbert syndrome (GS, 25-30 % of residual *UGT1A1* activity) affects 5% of the normal population and is caused by promoter region mutations in the *UGT1A1*7* gene, with a maximum serum bilirubin rising to 5 mg/dl, during periods of stress, in these children.¹³

The use of phenobarbitone in pediatric CNS type 2 has been well-documented, showing long-term safety and effectiveness. Phenobarbitone therapy is considered the gold standard of treatment in CNS type 2, inducing *UGT1A1* activity via activation of nuclear receptors such as CAR (constitutive androstane receptor) and PXR (pregnane X receptor).⁷ It increases bilirubin conjugation, thereby reducing serum levels significantly. In our cases, both siblings responded well to phenobarbitone, underscoring its efficacy. Calcium phosphate in CNS type 2 acts by binding unconjugated bilirubin in the intestinal lumen, thereby reducing its enterohepatic recirculation. Though less potent alone, it can be useful as an adjunct in severe cases.¹⁴

Whereas CNS type 1 cases are marked by large truncating deletions or exon skipping or nonsense/stop codon mutations in the *UGT1A1* gene, CNS type 2 patients have mostly missense/point mutations in the *UGT1A1*.¹⁰ The spectrum of *UGT1A1* variants varies greatly between different ethnicities. The compound heterozygous and homozygous G71R and Y486D variants are commonly most associated with East Asian CNS II patients from Japan and China.^{15, 16} Other variants of significance include the Q357R, (TA)₇, R341*, and A401P in Tunisian, Caucasian, Croatian and French populations as part of “founder effect”.¹⁰ Our report is also unique because it documents two consecutive siblings affected by CNS type 2 with the same *UGT1A1* missense pathogenic mutation, both demonstrating a robust response to *UGT1A1* induction therapy. Reports of siblings with genetically confirmed CNS type 2 are extremely limited, particularly from South Asia. Our study found the presence of a homozygous Y486D (p.Tyr486Asp) mutation, which is usually involved in the metabolism of irinotecan to its active metabolite SN-38 (7-Ethyl-10-hydroxycamptothecin), leading to irinotecan toxicity in the presence of this variant, and has not previously been reported from India.¹⁷

Previously, the P176L (p.Pro176Leu) has been mentioned in a 16-year-old girl from India with previous two sibling deaths in the early neonatal period. She had undergone exchange transfusions twice at day 5 and day 20 of postnatal life and did well on prolonged phenobarbitone therapy with a good neurodevelopmental outcome and normal intelligence on follow-up.¹³ There have also been reports of CNS type 1, CNS type 2 and GS in the same family, albeit a different variant in the *UGT1A1* gene.⁵ This explains the clinical heterogeneity of CNS in infants, with the same familial mutations having a myriad of varied presentations, probably hinting at a role of other epigenetic factors in the disease pathophysiology. Even in our case, the first sibling had a total serum bilirubin of 31 mg/dl, which is ideally seen in CNS type 1, but the behaviour of the disease process was in line with CNS type 2. Other worldwide reports of familial presence of CNS described in 20 Egyptian patients show nine siblings to have died across five families, most probably due to CNS type 1.¹⁰ Similarly, sibling recurrence has been noted to be in five Croatian families by Kovačić et.al.¹¹

Alternative therapies of severe hyperbilirubinemia in CNS type 2 include plasmapheresis and exchange transfusion, used during acute crises with dangerously high bilirubin.⁷ Auxiliary partial orthotopic liver transplantation (APOLT) remains the definitive cure, though associated with lifelong immunosuppression and risks. CNS type 1 children rarely survive without APOLT. Experimental modalities, such as allogenic hepatocyte transplantation into the portal vein and AAV serotype 8-mediated gene therapy, are under evaluation, with reports suggesting their feasibility.¹⁸⁻²⁰ In our cases, phenobarbitone alone (with calcium phosphate in the elder sibling) was sufficient. If bilirubin levels had remained uncontrolled, escalation to exchange transfusion or transplantation would have been considered. The absence of adverse drug effects further reinforces phenobarbitone's safety in pediatric practice.

One of the limitations of our study was the absence of any knowledge of the long-term neuro-developmental outcome of the two cases, which will subsequently be known in follow-up. Further work-up in future should entail assessment of cognitive function and hearing in all babies with neonatal onset of CNS type 2.

Conclusion

Thus, CNS type 2 should be suspected in infants with persistent unconjugated jaundice unresponsive to phototherapy. Phenobarbitone remains the first-line therapy and is highly effective, reducing bilirubin level by up to two-thirds. Family recurrence emphasises the need for genetic confirmation, counselling, and screening. Adjuncts like calcium phosphate may aid management, while advanced therapies are reserved for non-responders. These cases add to the scarce literature on multiple affected siblings with CNS type 2 and confirm phenobarbitone's long-term safety.

Acknowledgement

The authors are grateful to the Neonatal Intensive Care Unit (NICU) team at AIIMS, Rishikesh, for being involved in the management of the second sibling in this study. The authors have asked permission from the patient's parents to write this case report and publish it in a scientific journal.

Conflict of Interest

The authors declare no conflicts of interest.

Funding Statement

This study received no external funding.

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Literature Review

Nutritional Formula Selection in Pediatric High-Output Stoma with Acute Kidney Injury: A Review Article

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e-ISSN: 2830-5442

Corresponding author:Gisheila Ruth Anggitha
gisheilaruth@gmail.com**Published:**30th November 2025**DOI:**<https://doi.org/10.58427/apghn.4.4.2025.208-218>**Citation:**Anggitha GR, Widodo AD, Singgih AH. Nutritional formula selection in pediatric high-output stoma with acute kidney injury: a review article. *Arch Pediatr Gastr Hepatol Nutr.* 2025;4(4): 208-218**Abstract:**

Background: High-output stoma (HOS) is a common complication in pediatric patients with ileostomy, often leading to dehydration, electrolyte imbalance, and malnutrition. These complications increase the risk of acute kidney injury (AKI), which is associated with high morbidity and mortality. Nutritional management in children with HOS and AKI is challenging, requiring careful formula selection to maintain adequate energy and protein intake, fluid and electrolyte balance, and optimize gastrointestinal tolerance.

Discussion: In children with HOS and AKI, the selection of an appropriate enteral formula represents a critical component of nutritional management, aiming to mitigate dehydration, electrolyte disturbances, and protein-energy malnutrition. Isotonic or mildly hypotonic solutions are preferred to minimize osmotic losses. Electrolyte composition must be adjusted to account for impaired renal handling in AKI. Semi-elemental formulas are generally recommended as first-line therapy due to their enhanced absorptive properties and relatively lower potassium and phosphate content compared with polymeric preparations. Transition to polymeric formulas may be considered once stoma output stabilizes and renal function improves. Elemental formulas are reserved for severe malabsorption, intolerance, or when strict electrolyte restriction is required. Continuous enteral infusion is preferred during the acute phase to reduce stoma output volume and nutrient loss, with a gradual transition to intermittent bolus feeding to promote intestinal adaptation and stimulate gut hormone.

Conclusion: Individualized nutritional management is essential in pediatric patients with HOS and AKI. Semi-elemental formulas, electrolyte adjustments based on renal function, and tailored feeding strategies help maintain fluid–electrolyte balance, prevent malnutrition, and support recovery and growth.

Keywords: acute kidney injury, formula, high-output stoma, nutrition, pediatric

Introduction

High-output stoma (HOS) is a common complication among pediatric patients with ileostomy, frequently resulting in dehydration, electrolyte disturbances, and malnutrition. Persistent fluid loss associated with HOS increases the risk of acute kidney injury (AKI), which is closely linked to higher morbidity and progression to chronic kidney disease (CKD).¹⁻³ Nutritional therapy plays a pivotal role in mitigating these complications; however, no standardized guideline currently exists for formula selection or dietary management in pediatric patients with both HOS and AKI. The osmolality of enteral formulas directly influences stoma output, while electrolyte composition must be adjusted according to renal function. In patients with acute renal failure, protein intake also warrants particular attention, not only to meet energy and growth requirements, but also to accommodate the kidney's reduced capacity to metabolise nitrogenous waste products derived from protein. Despite its clinical importance, this aspect has been insufficiently addressed in previous literature.

Furthermore, energy and protein requirements must be met while considering the absorptive capacity of the gastrointestinal tract. Appropriate formula selection is therefore crucial to maintaining fluid–electrolyte balance, supporting intestinal adaptation, and meeting the needs of growth and development.⁴⁻⁶ This narrative review aims to discuss evidence-based strategies for nutritional management and formula selection in pediatric patients with HOS and AKI to support rational, safe, and effective therapy.

Methods

This narrative review examined literature published between 2015 and 2025 concerning the nutritional management of pediatric patients with high-output stoma (HOS) and acute kidney injury (AKI). Relevant studies were identified through comprehensive searches of PubMed and Google Scholar, supplemented by targeted Google searches to capture additional gray literature. Search keywords included pediatrics, high-output stoma, ileostomy, acute kidney injury, nutritional medical therapy, and feeding strategies.

Studies were included if they met the following criteria: (1) published in peer-reviewed journals between 2015 and 2025; (2) written in English; (3) involved pediatric patients (<18 years) diagnosed with HOS, AKI, or both; and (4) discussed nutritional management, formula composition, or feeding strategies. Given the limited number of studies focusing exclusively on ileostomy, articles addressing nutritional management across all stoma types, including jejunostomy, ileostomy, and colostomy, were also included, provided that relevant information could be applied to HOS management.

Exclusion criteria included studies involving only adult populations, animal or in vitro models, conference abstracts without full text, and papers unrelated to nutrition or feeding management. Given the scarcity of randomized controlled trials and the heterogeneity of the available evidence, a narrative review design was selected to allow a comprehensive synthesis of current knowledge. All eligible articles were reviewed in full, and findings were thematically organized into three main domains: (1) nutritional management in children with ileostomy and HOS, (2) nutritional management in children with AKI, and (3) considerations for formula selection in patients presenting with both conditions.

Children with High-Output Ileostomy

Ileostomy is a surgical procedure in which a portion of the small intestine (ileum) is brought to the surface of the skin, creating an opening on the anterior abdominal wall. In the pediatric population, this procedure is most performed for congenital conditions such as intestinal atresia, intussusception, and Hirschsprung's disease.⁷ In a study by Massenga et al., the most frequent indications for intestinal stoma in children were anorectal malformations (89.4%) and Hirschsprung's disease (9.8%).⁸

Following postoperative recovery, ileostomy output generally follows the normal pattern of intestinal fluid transport. Over the course of several days to weeks, the output volume typically decreases through a process known as intestinal adaptation. This adaptation occurs through a combination of hormonal, luminal, and mechanical stimuli, leading to structural changes in the intestinal mucosa. Mucosal hypertrophy and hyperplasia are frequently observed as part of this adaptive process.³

High-output stoma (HOS) represents one of the most frequent complications in pediatric patients with enterostomy, with an estimated incidence of approximately 6%.³ High-output ileostomy (HOI) may present as a transient phenomenon prior to the completion of intestinal adaptation or may be precipitated by intercurrent conditions such as infection. A universally accepted definition of HOI in children has not been established, and threshold criteria remain heterogeneous across studies. Vriesman et al. defined HOI as a stoma output exceeding 20 mL/kg/day in infants or >2 L/day in older children. Van Zoonen et al. applied a cutoff of >50 mL/kg/day, whereas Wessel et al. proposed >40 mL/kg/day as a diagnostic criterion.^{2, 5, 9, 10}

The acute phase of HOS generally refers to the early postoperative period, typically within the first few weeks after stoma creation, when output is excessively high due to mucosal inflammation, edema, and incomplete intestinal adaptation. During this phase, aggressive fluid and electrolyte management is prioritized, while nutritional therapy is carefully initiated. As intestinal adaptation progresses and stoma output decreases, patients enter the stabilization phase, in which formula composition and

nutrient density can be gradually optimized to support long-term growth and recovery.^{2,5,9,10}

Excessive stoma output is associated with dehydration, electrolyte imbalances, and malnutrition, and therefore necessitates prompt and comprehensive management. Tight regulation of enteral fluid intake is essential. Both hypo-osmolar and hyperosmolar solutions should be avoided, as they may exacerbate stoma losses. Hypotonic fluids with osmolarity <200 mmol/L (e.g., plain water, sugar-free beverages) promote sodium efflux into the intestinal lumen, increasing stomal sodium loss and output volume. This further stimulates thirst and perpetuates a deleterious cycle of fluid loss and worsening dehydration.^{5,6}

Similarly, hyperosmolar solutions such as fruit juices induce luminal fluid shifts into the duodenum and jejunum, further augmenting stoma output. Optimal fluid absorption is achieved with isotonic (270–290 mmol/L) or mildly hypotonic (240–250 mmol/L) oral solutions containing both glucose and electrolytes to maximize sodium-coupled transport. During the acute phase of HOI, intravenous fluid therapy is frequently required to achieve hemodynamic stabilization.^{5,6}

At present, there are no evidence-based guidelines specifically addressing the nutritional management of infants or children with ileostomy. Existing recommendations are largely based on expert opinion and clinical experience rather than robust clinical trials. Breast milk remains the preferred source of nutrition for infants aged 0–6 months, and several studies have suggested that breastfeeding is associated with a shorter duration of parenteral nutrition in neonates with short bowel syndrome. For infants in whom breastfeeding is not feasible, extensively hydrolysed or amino acid–based formulas are commonly recommended. Amino acid–based formulas have demonstrated clinical benefit in children with short bowel syndrome, while extensively hydrolysed formulas may be advantageous in those with persistent feeding intolerance. Nevertheless, comparative evidence between standard polymeric, extensively hydrolysed, and amino acid–based formulas remain scarce.^{6,11}

Insoluble fiber should be avoided in patients with an ileostomy, as it may increase stoma output by 20–25%. In contrast, soluble fiber improves stool consistency and slows intestinal transit. Partially hydrolyzed guar gum has been shown to reduce stoma output and improve stool form in both adults and children with short bowel syndrome when given at 2–6 g per meal.^{6,12}

Children with Acute Kidney Injury

Acute kidney injury (AKI) occurs in approximately 1–25% of intensive care unit patients and 1–7% of all hospitalized patients. Even mild AKI increases the risk of

hypertension and progression to CKD. Management is primarily supportive, emphasizing hemodynamic stability, fluid balance, electrolyte correction, and acid-base homeostasis. No targeted pharmacologic therapy currently exists. Initial steps include clinical assessment and individualized fluid therapy guided by volume status, with close monitoring of urine output and fluid balance. Electrolyte management is critical—potassium and phosphate restriction is necessary in oligouria or anuria, as hyperkalemia poses a life-threatening risk for arrhythmia. Sodium intake should be limited to 2–3 mEq/kg/day to prevent fluid overload and hypertension.^{13, 14}

Nutritional disturbances are common in pediatric patients with AKI, arising from reduced intake, malabsorption, increased nutrient losses, hypermetabolism, and altered nutrient utilization. In the acute phase, management focuses on maintaining fluid balance and optimizing electrolyte and mineral levels, while post-stabilization goals include supporting metabolic recovery, preventing muscle loss, and promoting functional rehabilitation. Adequate energy provision from protein, carbohydrates, and fat is critical but challenging due to risks of under- or overfeeding; indirect calorimetry is the gold standard, with predictive equations such as the Schofield formula as alternatives. Critically ill children or those on continuous kidney replacement therapy (CKRT) may require 120–130% of calculated energy needs.^{4, 14, 15}

Children have higher protein requirements due to growth and development. AKI and advanced CKD increase catabolism and negative nitrogen balance, necessitating sufficient protein to preserve muscle mass, support tissue repair, and improve outcomes. Protein intake of 1–1.5 g/kg/day is recommended for non-dialyzed AKI, increasing to 1.5–3 g/kg/day during CKRT to offset amino acid losses. Polymeric formulas are preferred, with semi-elemental options reserved for gastrointestinal dysfunction or malabsorption.^{4, 15}

Electrolyte disturbances are common in pediatric AKI and CKD. In the absence of pediatric-specific guidelines, daily reference intakes for healthy children can guide initial management, with adjustments for fluid losses, urine output, and dialysis modality (**Table 1**).⁴ Hyperkalemia, due to impaired renal excretion, often requires dietary potassium restriction, while replacement may be needed in cases of gastrointestinal loss. Hyperphosphatemia is frequent, and dietary phosphate restriction is recommended, especially in CKD stages 4–5. Sodium intake should be individualized, with fluid restriction for dilutional hyponatremia; most non-dialyzed AKI patients require both sodium and fluid limitation until renal function improves.^{4, 14, 16}

Table.1 Electrolyte Requirements in Healthy Children and AKI⁴

Electrolyte	Healthy children		Children with AKI		
	ASPEN	ESPEN	AKI without KRT	PD	CKRT
	Infant/children	Teenager and children >50 kg	0 – 18 years		
Sodium (mEq/kg/day)	2–5	1–2	1–3	↓	↓
Potassium (mEq/kg/day)	2–5	1–2	1–3	↓	=
Phosphate (mMol/kg/day)	0,5–2	10–40 mmol/day	0–6 months: 0,7– 1,3 7–12 months: 0,5 1–18 months 0,2–0,7	↓	=↓
Magnesium (mMol/kg/day)	0,15–0,25	5–15 mmol/day	0–6 months: 0,1–0,2 7–12 months: 0,15 1–18 months 0,1	=	=

ASPEN: American Society for Parenteral and Enteral Nutrition; ESPEN: European Society for Clinical Nutrition and Metabolism; AKI: acute kidney injury; KRT: kidney replacement therapy; PD: peritoneal dialysis; CKRT: continuous kidney replacement therapy

Nutritional Formula Selection for Children with HOS and AKI

In patients with HOS and AKI, prompt rehydration with sodium-rich fluids (100–150 mmol/L) is critical to prevent progression to CKD. Oral fasting may be used temporarily to reduce stoma output, and dialysis is generally avoided to prevent further fluid loss. After renal function stabilizes, management focuses on reducing stoma output, tapering intravenous fluids, and following short bowel syndrome principles when no underlying cause is identified.^{5,6}

A wide spectrum of pediatric formulas is available, each differing in energy density, protein quality, and electrolyte composition, which necessitates careful selection in children with HOS and AKI (**Table 2 and Table 3**). Polymeric formulas are generally suitable for patients with preserved gastrointestinal function, as they provide complete macronutrient and micronutrient profiles with moderate osmolality.¹⁷ However, these formulas typically contain relatively high concentrations of potassium and phosphate.

In patients with AKI accompanied by electrolyte imbalance, potassium and phosphate intake should be carefully adjusted to avoid hyperkalemia and hyperphosphatemia.⁴

Table 2. Comparison of Formula Types for Children with High-Output Stoma (HOS) and Acute Kidney Injury (AKI)^{6, 17, 18}

Formula Type	Examples (Available in Indonesia)	Protein Source Content	Osmolarity	Electrolyte Content (K, P)	Advantages	Disadvantages	Recommended Use
Polymeric	Pediasure Complete®, Nutren Junior®, Nutrinidrink®	Intact whole protein	Moderate	Relatively high	Complete nutrition; well-tolerated if gut function intact; moderate osmolality	Risk of hyperkalemia or hyperphosphatemia in AKI/CKD; Nutrinidrink® has higher osmolality, may increase stoma output	Stable HOS with adequate gut function; no significant electrolyte imbalance
Semi-elemental	Peptamen Junior®	Hydrolyzed peptides (easily absorbed)	Moderate	Lower than polymeric	Easier digestion and absorption; supports mucosal integrity; contains soluble fiber that improves stool consistency	Slightly higher cost; limited availability in some settings	First-line choice in active HOS, malabsorption, or feeding intolerance
Elemental	Neocate LCP®, Neocate Junior®, Elecare® Infant	Free amino acids	High	Lowest among all formulas	Suitable for strict electrolyte control; hypoallergenic; best for severe malabsorption	Very high osmolality (may worsen stoma output); risk of osmotic diarrhea; expensive	Severe intolerance, multiple food allergies, or refractory malabsorption unresponsive to other formulas

When malabsorption or feeding intolerance is present, semi-elemental formulas should be considered as the first-line option.¹⁷ Semi-elemental formulas contain hydrolyzed protein peptides and have a moderate osmolality, which facilitates digestion and absorption while minimizing the risk of osmotic diarrhea. Moreover, the presence of soluble fiber, such as partially hydrolysed guar gum, supports intestinal mucosal health, modulates gut microbiota, and improves stool consistency without significantly increasing stoma output. These properties make semi-elemental formulas

particularly advantageous in children with active HOS or those with impaired intestinal adaptation.^{5,6}

Table 3. Comparison of Nutritional Composition of Formula (per 100 mL)

Formula	Energy (kcal)	Protein (g)	Lipid (g)	Carbohydrate (g)	Fiber (g)	Sodium (mEq)	Potassium (mEq)	Phosphate (mMol)
Pediasure Complete® ¹⁹	100	4,0	3,3	14,0	0,7	1,65	4,9	1,12
Nutren Junior® ²⁰	100	3,1	4,3	12,0	1,1	1,65	3,85	0,95
Nutrinidrink® ²¹	150	3,3	6,8	18,8	0	2,91	3,59	0,79
Peptamen Junior® ²²	100	3,0	3,3	14,7	0,6	2,96	2,74	0,52
Neocate LCP® ²³	66	1,83	3,3	7,3	0	1,26	1,87	0,53
Neocate Junior® ²⁴	100	3,4	4,6	11,3	0,4	2,65	2,95	0,79
Elecare® ²⁵	68	2	3,2	7,3	0	1,3	2,59	0,6

Elemental formulas consist of free amino acids as their primary protein source. Compared with other formulas, they provide lower amounts of energy, protein, and electrolytes. Their reduced electrolyte content may be advantageous for children with AKI who require strict electrolyte control, such as those with hyperkalemia or hyperphosphatemia.²⁶ However, elemental formulas have a relatively high osmolarity, which may increase stoma output. Therefore, their use should be limited to cases with severe gastrointestinal intolerance or when other formula types are not tolerated.^{5,26}

Nutritional management of children with HOS and AKI should be individualized, targeting fluid–electrolyte homeostasis and sufficient energy–protein intake to prevent catabolism and support growth. Semi-elemental formulas are preferred during the active phase because of their enhanced absorption, moderate osmolarity, and relatively lower potassium and phosphate content compared with polymeric formulas—an important consideration in AKI, where restriction of these electrolytes is often required. Once output stabilizes and gastrointestinal function improves, polymeric formulas can be gradually reintroduced to support intestinal adaptation, while elemental formulas should be reserved for severe malabsorption or intolerance due to their high osmolarity and risk of exacerbating fluid losses.

Feeding Technique Considerations in Children with HOS and AKI

The mode of formula delivery is a critical determinant of nutritional outcomes in children with HOS and AKI. Two principal strategies are employed, such as intermittent bolus feeding and continuous enteral feeding, each with specific physiological implications.¹⁸

Intermittent bolus feeding most closely mimics normal feeding physiology, promoting cyclical gut hormone secretion and exerting a trophic effect on the intestinal mucosa; however, large bolus volumes may aggravate stoma output and are often poorly tolerated in the presence of vomiting or abdominal distension. In contrast, Continuous enteral feeding has been shown to reduce stool losses by approximately 31–62% and support weight gain in infants with chronic diarrhea or short bowel syndrome. Nevertheless, this method may decrease intestinal motility, predispose to small bowel bacterial overgrowth, and limit patient mobility due to the need for constant tube connection.^{6, 18}

Given these factors, continuous feeding is generally preferred during the early phase of HOS or when stoma output is very high, as it minimizes fluid and energy losses. Transition to intermittent bolus feeding should be considered once stoma output becomes more controlled to promote long-term intestinal adaptation and improve patient quality of life.^{6, 18}

Conclusion

Nutritional management of pediatric patients with high-output stoma (HOS) and acute kidney injury (AKI) requires an individualized and integrated approach. Formula selection should balance the need to reduce stoma output with careful electrolyte and protein control according to renal function. Semi-elemental formulas are preferred during the acute phase, while polymeric formulas may be introduced once output and renal parameters stabilize. Continuous feeding limits losses during high-output phases, while intermittent bolus promotes intestinal adaptation. Close monitoring of hydration, electrolytes, and nutritional status is essential to ensure safe, effective, and growth-supportive therapy.

Acknowledgement

The authors have no acknowledgments to declare

Conflict of Interest

None declared.

Funding Statement

The authors received no specific grant from any funding agency in the public, commercial, or not-profit sectors.

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Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

www.apghn.com

Volume 4 / No. 4
November 2025



Published by
Indonesian Society of Pediatric Gastroenterology, Hepatology, and Nutrition

