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Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Original Article

The Role of Green Banana in The Dietary Management of Children with Diarrhea: A Systematic Review and Meta Analysis

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Abstract:

Background: Diarrheal disease is a leading cause of morbidity and mortality among children under five, particularly in developing countries. Green bananas have shown therapeutic potential in managing pediatric diarrhea. This systematic review and meta-analysis compared the effectiveness of green banana supplementation versus non-green banana dietary management in children with diarrhea, alongside the use of ORS (oral rehydration solution) and Zinc. Outcomes assessed were recovery days, dehydration status, and progression to persistent diarrhea.

Methods: A systematic search was conducted across PubMed, Cochrane, Scopus, and ProQuest databases, following the PRISMA guidelines. Qualitative analysis was assessed using the RoB 2.0. Quantitative analysis was performed using RevMan 5.4 with forest plot visualization.

Result: From 57 identified studies, eight were included for review (seven randomized controlled trials and one pilot study). Among 1,486 children receiving green bananas, 1,370 recovered from diarrhea within seven days. Meta analysis showed significantly improved diarrheal recovery with green banana on day 3 (OR 3.41, 95% CI: 2.93-3.98, P<0.00001), day 5 (OR 3.48, 95% CI: 2.15-5.62, P<0.00001), and day 7 (OR 2.86, 95% CI: 2.14-3.82, P<0.00001). Green banana supplementation also showed less frequent dehydration (OR 0.38, 95% CI: 0.16-0.92, P=0.03) and reduced the progression to persistent diarrhea (OR 0.29, 95% CI: 0.21-0.39, P<0.00001).

Conclusion: Green banana with high pectin and amylose-resistant starch (ARS), is an effective dietary adjunct in the management of pediatric diarrhea, in terms of improving recovery, reducing dehydration, and preventing prolonged diarrhea in children due to their antimicrobial and anti-inflammatory compounds.

Keyword: children, dehydration, diarrhea, green banana, pediatric

Introduction

Diarrheal disease remains as one of the major causes of morbidity and mortality, particularly among children in developing countries. Diarrheal affecting children under five years old for 63% of global diarrheal burden. In developing countries, diarrhea is the second major cause of infant mortality as sanitation and clean water supply are poor. In South America, Asia, and Africa, diarrhea can affect one out of eight deaths in Children under 5 years per year.[1-3]

The management of pediatric diarrhea depends on its severity and underlying etiology, with antibiotics being reserved only for specific cases. Generally, the standard treatment of diarrhea primarily focuses on preventing dehydration and maintaining intestinal health. The treatment includes oral rehydration solution (ORS), continued oral feeding or nutritional support, zinc supplementation, and anti-infective agents. Zinc is routinely given to children in areas with a high risk of malnutrition, as it has been proven to effectively reduce the duration and severity of diarrheal episodes.[4, 5]

Green banana has nutritional and physiological benefits for human, as they are rich in dietary fibers, minerals (such as zinc, magnesium, potassium, phosphorus, and potassium), vitamins (such as Vit C, B6, and provitamin A), phenolic compounds, and resistant starch. Since the ancient times, green banana has been utilized as a traditional home remedy in the Indian subcontinent, its anti-diarrheal properties are attributed to the production of short-chain fatty acids (SCFA) in the colon from its amylase-resistant starch content, which enhances colonic water and electrolyte absorption.[6]

In many communities, unripe green banana has traditionally been used in the treatment of intestinal disorders, including diarrhea.[7, 8] Rabbani et al. showed that green banana (Musa paradisiaca) supplementation combined with a rice-based diet accelerated recovery from persistent diarrhea, while more recent studies by Sarmin, supported its potential therapeutic role.[7, 8] However, the available evidence remains inconclusive, as most studies were conducted with relatively small sample sizes, limited settings, and heterogeneous methodologies.[7] Therefore, the potential therapeutic role of green banana in diarrheal cases, as well as the uncertainties surrounding its use, still warrants further investigation.

To our knowledge, no previous systematic reviews have studied the role green banana in the dietary management of children with diarrhea. Thus, this systematic review and meta-analysis aims to identify and evaluate the role of green banana as a dietary management of children under five years old with diarrhea, specifically assessing its impact on recovery duration, dehydration status, and prevention of progression to persistent diarrhea.

Method

Search Strategy

This systematic review has been registered in PROSPERO with registration number CRD420251125670. A systematic search was conducted across four databases (PubMed, Cochrane, Scopus, and ProQuest), according to the PRISMA guidelines. The search strategy was structured based on the Population, Intervention, Comparison, and Outcome (PICO) framework. The population for this study was pediatric patients under five years of age diagnosed with diarrhea. The intervention group was patients receiving green banana supplementation as part of their diarrheal management, while the comparison or control group was patients receiving only standard care, such as ORS and zinc supplementation. Primary outcomes assessed were recovery duration, dehydration status, and progression to persistent diarrhea. Search terms used are listed in **Table 1.**

Table 1. Search strategy.

Databases/ Registers	Keywords
PubMed	((((Children) OR (paediatric)) OR (Gastroenteritis)) AND ((Green banana) OR (Musa paradisiaca))) AND ((((Diarrhea) OR (Gastroenteritis)) OR (Dysentery)) OR (Enteritis)).
Cochrane	Children in Title Abstract Keyword AND diarrhea in Title Abstract Keyword AND green banana in Title Abstract Keyword
Scopus	((((Children) OR (paediatric)) OR (Gastroenteritis)) AND ((Green banana) OR (Musa paradisiaca))) AND ((((Diarrhea) OR (Gastroenteritis)) OR (Dysentery)) OR (Enteritis))
Proquest	abstract(Children) AND abstract(Diarrhea) AND abstract(green banana)

Study Selection and Eligibility Criteria

Inclusion criteria were: (1) children under 18 years of age diagnosed with diarrhea, (2) intervention group received green banana and control group received standard care for diarrhea, (3) outcomes were recovery days from diarrhea, dehydration status, and the progression to persistent diarrhea, (4) papers published in English with full-text availability. Exclusion criteria were as follows: (1) absence of recovery days, (2) unavailable full texts. Duplicate studies were removed using EndNote Software.

Heterogeneity among study results was assessed using the I^2 statistic and visually inspected in forest plots. Meta-regression was not conducted because the number of eligible studies was too limited to provide reliable estimates.

Data Collection

Four independent reviewers screened titles and abstracts across the four databases, followed by full-text reviews to ensure eligibility. No automation tools were used in the screening or data extraction process as all steps were conducted manually by the reviewers.

The extracted data includes study characteristics (author, location, study design, year of publication, sample size, population criteria, mean age, duration of diarrhea, body weight) and outcomes (recovery days, dehydration status, and progression to persistent diarrhea) for both intervention and control groups. To ensure comparability, outcomes were extracted only if they were explicitly defined and reported across studies. When differences in definitions or measurement methods were identified, the reviewers discussed them and reached consensus on whether the data were compatible for inclusion.

Quality Assessment

The tools used for the assessment of the studies were based on the study design. Risk of Bias was evaluated using the Cochrane Risk of Bias 2 (RoB 2.0) tool, consisting of five domains: (1) randomization process, (2) bias due to deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported results. The studies were scored as low risk, high risk, or some concerns. Visualization of the bias was generated by the ROBVIS tool, generating traffic-light and weighted bar plots. The studies were then appraised as included and excluded. In addition, the risk of bias due to missing results in the synthesis (such as reporting bias) was assessed qualitatively and considered during the interpretation of the results.

Statistical Analysis

The outcomes were categorized into three groups: (1) recovery days of diarrhea (assessed at day 3, 5, dan 7), (2) dehydration status, and (3) progression to persistent diarrhea. All data were analyzed using the RevMan 5.4 software. Since all the outcomes in this review were dichotomous, we used the odds ratio (OR) with 95% confidence intervals (CI) as the effect measure. Inverse variance was employed as a statistical technique utilizing a fixed effect model, with the mean difference serving as the effect measure for data analysis. The 95% confidence interval and heterogeneity were assessed and displayed in the forest plot.

Result

Study Selection

Through the four databases (PubMed, Cochrane, Scopus, and Proquest), a total of 57 studies were obtained from the initial search. After removing duplicates, 35 studies were screened, and 18 were excluded based on the title and abstract review due to inappropriate intervention or ineligible study design. In addition, 3 articles were not retrieved because the full text was unavailable. Fourteen full-text articles were assessed for eligibility, of which six were excluded: 2 did not meet the PICO criteria, 2 was an editorial comment, 1 was only a protocol, and 1 was a literature review. Ultimately, 8 studies (7 randomized controlled trials and 1 pilot study) met the inclusion criteria and were included in this review and meta-analysis. The study selection process is illustrated in **Figure 1.**

Study Characteristics

Seven RCTs and one pilot study were included in this review, comprising 3,778 children with an overall age of under five years.[7-14] The majority of these studies were in Bangladesh, South Asia, with one study (Acosta et al.) from Venezuela.[9] Authors included all classifications of diarrhea: three focused on acute diarrhea, four on persistent diarrhea, and one on both acute and prolonged diarrhea. Detailed study characteristics, including sample size, body weight, and mean age, are summarized in **Table 2.**

Table 2. Included studies characteristics.

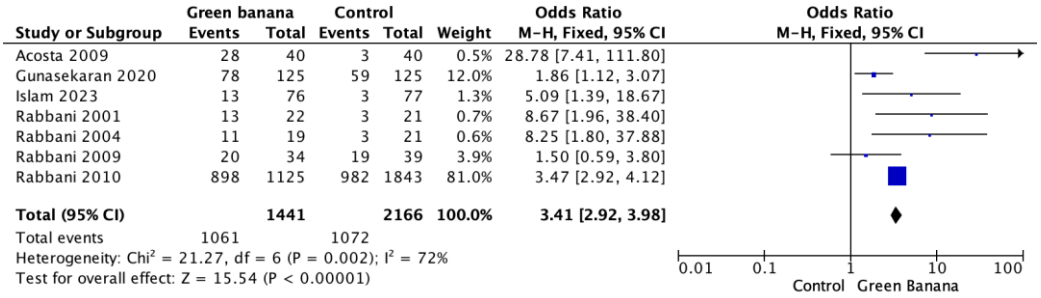
Author, Location	Study Population	Study Design	Samples included	Classification of Diarrhea	Body Weight kg (mean ± SD)		Age in months	
					Green Banana or Pectin	Control	Green Banana or Pectin	Control
Rabbani et al, 2001[7] Bangladesh	Boys, ages between 5 to 12 months	RCT	62	Persistent	Green banana: 6.5 ± 1.8 Pectin: 6.7 ± 1.2	6.8 ± 2.3	Green banana: 8.25 ± 2.9 Pectin: 8.75 ± 3.1	9.1 ± 2.5
Rabbani et al, 2004[8] Bangladesh	Boys, ages between 5 and 12 months	RCT	57	Persistent	Green banana: 7.0 ± 2.2 Pectin: 6.9 ± 1.9	7.1 ± 2.0	Green banana: 8.61 ± 2.0	8.9 ± 2.1

							Pectin: 9.1 ± 2.1	
Acosta et al, 2009[9] Venezuela	Children, ages between from 1-28 months	RCT	80	Persistent	6.0 ±1.6	6.3 ± 1.7	8.8 ± 5.0	Yoghurt -based: 9.5 ± 4.6
Rabbani et al, 2009[10] Bangladesh	Children, age between 6 to 60 months	RCT	73	Acute	8.6 ± 1.7	7.5 ± 1.4	17.4 ± 9.8	16.3 ± 6.5
Rabbani et al, 2010[11] Bangladesh	Children, ages between 6–36 months	RCT	2968	Acute & Prolonged	Acute: 8.4 ± 2.8 Prolonged: 8.0 ± 1.5	Acute: 8.2 ± 2.7 Prolonged: 7.8 ± 1.6	Acute = 18.4 ± 8.8 Prolonged = 17.5 ± 8.5	Acute = 18.7 ± 8.5 Prolonged = 7
Gunasekaran et al, 2020[12] Bangladesh	Children, ages between from 9 months to 5 years	RCT	250	Acute	N/A	N/A	23 ± 13.7	22.8 ±3
Islam et al, 2023[13] Bengal	Children, ages between 6 and 60 months	Pilot study	153	Acute	N/A	N/A	32.4 ± 4.8	34.8 ± 3.6
Sarmin et al, 2023[14] Bangladesh	Children, ages between 6-36 months	RCT	135	Persistent	N/A	N/A	median age: 8 months, interquartile 7-10 months	N/A

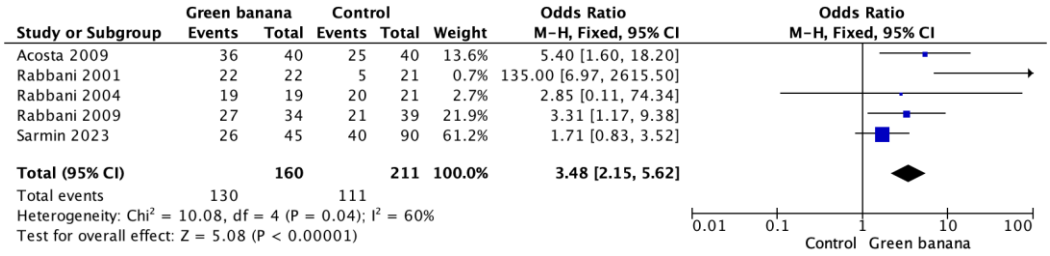
Data synthesis

a.) Recovery days of diarrhea

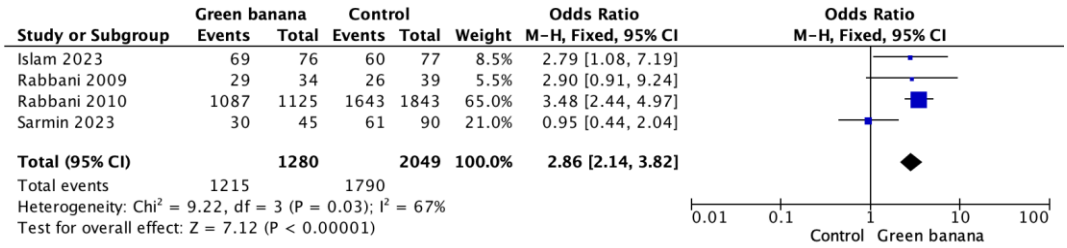
Across eight studies, 1,370 out of 1,486 children receiving green banana supplementation recovered from diarrhea within seven days. Meta-analysis showed significant improvement in recovery rates in children receiving green banana at day 3 (OR 3.41, 95% CI: 2.93-3.98, P<0.00001), day 5 (OR 3.48, 95% CI: 2.15-5.62, P<0.00001), and day 7 (OR 2.86, 95% CI: 2.14-3.82, P<0.00001). These results indicate that green bananas significantly accelerate the recovery from diarrhea **(Figure 2).**



a.) Forest plot for recovery day 3.



b.) Forest plot for recovery day 5.



c.) Forest plot for recovery day 7.

Figure 2(a-c). Forest plot for the recovery day of diarrhea.

b.) Dehydration status of diarrhea

Two studies assessed the dehydration status of diarrhea. Gunasekaran et al. reported that 2 out of 125 patients had dehydration in the green banana group, indicating that green banana can reduce dehydration (OR 0.14, 95% CI: 0.03 - 0.63), whereas Rabbani et al., found no significant association (OR 1.03, 95% CI: 0.29-3.62) between green banana consumption and dehydration status.[12, 13] The pooled analysis indicated a significant reduction in dehydration risk with the supplementation of green banana (OR 0.38, 95% CI: 0.16-0.92, P=0.03) **(Figure 3).**

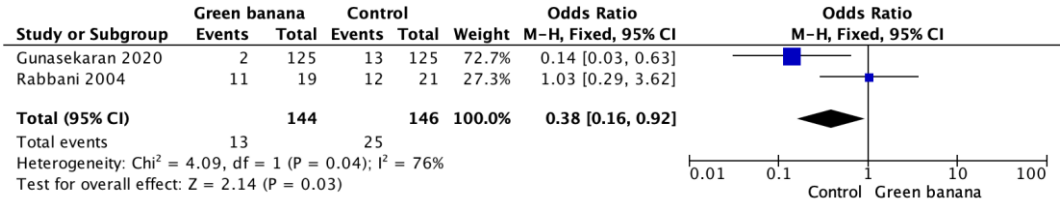


Figure 3. Forest plot for the dehydration status of diarrhea.

c.) Progression to persistent diarrhea

There were four out of eight studies that classified diarrhea as acute diarrhea, with three of them mentioning the progression from acute to persistent diarrhea (Gunasekaran et al., Islam et al., and Rabbani et al).[11,12,13] The meta-analysis showed that green banana significantly reduced the risk of progression from acute to persistent diarrhea (OR 0.29, 95% CI: 0.21-0.39, P<0.00001) **(Figure 4)**.

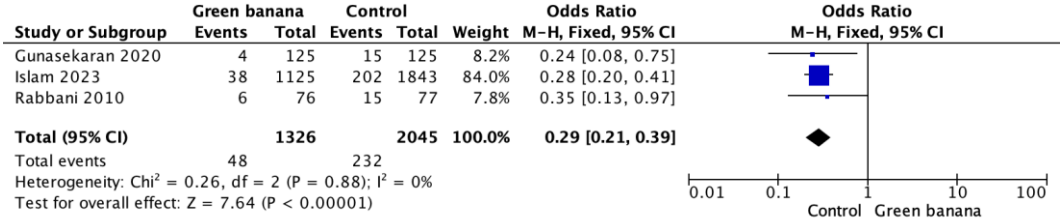


Figure 4. Forest plot for the progression to persistent diarrhea.

Risk of Bias

Our comprehensive risk of bias assessment for this meta-analysis revealed consistently strong methodological quality across the included studies. All 8 studies demonstrated predominantly low risk of bias across the five critical domains examined using the RoB 2.0 tool.

While minor methodological variations were noted in individual studies, particularly in Rabbani et al.[7] regarding selective reporting and in Rabbani et al.[12] concerning aspects of the randomization process, these variations did not compromise the overall methodological soundness of the research.

However, we acknowledge that such methodological variations may have contributed to some degree of heterogeneity observed in the pooled results. Despite these variations, we concluded that the body of evidence compiled for this meta-analysis rests on a foundation of methodologically sound research, with all studies meeting our predetermined criteria for inclusion. This enhances our confidence in the pooled results and strengthens the reliability of the findings of our study **(Figure 5).**

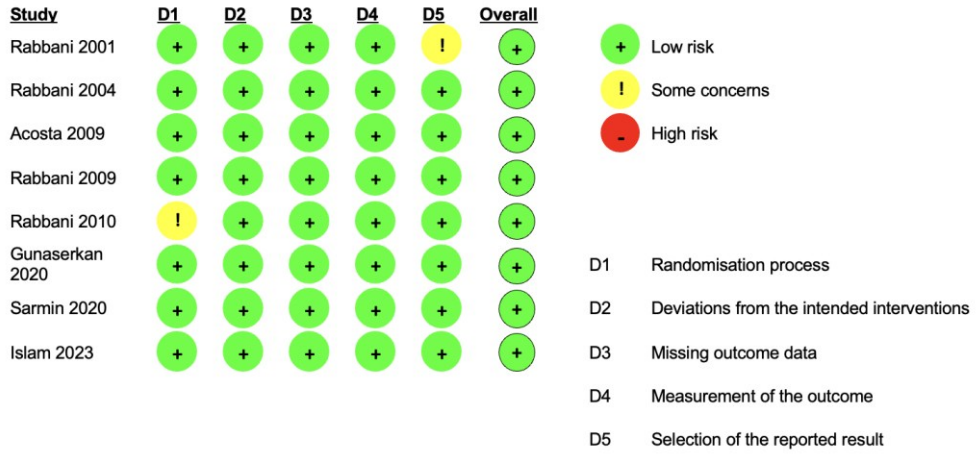


Figure 5. Risk of Bias.

Discussion

This meta-analysis demonstrates that green banana supplementation significantly improves diarrheal recovery outcomes in children under five years of age. Evidence in this paper shows substantial benefits across multiple outcomes, particularly in reducing recovery time.[15, 16]

Our analysis revealed that children receiving green banana were significantly more likely to recover from diarrhea by day 3 (OR 3.41, 95% CI: 2.93-3.98, P<0.00001), day 5 (OR 3.48, 95% CI: 2.15-5.62, P<0.00001), and day 7 (OR 2.86, 95% CI: 2.14-3.82, P<0.00001) compared to controls. This consistent pattern of improvement across different time points strengthens the evidence for green banana's therapeutic efficacy. The high recovery rate in the intervention group (1,370 out of 1,486 children) further supports this conclusion.[11, 12]

In addition, green banana supplementation also showed benefits in reducing dehydration, a critical complication which contributes to morbidity and mortality in children.[17] The pooled analysis of dehydration status (OR 0.38, 95% CI: 0.16-0.92, P=0.03) indicates that children receiving green bananas were less likely to experience dehydration, though it should be noted that only two studies assessed this outcome with somewhat conflicting results.[7, 13] While Gunasekaran et al.[13] found a significant reduction in dehydration (OR 0.14, 95% CI: 0.03-0.63), Rabbani et al.[9] found no

significant association (OR 1.03, 95% CI: 0.29-3.62).[9-12] This discrepancy warrants further investigation in future studies.

Perhaps most notably, it is shown in this paper that green banana supplementation significantly reduced the risk of acute diarrhea progressing to persistent diarrhea (OR 0.29, 95% CI: 0.21-0.39, P<0.00001).[12-14] This finding is particularly important in clinical practice, as persistent diarrhea is associated with increased risk of malnutrition, growth faltering, and mortality in children.[17]

The geographically confined nature of seven out of eight studies to Bangladesh also means it is doubtful if the effects are generalizable to other groups of people who eat differently, have different gut microbiota patterns, and exposure environments.[14]s[8] Even that single study carried out in Venezuela by Alvarez-Acosta et al., reported the same favorable impacts, meaning green banana may work in non-South Asian populations, but this needs further evidence in different settings.[10]

Most of the studies recruited male children or did not report gender distribution, which might limit the ability to generalize outcomes across genders.[7-14] The studies further covered various categories of diarrheal duration (acute, prolonged, and persistent), indicating green banana can be beneficial in a range of diarrheal manifestations, but possibly through different mechanisms.[12]

The literature indicates a number of possible mechanisms by which green banana exerts its anti-diarrheal action.[6] Green bananas are a source of resistant starch, which can function as a prebiotic, stimulating the growth of beneficial gut flora and increasing the production of short-chain fatty acids.[18] These fatty acids, especially butyrate, play a key role in colonic health and water absorption.[19] Green bananas also have bioactive compounds with possible antimicrobial and anti-inflammatory activities that could restore gut homeostasis.[20]

While our findings are strongly indicative of the therapeutic potential of green banana in pediatric diarrhea, several limitations need to be acknowledged. The studies varied in reporting such essential variables as body weight and precise age, which affect dosing recommendations. Further, data on the preparation, administration, and dosage of green banana varied between studies, preventing the identification of optimal treatment regimens.[7-14]

Further research should also seek to standardize the preparation of green banana, determine dose-response approaches on a relative basis of age and weight, examine potential synergisms with other drugs, and elucidate the resulting specific biochemical foundation for the derived clinical effects. They should also be conducted in other regions to determine if the results have generalizability.

In conclusion, the present meta-analysis offers strong evidence that green banana supplementation is useful in recovery from diarrhea, avoids risk of dehydration, and prevents advancement to chronic diarrhea in children under five years. Due to its efficacy, accessibility, and low cost, green banana is a promising adjunct therapy for childhood diarrhea, particularly in resource-limited countries where diarrheal disease burden is most relevant.

Limitation of the Study

In this systematic review, studies were mostly conducted in Asian countries, thus not covering many countries from other continents. Further research on green bananas as a therapy for diarrhea in non-Asian countries is needed.

Conclusion

This systematic review and meta-analysis provide compelling evidence that green banana is significantly effective as a dietary supplement in the management of diarrhea among children under five. Across the eight included studies, children who received green banana in addition to standard treatment demonstrated a faster recovery time, reduced risk of dehydration, and a markedly lower likelihood of progressing to persistent diarrhea. These benefits are likely attributable to the high content of pectin, resistant starch, and bioactive compounds in green banana, which enhance colonic absorption, improve gut microbiota, and support intestinal health.

Given its affordability, accessibility, and favorable safety profile, green banana represents a promising adjunct to existing diarrhea management protocols, especially in resource-constrained settings. Nevertheless, variations in study location, sample demographics, and preparation methods warrant further research to establish standardized dosing, optimize treatment regimens, and validate generalizability across diverse populations. In summary, green banana is a practical and effective dietary strategy that should be considered in the comprehensive management of pediatric diarrhea.

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The authors would like to acknowledge the authors from included studies who have done research in the pediatric field, particularly on the green banana supplementation for diarrhea.

Conflict of Interest

There is no conflict of interest.

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Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Original Article

Unlocking The Efficacy of Tetrahydrobiopterin (BH4) Towards Metabolic Profile and Growth Status in Children with Phenylketonuria: A Meta Analysis

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Razan RA, Widjaja NA, Lorenza A, Andhary VS, Ananda ND. Unlocking the efficacy of tetrahydrobiopterin (BH4) towards metabolic profile and growth status in children with phenylketonuria: a meta analysis. *Arch Pediatr Gastr Hepatol Nutr.* 2025;4(3).111-128

Abstract:

Background: Phenylketonuria (PKU) is one of the most common types of inborn error of metabolism. Low-phenylalanine diet has been the main treatment for children with PKU. However, recent therapeutic alternatives have emerged as a solution in children with PKU in the form of tetrahydrobiopterin (BH4). This meta analysis aims to assess the effectiveness of BH4 in terms of response rate, metabolic profile and growth status.

Methods: Meta analysis was conducted by searching databases such as PubMed, ScienceDirect, Cochrane Library, medRxiv, and Scopus based on the Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA) guidelines. Data synthesis and analyses were conducted using R version 4.5.1 (R Foundation for Statistical Computing).

Result: Fifteen studies were involved in this research, consisting of 1280 children (1063 given BH4). Eight studies reported BH4 reduced plasma phenylalanine concentration by around (686.83 mg/day [95% CI 394.85 to 978.82], p <0.001). Additionally, two studies reported a reduction in plasma phenylalanine concentration, measured in mg/kg/day, following BH4 administration. Children given BH4 and low phenylalanine diet combination showed a higher response rate compared to BH4 only (100% vs 76%). Two studies showed no difference in growth outcomes, which remained within the normal range.

Conclusion: BH4 shows promise as an adjunct therapy for children with PKU, but confirmation through larger, standardized, long-term studies assessing outcomes such as growth status and long-term neurocognitive outcome is needed.

Keyword: BH4, children, growth status, metabolic profile, phenylketonuria

Introduction

Phenylketonuria (PKU) is a rare autosomal recessive disorder resulting from a deficiency in the hepatic enzyme phenylalanine hydroxylase (PAH), which catalyzes the conversion of phenylalanine to tyrosine. The accumulation of phenylalanine in the blood and brain, if left untreated, can lead to severe intellectual disability, behavioral issues, and developmental delays.[1] Globally, the incidence of PKU varies significantly, with reported prevalence rates ranging from 1 in 10,000 to 1 in 15,000 live births in Europe and the United States.[2]

The primary treatment strategy for managing PKU has long centered on a lifelong, strictly controlled low-phenylalanine diet, typically initiated in infancy to prevent toxic accumulation of phenylalanine in the blood and central nervous system. This dietary intervention is effective in minimizing neurocognitive impairment and supporting normal development. However, maintaining strict dietary adherence becomes increasingly difficult with age, particularly during adolescence, often leading to poor compliance, reduced quality of life, and suboptimal long-term metabolic outcomes).[3]

In recent years, tetrahydrobiopterin (BH4), a natural cofactor of PAH has emerged as a pharmacological option for a subset of patients with residual PAH activity. By enhancing the enzyme's function, BH4 responsiveness allows more flexible diet and improved phenylalanine tolerance.[4] Sapropterin dihydrochloride, a synthetic formulation of BH4, has been approved for clinical use and shown to be effective in lowering phenylalanine levels, especially when used in combination with dietary management.[5]

Despite its increasing use, the broader impact of BH4 on growth status, safety profile, and metabolic tolerance remains an area of ongoing research, particularly in pediatric populations. Given the inconsistency in treatment responses and limited data, a comprehensive review is needed to elaborate BH4's role in PKU management. This meta analysis discussed current evidence on the efficacy of BH4 supplementation in children with PKU, focusing on response rates, metabolic profile, and growth outcomes.

Method

Conduct of Review

This review was planned and conducted following the Cochrane Handbook for Systematic Reviews of Interventions. The results were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Given the anticipated substantial variability among studies, stemming from differences in study design and participant characteristics, we predetermined the use of a random effects model employing restricted maximum likelihood (REML) methodology for data pooling. The evaluation of statistical heterogeneity across the

studies was conducted using Cochran's Q and I^2 statistics. Values of 25%, 50%, and 75% for I2 are proposed to signify low, moderate, and high heterogeneity, respectively. The pooled mean change was used to estimate within-group differences (baseline and post-intervention) under the assumption that the correlation coefficient was 0.5. Data synthesis and analyses were conducted using R version 4.5.1 (R Foundation for Statistical Computing, https://www.r-project.org/).

Search Strategy

We conducted a comprehensive search in Pubmed, Sciencedirect, Cochrane Library, medRxiv, and Scopus for studies focusing on BH4 with outcomes of metabolic profile and growth status in children. Our search strategy included the following keywords: ("Tetrahydrobiopterin" OR "BH4" OR "Sapropterin" OR "Low Phenylalanine Diet") AND ("Phenylketonuria" OR "PKU"). We manually screened the bibliographic references of all selected studies in the Pubmed, ScienceDirect, Cochrane Library, medRxiv, and Scopus database. The final search was completed in August 2025.

Inclusion Criteria

We included randomized controlled trials, cohort, cross-sectional, and other observational studies involving children with phenylketonuria, especially studies focusing on BH4 with outcomes of metabolic profile and growth status.

Study Selection and Data Extraction

Titles and abstracts retrieved from the database were independently screened by four reviewers to identify relevant studies that met the selection criteria outlined above, who also independently assessed eligibility by further reviewing the full text. Disagreements were resolved through consultation with a fifth reviewer. Disagreements were determined when two or more reviewers assigned ratings that varied by more than 1 point on a 5-point scale. In these instances, a discussion was held among all reviewers, including a fifth independent reviewer who had not previously evaluated the manuscript. In this study, 12 of the 68 manuscripts (17.6%) necessitated the consensus process. The final score for each manuscript was established only after unanimous agreement was achieved among the review team.

Four reviewers extracted data independently and discrepancies were identified and resolved in consultation with a fifth reviewer. Standardized and pre-tested data collection tables were used to extract data from included studies using the Systematic Review Data Repository. The primary outcome of interest was phenylalanine intake per day before and after BH4 treatment.

Study Quality Assessment

We used the Cochrane Risk of Bias tool (RoB 2) for randomized controlled trials (RCTs), the Risk of Bias in Non-randomised Studies - of Interventions tool

(ROBINS-I) for non-randomized comparative studies (e.g., cohort, retrospective, or clinical trial without randomization), and the NIH Quality Assessment Tool for case series. Three reviewers independently assessed the RoB 2, ROBINS-I, and NIH Quality Assessment Tool quality of each study. Any disagreements between the reviewers were resolved by the fifth reviewer.

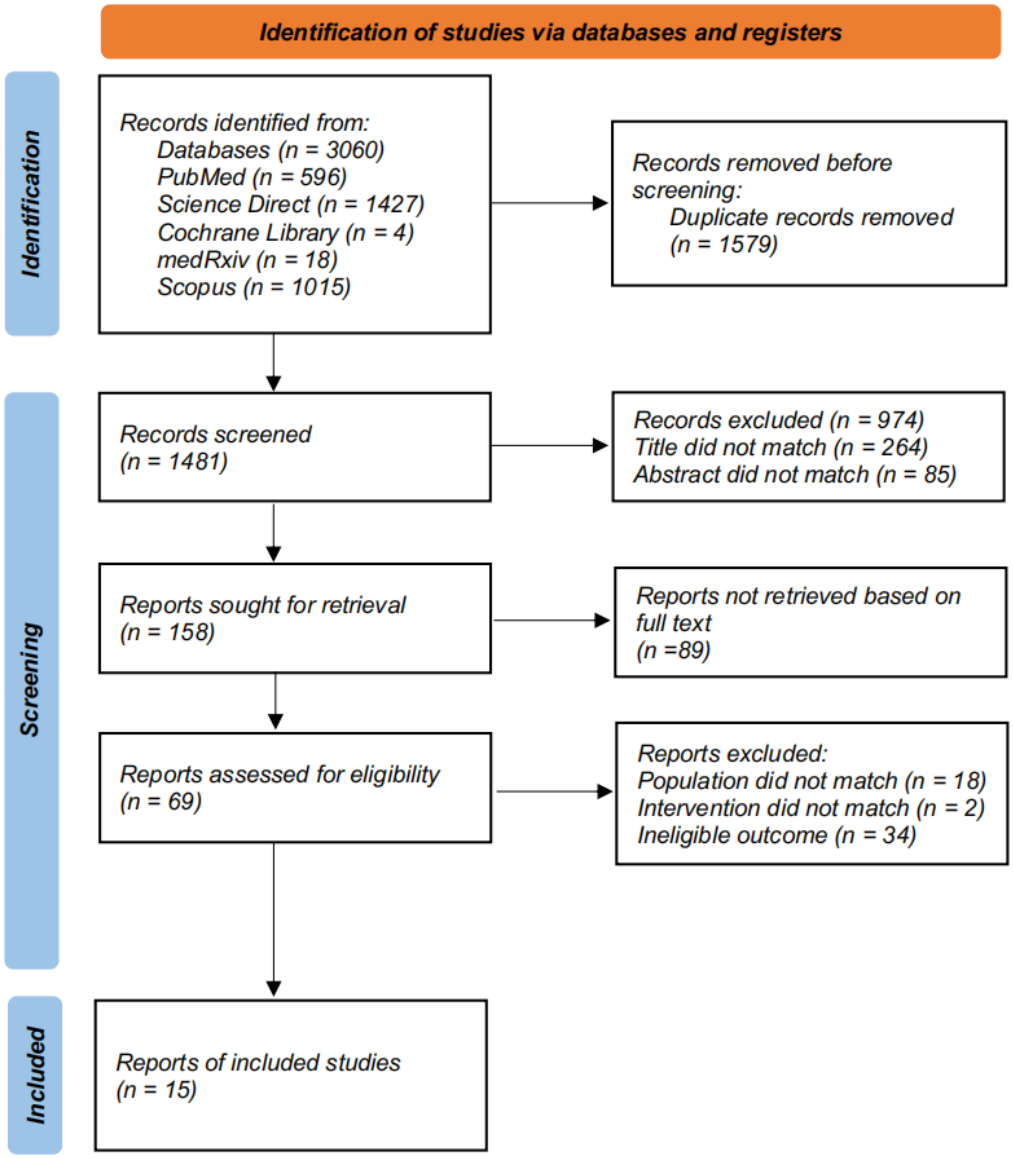

Figure 1. PRISMA flowchart on study screening and selection process

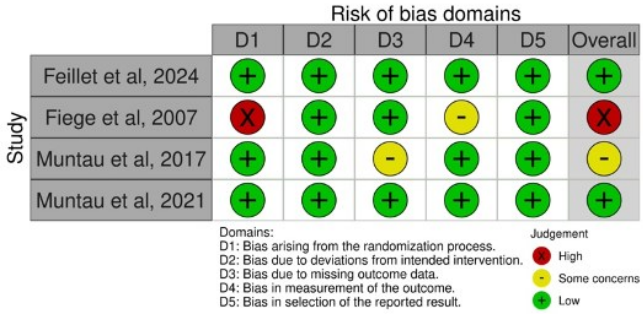

Figure 2. Quality assessment using Cochrane Risk of Bias tool for randomized controlled trials (RoB 2)

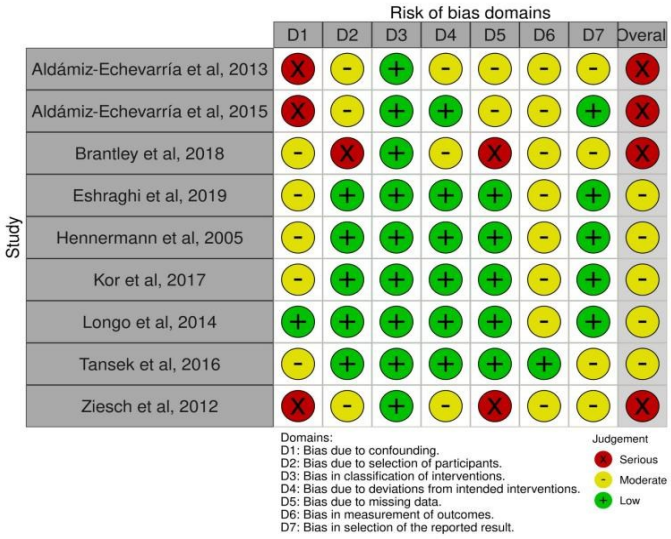

Figure 3. Quality assessment using Risk of Bias in Non-randomised Studies - of Interventions tool (ROBINS-I)

Table 1. Quality assessment using NIH Quality Assessment Tool for Case Series

	Tansek et al., 2012[6]	**Trefz et al., 2010[7]**
1. Clearly stated objective	Yes	Yes
2. Well-defined and representative population	Yes	Yes
3. Consecutive cases	Unclear	Yes
4. Comparable subjects	Yes	Yes
5. Intervention clearly described	Yes	Yes
6. Outcome measures clearly defined	Yes	Yes
7. Adequate follow-up	Yes	Yes
8. Results clearly reported	Yes	Yes
9. Appropriate statistical analysis	Yes	Partial
Overall RoB	Low	Moderate

Result

A total of 3060 articles were identified through the literature search, with 15 identified relevant to the topic and fulfilling the inclusion criteria as shown in **Figure 1**. The articles included were published between January 2005 - August 2025 involving 1280 pediatric patients who received BH4 administration in comparison to those on a low phenylalanine diet alone. **Table 2** presents the characteristics of the subjects.

We used the NIH case series tool for descriptive studies, ROBINS-I for non-randomized interventional and observational studies, and RoB 2 for randomised controlled trials to assess the risk of bias across the included studies in this review (**Figure 2, Figure 3, Table 1**), respectively. The overall risk of bias was deemed low for the randomised trials due to sufficient blinding, randomisation, and minimal missing data.[8-10] Despite being widely regarded as interventional, Fiege et al. in 2007 lacked randomisation and, as a result, were rated as having a high risk of bias when evaluated using RoB 2.[11] Confounding variables and the lack of blinding were the main causes of the non-randomized cohort and clinical studies' generally moderate risk of bias.[12-14] According to ROBINS-I, certain retrospective studies were deemed to be seriously at risk of bias due to limitations in outcome reporting and participant selection.[15-17] The NIH tool was used to evaluate case series.[6, 7] Although both were well-reported overall, assessments of low to moderate risk of bias were reached due to limitations like unclear consecutive recruitment and incomplete statistical analysis reporting. Overall, the highest certainty of evidence derives from the multicenter randomized trials[9, 10], while the observational and case series evidence should be interpreted with caution due to methodological limitations.

Table 2. The Characteristic of Subjects

Authors, year, country	Type of Study	Total Population		Characteristic Population		Age of BH4 treatment initiation, months		Response Definition
		I	C	I	C	I	C	
Kor et al., 2017[12] Turkey	Case Control	26	24	BH4 2x10 mg/kg/ day	BH4 SD (20 mg/kg /day)	55.9 ± 18.9 (53 [9–100])	48.3 ± 29.7 (40.5 [11–140])	Reduction of Phe levels at least 30% after 72 hours
Eshraghi et al., 2019[13]	Clinical Trial	24		BH4 SD (20 mg/kg/day) +		1-10 years		Reduction of Phe levels

Iran				Low Phe Diet 20–50 mg/kg				>30% after 48 hour BH4 administration
Aldámiz-Echevarría et al.,2015[16] Spain	Retrospective Study	22	44	BH4	Low Phe Diet	16.9 ± 10.4	-	Reduction of Phe ³50% after 24 hour BH4 administration
Trefz et al.,2010[7] Spain	Case Series	7	8	BH4	BH4 + Low Phe Diet	6.95 ± 12.02	77.87 ± 57.04	Reduction of blood phenylalanine >30%
Longo et al.,2014[18] USA, Canada	Cohort Prospective	55		BH4		3.14 ± 2.16		Reduction of blood Phe ≥30% after BH4 administration
Aldámiz-Echevarría et al.,2013[17] Spain	Retrospective Study	36	72	BH4 + Low Phe Diet	Low Phe Diet	5.0 ± 4.6 years	8.9 ± 5.0 years	Reduction of blood Phe ≥30% after BH4 administration
Ziesch et al.,2012[19] German	Prospective Clinical Study	8	6	BH4	Low Phe Diet	11.13 ± 4.4 years	9.23 ± 3.8 years	Reduction of blood phenylalanine >30% after BH4 administration
Brantley et al.,2018[15] USA	Cohort Prospective	11	8	BH4 + Low Phe Diet	Low Phe Diet	9.7 ± 3.4 years	10.4 ± 4.4 years	Reduction of Phe plasma at least 15%

Tansek et al.,2016[20] Slovenia	Retrospective Study	9	BH4 15.5 mg/kg, adjusted after	6.22 ± 3.0 years	Reduction of blood Phe at least 30% in 24 hours
Feillet et al.,2024[8] 9 European countries	Randomized control trials	481	BH4 20 mg/kg ± Low Phe Diet	<4 years (11) 4 - <12 years (329) 12 - <18 years (141)	≥30% reduction of blood Phe concnetration
Hennermann et al.,2005[14] Switzerland	Prospective Clinical Study	5	BH4-resplonsive PAH deficiency and a low phe tolerance of <20mg/kg	12.4 ± 18.1 months	≥30% reduction of blood Phe concentration in 8-24 hours
Tansek et al.,2012[6]	Case series	34	BH4 20 mg/kg	1 year - 18 years	≥30% reduction of blood Phe concentration in 24 hours
Fiege et al.,2007[11] Switzerland	Randomized control trials	293	BH4 20 mg/kg	1 year - 7 years	≥30% reduction of blood Phe concentration in 24 hours
Muntau et al.,2017[9] 9 countries	Randomized control trials	27 29	BH4 20 mg/kg + Low Phe Diet Low Phe Diet	27.2 ± 79.8 days 32.6 ± 72.2 days	≥30% reduction of blood Phe concentration in 24 hours

Muntau et al.,2021[10] 9 countries	Randomized control trials	25	26	BH4 20 mg/kg + Low Phe Diet	Low Phe Diet		≥30% reduction of blood Phe concentration in 24 hours

I: Intervention; C: Control

Eight comparisons, involving 619 participants, were aggregated to assess the primary outcome of blood phenylalanine levels after BH4 administration with low phenylalanine diet.[8, 12-15, 18-20] The use of BH4 shows significant benefits in reducing plasma phenylalanine concentration by around (686.83 mg/day [95% CI 394.85 to 978.82], p <0.001) (**Figure 4.)**. The statistical variability was substantial (I2 = 93.2%), with effect sizes of separate trials varying from 289.50 to 1502. The funnel plot (**Figure 5.**) shows some asymmetry, with fewer studies reporting smaller or no treatment effects on phenylalanine levels. This points to the possibility of publication bias or small-study effects. Additionally, the spread of points suggests variability among trials. This may reflect differences in genotype responsiveness, treatment protocols, and follow-up durations. Therefore, direct interpretation should be approached carefully. Additionally**,** two studies by Aldámiz-Echevarría et al. in 2013 and 2015 reported a reduction in plasma phenylalanine concentration, measured as mg/kg/day, after one and two years of BH4 administration in **Table 3**. [16, 17]

Table 3. Blood Phe Level Before and After BH4 (mg/kg day)

Author, year	Evaluation	Phe level before (mg/kg day)	Phe level after (mg/kg day)
Aldámiz-Echevarría et al, 2015[16]	1 year follow up	37.1 ± 19.1	53.0 ± 33.5
Aldámiz-Echevarría et al, 2013[17]	2 year follow up	29.9 ± 8.5	41.2 ± 6.5

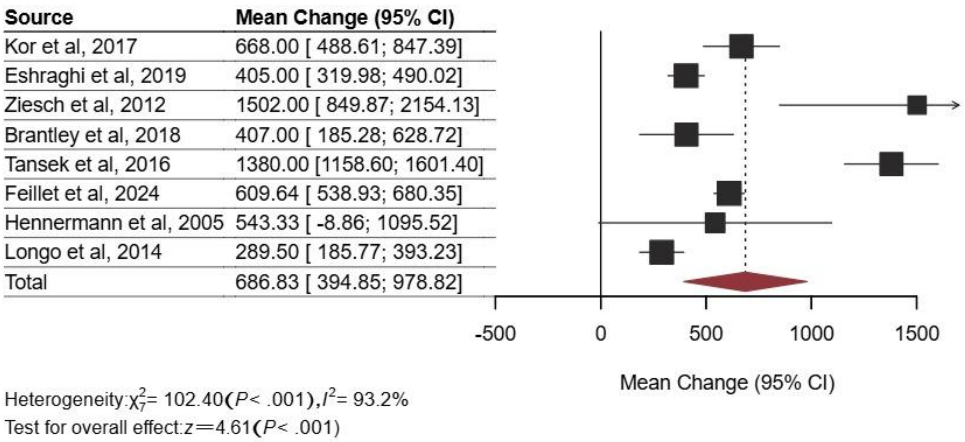

Figure 4. Forest plot about pooled standardized mean change of Blood Phe Level in children with PKU treated with BH4 administration + low Phe diet

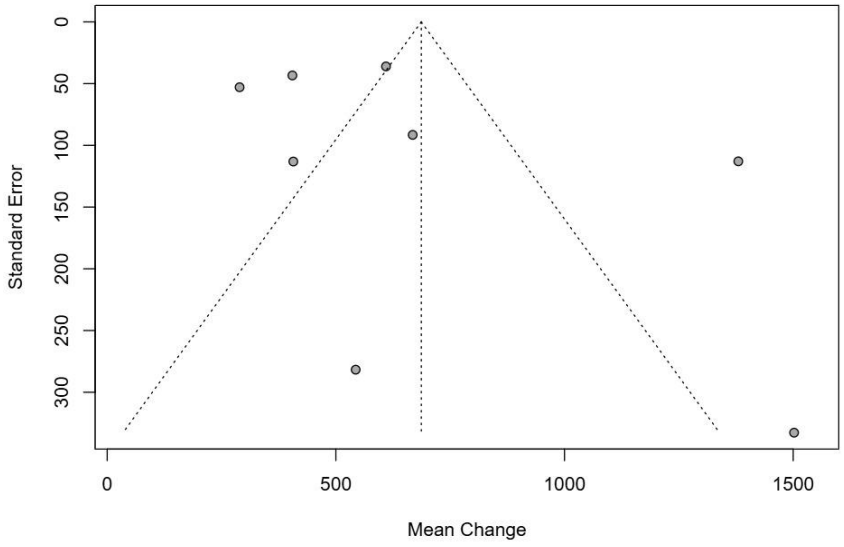

Figure 5. Funnel Plot about pooled standardized mean change of Blood Phe Level in children with PKU treated with BH4 administration + low Phe diet

Two studies evaluated the anthropometric status of children with PKU receiving a combination of BH4 and a low phenylalanine diet in comparison to those on a low phenylalanine diet alone in **Table 4**. Both studies showed that there was no significant difference in growth status between the two groups. [16, 17]

Table 4. Anthropometric Status

Author, year	Anthropometric Status							
	Weight Z-score		Height Z-score		Weight for Height Z-score		BMI Z-score	
	BH4 + Low Phe Diet	Low Phe Diet	BH4 + Low Phe Diet	Low Phe Diet	BH4 + Low Phe Diet	Low Phe Diet	BH4 + Low Phe Diet	Low Phe Diet
Aldámiz-Echevarría et al, 2015[16]	−0.19 ± 0.93	−0.48 ± 0.98	−0.52 ± 1.29	−0.78 ± 1.08	0.90 ± 1.42	1.26 ± 2.00	0.18 ± 1.00	−0.07 ± 1.03
Aldámiz-Echevarría et al, 2013[17]	− 0.75 ± 1.04	− 0.52 ± 0.85	− 0.73 ± 0.96	− 0.90 ± 1.00	NR	NR	0.37 ± 1.09	− 0.12 ± 0.89

In terms of response rate outcome, children given BH4 only showed a high response rate percentage of (76% [95% CI 49% to 92%]) in **Figure 6**.[6, 7, 11-14, 16-20] The statistical variability was substantial (I2 = 92.7%), with response rate of separate trials varying from 16% to 100%. The statistical variability was high (I2 = 92.7%), with response rates in separate trials ranging from 16% to 100%. The funnel plot for the pooled response rate to BH4 therapy (**Figure 7.**) shows mild asymmetry, with fewer studies reporting lower response rates. Smaller studies often report higher response rates, suggesting the possibility of small-study effects or publication bias. However, most studies are close to the pooled estimate, indicating a generally consistent treatment effect despite some potential bias toward positive results. Additionally, BH4 combined with low phenylalanine diet showed a higher response rate percentage of (100% [95% CI 0% to 100%]) in **Figure 8**.[7-10, 15] The statistical variability was not substantial (I2 = 0%), with response rate of separate trials varying from 58% to 100%. The funnel plot for the pooled response rate of BH4 combined with a low phenylalanine diet (**Figure 9.**) shows clear asymmetry, but the small number of available studies limits interpretation. The distribution indicates possible small-study effects, as smaller trials often report higher response rates. Furthermore, the wide range of effect estimates points to significant variability, which may come from differences in dietary compliance, genetic responses, and study design. Therefore, the results should be interpreted carefully.

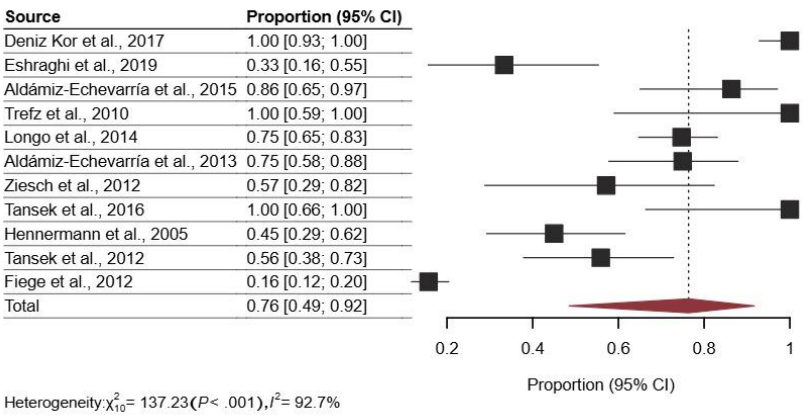

Figure 6. Meta-analysis and forest plot about pooled proportion of response rate in BH4 administration only.

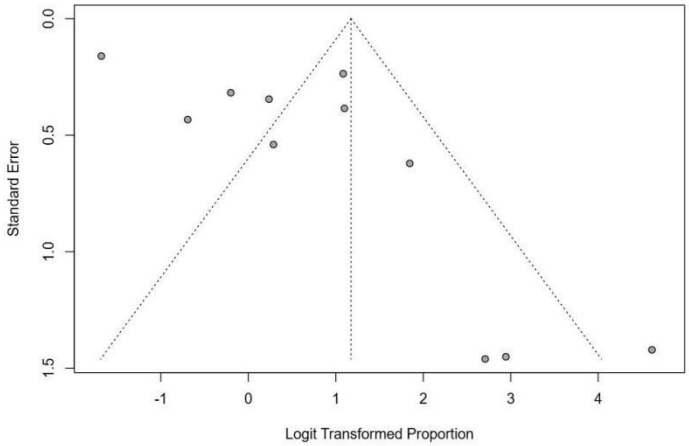

Figure 7. Funnel Plot about pooled proportion of response rate in BH4 administration only

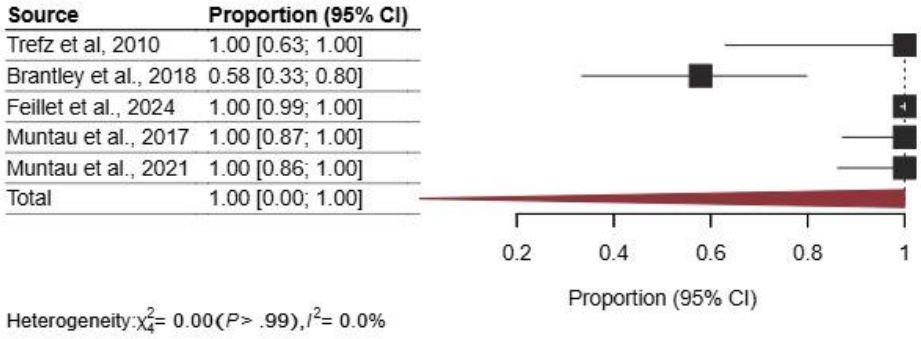

Figure 8. Meta-analysis and forest plot about pooled proportion of response rate in BH4 administration + low Phe diet

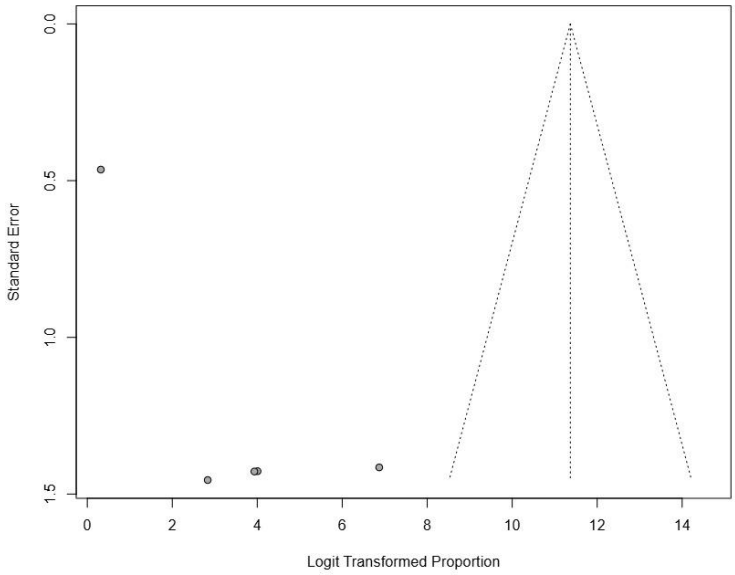

Figure 9. Funnel Plot about pooled proportion of response rate in BH4 administration + low Phe diet

Discussion

Dietary restriction of the amino acid phenylalanine is currently the main treatment for PKU. It preserves phenylalanine levels in the blood within the therapeutic range and prevent neurologic impairment. For PKU patients, BH4 was recommended as an adjuvant treatment, even though dietary restriction of the amino acid phenylalanine is still the primary treatment.[21] BH4 regulates by activating the PHA enzyme's residual activity.[22] In an attempt to lower the side effects of low-protein diets, typically seen in patients with PKU who are receiving early and ongoing treatment, BH4 treatment became an effective alternative along with PKU diet. This treatment enhances metabolic control and therapy compliance in BH4-responsive individuals by increasing their natural protein intake.[23] Treatment of PKU patients with BH4 has shown improvements in executive function, decreases in variability of blood phenylalanine levels, and enhancements in bone mineral accretion.[6, 8, 16] In this study, we conducted a meta analysis of studies focusing on BH4's effectiveness as it applies to growth status, metabolic profile, and response rate.

Research by Brantley et al. in 2018, with a prospective cohort, showed a decrease in phenylalanine levels in the blood of at least 15% with an administration of BH4 along with low phenylalanine diet.[15] However, compared to other research, BH4 only consistently reduced by at least 30% of phenylalanine levels. Phenylalanine levels in the blood may reduce by at least 30% in a day as BH4 is administered at a dose of 20 mg/kg/day, with or without a phenylalanine diet, based on several research in RCTs and prospective clinical studies.[8-11, 14, 19] This is similar to case series studies that shown at least 30% reduced blood Phe levels on BH4 treatment.[6, 7] The study conducted in

2013 by Aldámiz-Echevarría et al. showed that administering BH4 for 8 hours after a low-Phe diet led to a decrease in blood Phe levels of at least 30%.[17] Study in 2015 found that within 24 hours of administering BH4, Phe levels had decreased by at least 50%.[16] Within 24 hours after the administering of 15.5 mg/kg of BH4, blood phenylalanine levels were reduced by at least 30%, based to another retrospective study conducted in 2016.[20] According to a clinical trial investigation by Eshraghi et al. in 2019, phenylalanine levels decreased within 48 hours in 24 subjects that received 20 mg/kg/day of BH4 combined with a lower phenylalanine diet of 20–50 mg/kg/day.[13]

This meta analysis demonstrated a significant benefit of BH4 administration combined with a low phenylalanine diet in reducing plasma phenylalanine concentration (mean change 686.83 mg/day; 95% CI: 394.85–978.82, $p < 0.001$).[8, 12-15, 18, 20] However, substantial heterogeneity was present ($I^2 = 93.2\%$), with effect sizes of separate trials varying from 289.50 to 1502. Variability may be attributed to differences in sample size, baseline characteristics, and treatment protocols across studies. Additionally**,** two studies that reported plasma phenylalanine concentration with BH4 administration showed only a reduction (30.3 ± 4.2 vs 37.1 ± 5.0; 29.9 ± 8.5 vs 41.2 ± 6.5 mg/kg/day, respectively), highlighting that the effect may depend on concurrent dietary management.[16, 17] The funnel plot showed relative asymmetry, suggesting possible small-study effects or publication bias. These findings indicate that while BH4 appears beneficial, the magnitude of effect remains uncertain. Future investigation should be conducted in large-scale, multicenter settings with standardized treatment protocols and longer follow-up periods to reduce bias, improve comparability, and clarify the true therapeutic impact of BH4 administration.

In terms of response rate, children receiving BH4 administration only showed a high response rate percentage of 76% ([95% CI: 49–92%], p< 0.001), as shown in **Figure 6**.[6, 7, 11-14, 16-20] The statistical variability was substantial ($I^2 = 92.7\%$), with response rates ranging widely from 16% to 100%. The funnel plot **(Figure 7.)** revealed mild asymmetry, with smaller studies tending to report higher response rates, suggesting the possibility of small-study effects or publication bias. Nonetheless, most studies clustered near the pooled estimate, indicating a generally consistent treatment effect despite potential bias toward positive results. In contrast, BH4 combined with a low phenylalanine diet showed a higher response rate percentage of 100% ([95% CI: 0–100%], p>99) with no significant heterogeneity ($I^2 = 0.0\%$).[7-10, 15] Although the funnel plot showed asymmetry **(Figure 9.)**, interpretation was limited by the small number of available studies. Variability across trials may be influenced by dietary adherence, genetic differences, and study design, and thus the results should be interpreted with caution.

Z-scores on growth status in the HAZ, WAZ, WHZ, and BMI categories improved, indicating that patients being given BH4 in combination with low phenylalanine diet

had better nutritional status compared to low phenylalanine diet only.[16, 17] Regarding physical outcomes, previous studies showed that PKU patients mainly taking natural dietary sources for protein achieved normal growth with prolonged treatment of BH4.[17] However, a study conducted in 2015 found that after a year of BH4 treatment, there was no significant difference in Z-score for HAZ, WAZ or even BMI due to the lack of information on growth-related nutrients, the study stated that it was unable to rule out the potential of factors such as epigenetic variation, creatinine level and trace element that could result in insignificant anthropometric status for patients with PKU.[16]

Clinical study data suggests that preventing neurocognitive damage, particularly in the first few years of infancy, requires maintaining blood phenylalanine levels below predefined thresholds.[20] Although blood phenylalanine levels were closely monitored, outcomes were correlated with phenylalanine variability. However, studies showing neurocognitive outcomes are still limited.[18] The restricted type of food groups, in the low phenylalanine diets recommended for children with PKU causes problems for nutrition as well as food variety and satiety.[23] BH4 therapy may be able to prevent certain PKU diet adverse effects by enhancing the body's ability to metabolize hypostilation.[16] For many patients and their families, maintaining dietary adherence can result in significant time and financial costs, that may affect compliance. Patients are at risk of developing significant micronutrient deficiencies if they stop or reduce their protein intake without proportionally increasing their natural protein consumption.[24]

Patients with a free diet along with BH4 have been found to have a lower incidence of micronutrient deficiencies than those on a restricted protein diet.[25] Strict dietary intake may cause early growth retardation, which may affect developmental outcomes.[26] The growth period in "infancy" mainly nutrition-dependent and is gradually replaced by hormone-dependent during the "childhood" phase.[27] In certain patients with residual PAH enzyme activity, BH4 makes the enzyme more active by stabilizing it.[28, 29] According to a meta analysis at 2021, long-term BH4 treatment was associated to a significant increase in phenylalanine and natural protein intake, with most long-term patients achieving more than a twofold improvement in tolerance. The use of BH4 in long-term also showed a significant decrease in protein equivalent intake from protein subtitute with cofactor therapy. In the same studies, the long-term use of BH4 was also shown to significantly reduce the need for protein equivalent from protein subtitute, highlighting its beneficial effect in lowering dietary dependence through cofactor therapy. This finding suggest that BH4 not only improves metabolic control but also allows greater dietary flexibility, althought variability in individual response highlights the need for continued monitoring and patient-specific management.[29]

In summary, this study is the first meta analysis to evaluate the efficacy of BH4 only or as an adjunctive treatment along with low phenylalanine diet compared with low phenylalanine diets only, focusing on metabolic profile, growth status and response rate of BH4. However, the studies reviewed varied populations across different age groups and regions, potentially contributing to heterogeneity in the results. Additionally, the limited data on growth status and the absence of long-term neurocognitive outcomes further constrain the comprehensiveness of the findings. The small number of included studies also limits the broader applicability and long-term reliability of the conclusions. These limitations underscore the importance of conducting more extensive research with extended follow-up to strengthen the evidence base and clarify the sustained effects of BH4 treatment.

Conclusion

BH4 has shown to be effective as a treatment for children with PKU, with a high response rate and improvement of metabolic profile. BH4 can be considered as an alternative therapy instead of a low phenylalanine diet only. However, this study has considerable bias and significant heterogeneity. Therefore, further investigation should be conducted in large-scale, multicenter studies with standardized protocols and long-term studies assessing outcomes such as growth status and long-term neurocognitive are required to minimize bias and clarify the true therapeutic impact of BH4 administration.

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Conflict of Interest

None declared

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Case Report

Diagnostic and Management Approach of Obesity with Multiple Complications in a Child: A Case Report

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Abstract:

Background: Adults with obesity may already experience obesity during childhood or adolescence, highlighting the critical importance of early intervention. This is particularly concerning given that childhood obesity, a growing component of Indonesia's "triple burden of malnutrition," significantly increases the risk of developing severe non-communicable diseases and reducing life expectancy.

***Case*:** A 10-year-old male patient presented with a chief complaint of shortness of breath for the past two weeks, worsened when lying down and improved when sitting up. The patient also snored, often woke up due to difficulty breathing. The patient had experienced rapid weight gain since the age of 2 years. He ate in large portions, frequently snacked, and consumed sugary drinks daily. He had no regular physical activity and was mostly sedentary. He showed signs of obesity (BMI 35.8 kg/m^2), short stature, and physical abnormalities including a rounded face, double chin, acanthosis nigricans, and bowed legs.

***Discussion*:** Diagnosing obesity requires comprehensive history and physical examination to distinguish between primary and secondary causes. Our patient's early-onset obesity and hyperphagia prompted leptin level evaluation, although the result was within normal limit, leptin resistance or receptor imbalance was suspected. In this case, familial lifestyle factors appear to play a role, highlighting the importance of a family-centered approach. Management of obesity includes dietary modification, physical activity, sleep and behavioral regulation, and pharmacologic therapy when indicated.

Conclusion: An accurate diagnostic approach is crucial to guide optimal management strategies in complicated cases of obesity.

Keywords: children, diagnostic, management, obesity

Introduction

Obesity is one of Indonesia's "triple burden of malnutrition," falling under the category of overnutrition.[1] Globally, approximately one in five children are affected by obesity, a figure that has increased by 2.5% in the last two decades.[2] According to the 2018 Basic Health Research, the prevalence of obesity among children aged 5 to 12 years in Indonesia was 9.2%.[3] Obesity is a major risk factor for various non-communicable diseases (NCDs), which were estimated to contribute to 73% of all deaths in 2018.[4,5] Importantly, 15 – 30% of adults with obesity had already experienced obesity during childhood or adolescence.[6]

Children with obesity face a two-fold increased risk of developing cardiovascular diseases in adulthood.[7] This heightened risk comes from factors such as elevated blood pressure, increased cholesterol levels, and the accumulation of plaque in blood vessels. Other complications arising from childhood obesity include type 2 diabetes mellitus, hypertension, dyslipidemia, fatty liver disease, respiratory disorders like obstructive sleep apnea syndrome (OSAS), and other metabolic disturbances. Children with complicated obesity tend to experience chronic diseases earlier in adulthood, leading to a reduced life expectancy compared to those with uncomplicated obesity.[8-10]

Furthermore, approximately one in ten obese children experience depression due to social stigma and emotional distress, a higher rate than in overweight children.[11] Given the wide range of complications posed by obesity, the aim of this case report is to explore comprehensive diagnostic and management approaches. These approaches include dietary modifications, increased physical activity, and psychosocial support, all intended to mitigate the negative impacts of obesity and its complications, thereby improving the quality of life for affected children.

Case

A 10-year-old male patient presented to the Pediatric Nutrition and Metabolic Disease clinic at Dr. Cipto Mangunkusumo Hospital (CMH). He was referred from a regional hospital with a chief complaint of progressively worsened shortness of breath for two weeks prior to hospital admission. The patient's history revealed a rapid weight gain beginning at the age of two, reaching 50 kg by age five. He exhibited a large appetite, ate more than three times a day with each meal portion equivalent to twice as much as an adult. In addition to large meals, he frequently consumed snacks due to persistent hunger, even less than an hour following a meal. He reported no fruit consumption as he disliked it.

Two years prior to admission, the patient began experiencing shortness of breath during light activities and reported easy fatigability, which led to reluctance in participating in school sports. For the past year, he noted breathlessness even when walking short distances, such as to the bathroom.

Two weeks prior to admission, the patient was hospitalized at a regional hospital due to shortness of breath, high blood pressure, and swelling extending from his abdomen to his genitalia. He was diagnosed with cardiomegaly and received diuretics and antihypertensive medication captopril 25 mg twice daily. At that timehis shortness of breath was most pronounced when lying flat and improved in a sitting position. He denied chronic cough, drastic weight loss, or prolonged fever, but he frequently experienced recurrent cough and cold, attributed to allergies. The patient found it more comfortable to sleep with two pillows or in a sitting position. His symptoms were also accompanied by snoring and frequent awakenings due to breathlessness during sleep.

A dietary intake analysis at home revealed the patient typically consumed 3–4 meals per day, with each meal consisting of 2–2.5 portion of carbohydrate (rice), 1.5–2 portion of animal protein, 0.25–0.5 portion plant-based protein, and 2–3 tablespoons of vegetables. His vegetable intake was limited to a few types, such as water spinach and long beans. Fruit intake was rare, with bananas being the only preferred fruit. According to the mother, the child often purchased snacks without parental supervision, such as one portion of meatballs, chicken noodle, cakes, sweet bread, and commercially sweetened tea beverages up to 4–5 times a day. The patient did not engage in regular physical activity. He also frequently felt drowsy and was unable to walk long distances due to feeling heavy-breathed. At home, he mostly lay down, watched television, or slept. There was no history of steroid use.

The patient was the first of two siblings, born full-term via normal spontaneous vaginal delivery at a hospital. His birth weight was 2800 grams; birth length and head circumference data were unavailable. The patient's younger brother was 4 years old, healthy, and was not obese like him.

The patient's father had been obese since childhood, frequently consumed snacks, was an active smoker, and had a low level of physical activity. The patient's mother began gaining weight after marrying the patient's father. Upon encounter, the father weighed 97 kg with a height of 170 cm (BMI 33.5 kg/m^2), while the mother weighed 73 kg with a height of 153 cm (BMI 31.2 kg/m^2). There was no family history of similar complaints, nor any history of heart disease, hypertension, or diabetes mellitus.

On examination, the patient's blood pressure was 131/73 mmHg (P95+12 to P95+30), consistent with hypertension. All other vital signs were within normal limits. The patient weighed 56 kg and was 125 cm tall, with a body mass index (BMI) of 35.8 kg/m^2. His head circumference (HC) was 53 cm. Based on the Centers for Disease Control (CDC) growth curves, the patient's weight-for-age was 179% (56/32), height-for-age was less than the 3rd percentile (125/138), weight-for-height was 233% (56/24), and BMI-for-age was greater than the 95th percentile (35.8/16.7). The head

circumference-for-age was at the median (53/53). These measurements indicated that the patient's nutritional status was obese with short stature.

The patient presented with a rounded face, chubby cheeks, double chin, and a short neck with acanthosis nigricans. The physical examination showed enlarged tonsils (T3/T3) without visible crypts or detritus, enlarged breasts, a distended abdomen with folded walls, a buried penis with intrascrotal testes (3ml bilaterally, Tanner stage G1P1 and normal stretched penile length. His digits appeared short, with no edema, and there were bowing of the lower extremities, with normal range of motion in all extremities.The patient underwent routine blood tests (hemoglobin 12.4 g/dL, hematocrit 41.3%, leucocyte 11,480/uL, thrombocyte 321,000/uL), lipid profile (high-density lipoprotein (HDL) 35 mg/dL, low-density lipoprotein (LDL) 123 mg/dL, triglyceride 67 mg/dL), uric acid (3 mg/dL), liver function (SGOT 29 U/L, SGPT 30 U/L), renal function (ureum 10.7 mg/dL, creatinine 0.3 mg/dL, glomerulus filtration rate 171 ml/minute/1,73m^2), electrolytes (sodium 138 mEq/L, potassium 4.1 mEq/L, chloride 104.6 mEq/L), and blood glucose parameters (HbA1c 5.2% and fasting blood glucose 65 mg/dL), all of which were within normal limits. The patient also underwent a leptin laboratory test with a result of 44 ng/mL, and whole exome sequencing was planned due to suspicion of a genetic defect.

The patient was diagnosed with obesity and short stature, suspected with primary obesity with a differential diagnosis of secondary obesity due to possible leptin hormone deficiency, complicated by congestive heart failure (New York Heart Association Class (NYHA) class III) secondary to hypertension and severe obstructive sleep apnea syndrome (OSAS), and tonsillar hypertrophy. Admission was planned for nutritional management (1,920 kcal/day divided in three main course meals, with fruit as snacks, and water as the only permitted beverage), antihypertensive therapy, and multidisciplinary consultations.

Over 4 days of hospitalization, the patient continued to sleep with 2–3 pillows and exhibited persistent snoring. The patient experienced nocturnal desaturation episodes during sleep, requiring supplemental oxygen via nasal cannula. Blood pressure remained between the P95 and P95+30 range.

On day 5 of hospitalization, the patient underwent echocardiography, which revealed tricuspid and mild aortic valve regurgitation with an ejection fraction of 60%. Captopril (12.5 mg orally every 8 hours) was continued, with follow-up echocardiography scheduled in 6 months. The respirology team recommended nightly continuous positive airway pressure (CPAP). The nephrology team advised continuation of antihypertensive therapy and a low-sodium diet. The rhinolaryngscopic evaluation by ear, nose, and throat (ENT) team showed adenoids occupying 60% of the choanae, nasopharyngeal reflux, laterolateral oropharyngeal

narrowing, and grade 1 lingual tonsil hypertrophy. Subsequently, fluticasone proprionate nasal spray was prescribed twice daily.

The persistent loud snoring with awakenings and oxygen desaturation (down to 93%) during sleep was still observed on the 6th day of hospitalization. The patient was only able to walk 50 meters without experiencing difficulty breathing. His chest X-ray revealed cardiomegaly and early pulmonary edema, prompting the addition of furosemide (10 mg orally twice daily). The physical medicine and rehabilitation team initiated a moderate-intensity aerobic exercise program (3–5 times per week) to improve the patient's physical tolerance.

The patient underwent a 24-hour polysomnography, which confirmed severe OSAS with desaturation phases down to 50%. Based on these results, CPAP therapy was initiated at a positive end-expiratory pressure of 5 mmHg. Following CPAP initiation, snoring and sleep apnea improved, and dyspnea decreased. With CPAP, the lowest recorded nocturnal oxygen saturation was 89%, with levels reaching up to 98%.

On day-13, drug-induced sleep endoscopy (DISE) and bilateral tonsilloadenoidectomy were performed. Following the procedures, snoring continued to improve, and CPAP therapy was maintained. The total duration of CPAP use was 7 days.

Two days following the surgery, the patient reported no complaints. The patient was discharged with routine medications (captopril 12.5 mg every 12 hours orally, furosemide 10 mg every 12 hours) and dietary education (3 large low-sodium meals with more vegetables and 2 fruit snacks per day).

During the hospital stay, the patient's weight decreased by 4000 grams (267 grams/day). The final diagnoses were severe OSAS, obesity with short stature (with differential diagnoses of suspected leptin receptor resistance and other secondary obesity types), NYHA Class III congestive heart failure secondary to hypertension and severe OSAS, grade 1 hypertension, and tonsillar hypertrophy post-tonsilloadenoidectomy. The patient did not meet the criteria for any metabolic syndrome. The patient was then scheduled for outpatient follow-up with Nutrition-Pediatric Metabolism and Respirology clinics.

Discussion

A 10-year-old male patient, who had been obese since the age of 2, presented with clinical manifestations of shortness of breath during sleep and while walking, indicating obesity-related complications. The initial approach to his obesity should involve distinguishing between primary and secondary causes through history-taking and physical examination, as outlined in **Table 1**. History-taking and physical

examination are essential to assess complications, evaluate all potentially affected target organs, identify possible comorbidities, and guide lifestyle modifications in patients with obesity.[12]

Table 1. Physical examination in obese children[12]

Organ system	Physical examination findings	Patient's physical examination
Integumen/ subcutaneous tissue	Acanthosis nigricans, skin tags, hirsutism, striae, pseudo gynecomastia (male), intertrigo, xanthelasma (hypercholesterolemia)	Acanthosis nigricans, pseudo gynecomastia
Neurology	Papilledema and/or decreased venous pulsation on fundoscopic examination	None
Head and neck	Tonsillar hypertrophy, airway obstruction	Tonsillar hypertrophy, laterolateral oropharyngeal narrowing
Cardiovascular	Hypertension, heart rate	Hypertension
Respiratory	Physical activity intolerance, asthma	Physical activity intolerance
Gastrointestinal	Hepatomegaly and hepatic tenderness (non-alcoholic fatty liver disease), abdominal tenderness (secondary to gastroesophageal reflux or gallbladder stone)	None
Musculoskeletal	Pes planus, groin pain, waddling gait, tibia vara (Blount disease), arthralgia in the lower extremities, and restricted joint movement.	Short digits and bowing of the lower extremities
Endocrine	Goiter, extensive striae, hypertension, dorsocervical fat pad, pubertal stage, and decreased growth velocity	Dorsocervical fat pad, hypertension
Psychosocial	Flat affect and low mood, low self-esteem, and social withdrawal	Frequently falls asleep during class

Others	Short stature, disproportion, dysmorphic features, developmental delay	Short stature

The patient was initially suspected to have primary obesity due to excessive caloric intake unbalanced by inadequate physical activity. This was supported by a family history of obesity in both parents and a permissive parenting style, allowing the patient to have unrestricted access to food and no regular physical activity at home. However, the possibility of secondary obesity was considered upon finding that the patient's height was classified as short stature, falling below the range of his genetic height potential (159.5 – 176.5 cm). Such abnormalities necessitate further differentiation based on the age of onset, which is important for differentiating the underlying causes of obesity in children, as outlined in **Figure 1.**

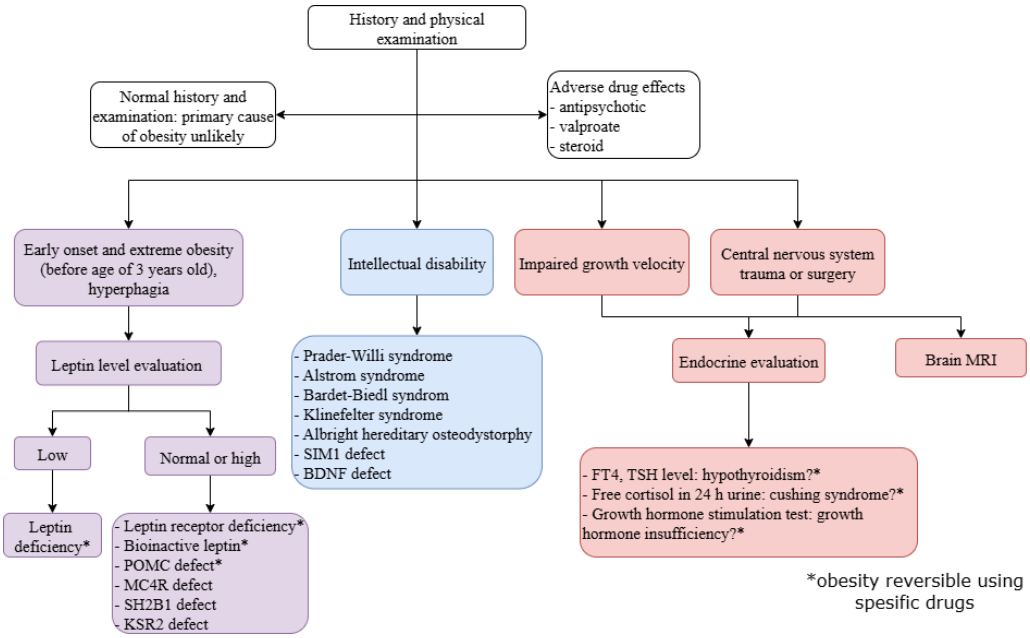

Figure 1. Algorithm for differentiating obesity etiologies.[13]

The patient also experienced hyperphagia, without any psychomotor or intellectual impairment, prompted consideration of a leptin hormone disorder affecting appetite regulation. While his leptin was elevated (cut-off value: 13.4 ng/mL) making leptin hormone deficiency unlikely, leptin receptor resistance remains a possibility.[14] Other genetic differential diagnoses were considered and ruled out: Proopiomelanocortin (POMC) gene defects were unlikely, as the patient did not present with red hair and pale skin; Melanocortin 4 Receptor (MC4R) gene defects were with the patient's short stature, as these typically cause increased linear growth; Src Homology 2 B Adaptor Protein 1(SH2B1) gene defects were unlikely given the lack of behavioral problems;

and Kinase Suppressor of Ras 2 (KSR2) gene defects were not supported, as the patient did not exhibit bradycardia.

Leptin, primarily produced by adipocytes and, to a lesser extent, by muscle cells, is crucial for regulating body weight, energy balance, and appetite. It signals the hypothalamus regarding the status of the body's energy reserve, particularly fat stores. This signaling subsequently influences feeding behavior.[15, 16] This patient had excessive fat storage, which theoretically should lead to increased leptin production, signaling the body to suppress appetite and enhances energy consumption. However, leptin resistance or an imbalance in leptin receptors are commonly observed in obesity. An increase in fat mass without a corresponding rise in energy consumption may contribute to this resistance.[16, 17]

The severity and duration of obesity significantly influence its complications, which can affect nearly every organ system, including the nervous, respiratory, cardiovascular, metabolic, gastrointestinal, renal, urinary, endocrine, musculoskeletal, dermatological, and psychosocial systems. In this patient, a respiratory complication, OSAS was confirmed by polysomnography (PSG). The severity of OSAS directly correlates with the degree of obesity. Studies indicate that a Body Mass Index (BMI) over 28 kg/m^2 increases the risk of OSAS by 4 – 5 times in children aged 2 to 18 years. Notably, severe obesity can lead to alveolar hypoventilation, resulting in oxygen desaturation.[9, 18, 19]

Hypertension is another common complication of obesity. Obesity can induce changes in cardiac morphology, myocardial dysfunction, and remodeling, ultimately leading to heart failure. Hypertension is also a known complication of OSAS. To confirm hypertension in children, ambulatory blood pressure monitoring (ABPM) is recommended. In cases like this patient's, the use of antihypertensive medications, specifically angiotensin-converting enzyme (ACE) inhibitors, can significantly improve cardiac function in obese children experiencing heart failure.[7]

Dyslipidemia should also be evaluated in obese children, as it increases their risk by about 1.7 times.[7] Although the patient did not present with hyperlipidemia, routine lipid screening performed between ages 9 – 11 years should be repeated between ages of 17 – 21 years old.[19-21] Another metabolic complication that may arise in children with obesity is type 2 diabetes mellitus. Insulin resistance is the key underlying mechanism of metabolic dysfunction in these patients. In this case, the presence of acanthosis nigricans served as a clinical marker associated with insulin resistance, indicating a future risk despite currently normal fasting blood glucose (65 mg/dL) and HbA1c levels (5.2%).

According to the International Society for Pediatric and Adolescent Diabetes (ISPAD) consensus, screening for glucose metabolism disorders is recommended for obese children aged 10 years or at puberty onset. This involves laboratory assessments like fasting blood glucose, HbA1c, and a 2-hour oral glucose tolerance test (OGTT). Furthermore, adiponectin, a hormone produced by adipose tissue that enhances insulin sensitivity, is typically reduced in obese individuals, contributing to insulin resistance.[19, 22, 23]

While the patient in this case did nott present with any neurological complication, a common issue observed was excessive daytime sleepiness, leading to students often falling asleep in class. This condition significantly reduces quality of life and can have a detrimental psychological impact on patients.[24]

Researches consistently show that childhood obesity can be effectively managed through weight loss, with better outcomes when initiated before puberty.[25] Family-based intervention approaches are particularly effective, demonstrating greater weight loss and an estimated increase in life expectancy of approximately 6–8 years. Even a modest weight loss of 5–10% can significantly improve cardiovascular function.[10, 13] A meta-analysis further supports this, reporting that a reduction in BMI of 1.25–1.3 kg/m^2 through lifestyle modification is associated with improved cardiometabolic outcomes in pediatric obesity.[26] In this case, the patient's parents exhibited a sedentary lifestyle, highlighting the need for a family-centered intervention approach.

Regulating nutritional intake is essential in the management of obesity, with strategies needing to be age-adjusted. For children aged 5 years and older, dietary recommendations include three main meals per day with 1 – 2 snacks. The daily food composition should consist of three portions of protein, 1–2 portions of milk, and 4–5 portions of non-starchy vegetables. Children should avoid sugary sweeteners and fast food. Portion sizes must be adjusted to the child's age, and positive reinforcement should be given whenever the child tries new food varieties.[27]

Gradual weight loss is crucial, with a safe reduction considered to be 2–4.5 kg or 0.5–2 kg per month.[28] In this case, the patient's estimated daily caloric intake was 2500 kcal, which was 131% of the Recommended Dietary Allowance (RDA) and significantly exceeded their daily requirement of 1900 kcal. Protein intake was also high at 75 grams (3 g/kg body weight).

To address this, a gradual dietary modification was implemented. The new plan adjusts caloric intake to meet daily requirements, focusing on staple foods and appropriate protein sources, and incorporating fruit-based snacks. This revised dietary plan includes three main meals and two snacks, providing a total of 1900 kcal (100% RDA) and 57 grams of protein (2.3 g/kg body weight).

For children over the age of 5, physical exercises and active play are essential, should be enjoyable, performed daily. Children need consistent encouragement and motivation to engage in physical activity as frequently as their healthy peers. Studies recommend at least 60 minutes of physical activity per day. To further increase motivation and adherence, older children can monitor their physical activity and food intake using mobile applications or other technological tools. These tools allow them to share their progress with peer groups, which can significantly boost their engagement.[27]

For children with heart failure, moderate-intensity activities such as walking or cycling, up to 60 minutes daily, are recommended. Daily home-based activities like sweeping and mopping are also encouraged. In this specific case, physical activity was initiated gradually, targeting 30 minutes of walking while maintaining a heart rate between 128 to 152 beats per minute. The patient successfully completed this activity without experiencing the previously reported shortness of breath. During outpatient follow-up, the patient was advised to continue walking, gradually increasing the duration to 60 minutes, 3 to 5 times per week.

Children with obesity have a higher risk of mortality due to complications that can affect nearly all organ systems. The prognosis for pediatric patients with obesity and multiple complications may vary, depending on the severity of the complications, the age at which obesity developed, and the effectiveness of the interventions implemented.[25]

Conclusion

Childhood obesity is a condition that demands serious attention due to its potential short- and long-term complications. Identifying the underlying cause of obesity is crucial to ensure appropriate and targeted management. Obesity management must be comprehensive, including adherence to dietary and physical activity recommendations, as well as pharmacologic treatment when indicated. Parental involvement is essential to maintain treatment consistency at home and to ensure regular follow-up for evaluating the effectiveness of interventions and monitoring the child's progress.

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Conflict of Interest

None declared

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Case Report

Syphilitic Hepatitis in Infancy Presenting with Cholestatic Jaundice and Inguinal Hernia: A Case Report

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Abstract:

Background: Congenital syphilis can involve multiple organ systems and, in rare cases, present with syphilitic hepatitis, a cause of cholestatic jaundice in infancy. Early recognition is challenging due to its non-specific presentation and overlap with other etiologies of neonatal cholestasis. This case highlights a rare case of a cholestatic infant with syphilitic hepatitis and concurrent inguinal hernia, emphasizing diagnostic challenges and management in resource-limited settings.

***Case*:** A 1-month-26-day-old infant presented with a left inguinal mass and jaundice. The mother had latent syphilis during pregnancy and received benzathine penicillin G only one week before delivery. The infant had persistent jaundice, pale stools, elevated direct bilirubin, transaminases, and alkaline phosphatase. Abdominal ultrasonography showed normal liver echotexture and gallbladder contractility, with no biliary dilatation. Based on clinical, laboratory, and maternal history, a presumptive diagnosis of biliary atresia with differential syphilitic hepatitis was made. Supportive therapy with ursodeoxycholic acid, fat-soluble vitamins, and antibiotics was initiated. The patient was referred for further evaluation by pediatric gastroenterohepatology.

***Discussion*:** The infant presented with postnatal jaundice, acholic stools, and elevated indirect bilirubin, initially raising suspicion of biliary atresia. However, the maternal history was positive for syphilis, making syphilitic hepatitis a presumptive diagnosis. Careful clinical evaluation and close serial follow-up are essential for establishing the diagnosis and guiding management. Early antenatal screening and timely maternal treatment remain key strategies to prevent vertical transmission.

Conclusion: Syphilitic hepatitis should be considered in the differential diagnosis of neonatal cholestasis, particularly in infants born to mothers with inadequately treated syphilis.

Keywords: congenital syphilis, inguinal hernia, neonatal jaundice, syphilitic hepatitis

Introduction

Congenital syphilis is a serious health problem caused by *Treponema pallidum* infection. It is transmitted vertically from mother to infant. Congenital syphilis infection in babies is often asymptomatic, so it is called "the great masquerader" because the clinical symptoms in babies are unclear and ambiguous, making it difficult to initiate treatment.[1] In Indonesia, syphilis screening is conducted during pregnancy through the antenatal triple elimination program.

The incidence of congenital syphilis in Southeast Asia has decreased by around 8% from the global burden of disease in 2016. However, it is still far from the target of eliminating congenital syphilis by 2030.[2] A research conducted at Wangaya Hospital in 2022 stated that 68.1% of cases were asymptomatic, while jaundice was the second most common manifestation (21.2%).[3] Examination of congenital syphilis in the form of Treponema Pallidum haemagglutinin assay (TPHA) and Venereal Disease Research Laboratory (VDRL) shows non-reactive results for several months in infants. Then, it led to delayed therapy, which affects the progression of the disease.

A rare complication of congenital syphilis is syphilitic hepatitis. The incidence of syphilitic hepatitis only occurs in 3% of congenital syphilis cases. Abnormally elevated liver enzymes and decreased albumin are used as indicators of diagnosis.[4] Complete eradication of *Treponema pallidum* from the liver is the main treatment of syphilitic hepatitis. The first-line treatment is penicillin as an antibiotic. This case report aims to give insight for clinicians in diagnosing syphilitic hepatitis in infants and children, especially in limited-resource settings.

Case

A female infant, 1 month and 26 days old, was brought by her mother to the Wangaya Children's pediatric outpatient clinic with the chief complaint of a lump on her left thigh, which had intermittently appeared and disappeared since September 2024. According to the mother, the infant had previously been treated by a midwife and was given only a topical analgesic spray. However, the lump continued to reappear. The patient also had desquamation on the face, body, and limbs without rash.

During the outpatient examination, the infant appeared yellowish (jaundiced), a previously unrecognized finding by the mother. The mother reported that the jaundice had been present for approximately one month (post-natal jaundice). She also stated that she was unable to provide exclusive breastfeeding for her baby due to insufficient breast milk production and work-related fatigue. Thus, the infant was primarily fed formula milk and cared for by extended family members. The infant occasionally vomited after milk feeds. It was also revealed that the infant has a history of pale-colored stools with a soft consistency. The patient's mother assumed this condition was normal.

The mother attended only two antenatal care (ANC) visits at the Primary Health Care Center during pregnancy. She rarely sought ANC due to her husband's busy work schedule and the absence of someone to accompany her. The syphilis infection was only diagnosed late in the pregnancy, between the 30th and 31st weeks of gestation.

Reactive results were found on the triple elimination tests (HIV non-reactive, HBsAg non-reactive, and TPHA is reactive), which were conducted during the 30th and 31st weeks of gestation. The mother underwent follow-up testing with VDRL and TPHA on June 6, 2024, which showed titers of 1:32 and 1:512, respectively. She was diagnosed with latent syphilis at 39 weeks of gestation and received three doses of Benzathine Penicillin G (2.4 million IU) administered on August 7, 14, and 21, 2024. Post-treatment serological results, obtained before delivery, revealed a TPHA titer 1:1.

The patient was the first child of the family, delivered via caesarean section at 39 weeks of gestation. The patient was diagnosed with latent syphilis infection with suspected intrauterine growth retardation (IUGR) due to comorbid maternal infection. The APGAR score was 6-7-8-9. The patient was born with a Finstrom score corresponding to 37 weeks and 4 days of gestational age, a low birth weight (LBW) of 2020 grams, and a birth length of 43 cm. At birth, the infant did not cry spontaneously and required neonatal resuscitation. The patient was admitted to the Neonatal Intensive Care Unit (NICU), where supportive care was provided. After the patient's condition stabilized in the NICU, a prophylactic injection of Benzathine Penicillin Antibiotic 100.000 IU was administered in the anterolateral aspect of the right thigh on August 30, 2024.

The examination for syphilis was conducted using the VDRL test, which showed a titer of 1:2. The IT-Ratio level was 0.06, indicating a possible risk of infection. The patient was hospitalized from birth until 7 days of chronological age for monitoring and supportive care until clinical improvement was observed. The patient's immunization record was incomplete, with the last documented vaccine being Hepatitis B.

The patient appeared moderately ill at the pediatric outpatient clinic visit on October 25th, 2024. At the time of examination, the infant was chronologically 1 month and 26 days old, with a body weight of 3.0 kg and a body length of 49 cm. Assessment of weight gain from birth to the current age, based on WHO weight increment plotting for 1 month, indicated growth faltering. The patient's anthropometric assessment showed a Body Height-for-Age (BH/A) z-score of -3.79 SD, indicating stunted (short stature), The Body Weight-for-Age (BW/A) z-score was -3.75 SD, consistent with underweight status. Meanwhile, the Body Weight-for-Height (BW/BH) z-score was -0.56 SD, suggesting a well-nourished condition.

On physical examination, the head showed no frontal bossing. The infant appeared lethargic but cried moderately. The conjunctiva was not pale, while the sclerae appeared icteric. The patient exhibited regular spontaneous breathing. The hair appeared to be slightly brownish. There was a secret positive on the nose with slimy consistency. No saddle nose deformity was found. The pharynx was not hyperemic, and the tonsils were not enlarged. No coated tongue was observed. Thoracic examination revealed bronchovesicular breath sounds, with no rhonchi or wheezing detected. No abnormalities were found in the abdominal area, hepatomegaly, or splenomegaly were not present. Skin was icteric (Kramer grade III-IV). Extremities appeared warm, with a capillary refill time (CRT) of less than 3 seconds. The patient was subsequently hospitalized for further examination.

Laboratory examination showed leukocyte levels of 9.50 x 10^3/µL, erythrocytes 4.21x 10^6/µL, hemoglobin 14.0 g/dl, hematocrit 40.5%, and platelet levels increased by 496 x 10^3/µL. Bilirubin analysis showed findings consistent with cholestasis, with total bilirubin levels of 11.46 (Ref: 0.2-1.0), direct bilirubin levels of 9.9 (Ref: 0.1-0.4), and indirect bilirubin levels of 1.56. The patient was also examined for coagulation factors, such as activated partial thromboplastin time (aPTT), prothrombin time (PT), and International Normalized Ratio (INR). The aPTT level was 31.2 seconds (Ref: 25.5 to 42.1), PT was 10.9 seconds (Ref: 9.5-11.7), and the INR level was 1.02. Coagulation factor studies were conducted due to the risk of gastrointestinal bleeding or perforation in congenital syphilis. Liver function tests revealed markedly elevated transaminase levels, with AST level 476 (Ref: 0-37) and ALT level 316 (Ref: 0-42). Serum albumin was within normal limits at 3.9 g/dl (Ref: 3.8-5.1). The alkaline phosphatase examination result was elevated at 439 U/L (Ref: 53-128). The C-Reactive Protein (CRP) levels were <5.0 mg/dl. Occult blood analysis was performed on the patient. Erythrocyte components were normochromic normocytic with poikilocytosis cell shapes. Leukocytes were dominated by mature lymphocytes. Platelet evaluation showed an increased count with the presence of giant platelets, indicating thrombocytosis. These findings were suggestive of an underlying liver disorder.

Urinalysis examination was performed to rule out other causes of intrahepatic cholestasis. The urinalysis examination showed yellow-colored urine, with negative results for leukocyte esterase, nitrite, ketones, urobilinogen, and bilirubin. The titers of leukocytes were 0-1 (Ref: 0-1), and no bacteria were found on the sample.

Three stool portion samples were collected from the patient. The first sample exhibits soft, pale in colour, and acholic. The second sample was also soft, pale-yellowish, and acholic. The third stool sample appeared soft with a pale-yellowish colour, and reduced acholia.

Two-phase ultrasonography showed a normal liver size and echotexture, normal echoparenchymal, sharp angles, flat edges, without visible widening of the Intra Hepatobiliary Bile Duct (IHBD) and Extra Hepatobiliary Bile Duct (EHBD), normal portal and hepatic veins, and with no visible masses/nodules/cysts. The gallbladder was normal in size, the walls were not thickened, there was no irregularity, and there were no stones or sludge. In the first phase, the size was 1.6x0.54 cm, and in the second phase, the size was 1x0.32 cm with a contraction index level of 77.61%. No free echo fluid was seen in the abdominal cavity. The results of the USG showed normal contractility of the gallbladder, no visible obstruction in the intra- or extrahepatic biliary tract, and the liver and gallbladder did not show any abnormalities.

Based on the findings from the patient's history, physical examination, and supporting examinations, the patient was diagnosed with extrahepatic cholestasis, suspected biliary atresia, and left lateral inguinal hernia, with differential diagnoses of intrahepatic cholestasis, suspected syphilitic hepatitis, and suspicion of urinary tract infection (UTI), accompanied by failure to thrive, good nutritional status. When hospitalized, the patient received D10% fluid rehydration and Cefotaxime antibiotic to treat the infection. After using antibiotics, the patient had improvement, such as a reduction to Kramer Stage III and more adequate breastfeeding. Supportive therapy with ursodeoxycholic acid (UDCA) was given 3 times daily (30 mg/kg/day) alongside multivitamin drops containing amino acids and vitamins A, D, E, and K.

After four days of inpatient treatment, the patient was referred to a higher-level hospital for further evaluation and management by a pediatric gastroenterologist and a pediatric surgeon, particularly to address other differential diagnoses of cholestasis and the suspected hernia defect.

Discussion

Most published cases of syphilitic hepatitis are from Western countries, where diagnostic resources are more readily available. According to the guidelines from the European Centre for Disease Prevention and Control, the prevalence of syphilitic hepatitis is still unclear, ranging from 0.1% to 39.8% cases per 100.000 live births.[2, 5] The condition of syphilitic hepatitis is one of the conditions of re-emerged disease besides non-communicable disease in low- and middle-income settings. According to a study by Luo et al in China, the prevalence of syphilis during pregnancy in Eastern China is around 0.3%.[2, 6] At present, many early-phase congenital syphilis cases have hidden clinical manifestations and abnormalities that are found only on laboratory examination. The pathogenesis of syphilitic hepatitis remains unclear, but it may involve immune-mediated injury induced by Treponema pallidum, which causes damage to liver cells and the intrahepatic duct system, leading to the onset of hepatitis.[4, 7] The importance of syphilis testing is to eliminate mother-to-child transmission of syphilis. If a pregnant woman has latent stage and asymptomatic

syphilis, appropriate management can prevent disease progression that may cause irreversible organ damage and other clinical manifestations. Based on a case-series study by Salome et al. in Italy, proper antenatal screening and early initiation of therapy were protective against vertical transmission to children (95% CI: 1.2–1.4; $p < 0.001$).[5]

This case differs from recently published reports and provides crucial insight into the diagnosis of syphilitic hepatitis presenting with postnatal jaundice in limited resources. The presumptive diagnosis for syphilitic hepatitis on limited source can be made using the diagnostic criteria of syphilitic hepatitis proposed by Mullick 2004 such as abnormal liver enzyme levels, evidence of syphilis infection, and exclusion of other diseases.[8]

In this case, the patient was born to a mother diagnosed with latent syphilis. The patient presented with jaundice, which was likely triggered by hepatocellular injury leading to bile duct obstruction. If left untreated, disease progression may result in liver cirrhosis. In this case, physical examination did not reveal hepatosplenomegaly. This is consistent with the clinical course, as hepatosplenomegaly in congenital syphilis most commonly presents during the neonatal period.[4, 9] Other stigmata of syphilis hepatitis, such as saddle nose deformity or chancre lesions, were not found in this patient.

The presence of acholic stools is suggestive of cholestasis, in which biliary atresia must remain the primary suspicion until definitively excluded. Although the ultrasound did not reveal a triangular cord sign as a sign of biliary atresia, three consecutive acholic stool examination must be considered to diagnose biliary atresia as a differential diagnosis. Due to cost-benefit considerations, the gamma-glutamyl-transferase (GGT) examination and intraoperative cholangiography were not assessed on this patient. Instead, a two-phase ultrasound examination was performed to examine bile contractility, with the patient was fasted for 4-5 hours before the examination. No abnormalities were reported from the ultrasound examination, suggesting a lower possibility of biliary atresia (BA).[10] However, further work-up is required to exclude BA as highlighted in previous publications.[11, 12]

Nevertheless, A study in China found that clinicians could diagnose cases of syphilitic hepatitis by relying on AST examination (median 123.7 U/L) and a decrease in albumin level (hypoalbuminemia). In this case, the AST was high (476), and the albumin level remained within the normal limit but closer to the lower end of the reference range. Hypoalbuminemia may indicate extensive hepatocellular damage, as albumin plays a key role in the transport of indirect bilirubin. A decreased albumin level also shows a chronic course of jaundice, and in this patient, early signs of hypoalbuminemia were already observed.[5] In this case, alkaline phosphatase was elevated, at 439 U/L. Elevated alkaline phosphatase is a marker of hepatocellular

damage related to spirochete dissemination in the liver, and it may also indicate bile duct obstruction, manifesting as jaundice.[5, 13]

Evaluation of the infant using TPHA or VDRL titers is essential to support the diagnosis of congenital syphilis. Rapid plasma reagen (RPR) as an indirect biomarker of damage to the cells of the spirochete and TPHA examinations in infants are recommended to be postponed, as testing too early may result in false-negative results due to "incubating congenital syphilis." Confirmatory examination is therefore advised at around 3 months of age. Cerebrospinal fluid analysis examination was not available at health facilities, so it was not performed.

Based on the clinical findings and supporting findings, the physician made a working diagnosis of possible congenital syphilis. In developed countries, liver biopsy is the diagnostic modality of choice to exclude other potential causes of liver disease. However, the diagnosis of syphilitic hepatitis can often be established based on clinical manifestations and basic laboratory examinations. *Treponema pallidum*, the causative agent of syphilis, is classified as a non-hepatotropic pathogen but has been recognized as a rare etiology of unidentified hepatitis in children.[9]

The patient received a single dose of prophylactic Benzathine Penicillin G 50 mg per kg/day after birth, in accordance with the guidelines from the Indonesia Ministry of Health. Benzathine penicillin injection was also given to the mother less than four weeks before delivery despite her TPHA titer being 1:1. In this patient, a Jarisch-Herxheimer reaction following penicillin administration was ruled out, as no transient worsening occurred within the typical 24-hour window.[9] In congenital syphilis, VDRL results rarely become seronegative following therapy; therefore, monthly clinical follow-up is recommended. The patient's parents were advised to come every month to evaluate the TPHA and VDRL titers.[7]

Therapy also focuses on cholestasis, including supplementation with fat-soluble vitamins A, D, E, and K for three months. This approach has been shown to support the resolution of jaundice, as measured by either the Kramer scale or bilirubin levels. Additionally, the administration of UDCA was beneficial as a hepatoprotector, aiding in bile flow stimulation and fat absorption, particularly in cases of liver injury related to syphilis infection.[5, 14]

Jaundice with elevated indirect bilirubin in infants older than 14 days should prompt consideration of abnormal underlying conditions, with cholestasis being an important differential to exclude. In infants under one year of age, cholestasis may occur due to immaturity of the hepatobiliary system, such as underdeveloped bile canaliculi and impaired bile flow. However, pathological causes must be carefully excluded, particularly vertically transmitted infections like those in the TORCH group, which

can be screened during antenatal care. The condition of intrahepatic cholestasis, besides congenital syphilis, must be considered, such as congenital hypothyroidism or TORCH infection, especially CMV infection, with prominent manifestations like blueberry muffin rash, hepatosplenomegaly, microcephaly, congenital heart defect, intellectual disability, or lethargy. These manifestations were not identified in the patient's clinical findings. Nevertheless, the possibility of CMV infection cannot be entirely excluded. Therefore, further work-up for CMV infection or other potential infectious etiologies should still be performed.

Clinicians should still consider urinalysis examination to rule out the cause of cholestasis due to urinary tract infection (UTI). The condition of urinary tract problems in infancy tends to be asymptomatic and is often skipped from evaluation.[15]

Several studies also mention that patients who experience intrahepatic cholestasis tend to experience growth failure. Research by Serra in Palermo, Italy, showed growth failure in affected infants was associated with feeding difficulties and an inadequate sucking reflex, which compromised the adequacy of nutritional intake and the ability to meet dietary needs. In this patient, evidence of growth faltering was observed.[15]

The lump in the left thigh was clinically suspected to be an inguinal hernia, with findings limited to one side. This is noteworthy because inguinal hernias are more commonly bilateral in preterm infants, whereas the patient in this case was born at term (39 weeks of gestation). The etiology of inguinal hernia involves a defect during embryogenesis, with the persistent processus vaginalis during the formation of the labia majora or minora in girls. On physical examination, the lump was associated with mild erythema of the overlying skin. However, the absence of a pediatric surgeon at our facility restricted confirmatory diagnosis and further evaluation. An abdominal CT scan was also not performed due to its limited diagnostic facility.[16] In this case, the inguinal hernia may represent an incidental finding, and a direct causal relationship with congenital syphilis cannot be established.

This case demonstrates that congenital syphilis diagnosed in the late third trimester may affect the developmental process of fetal organs. The cause of the defect in the formation of the inguinal ligament, which leads to an inguinal hernia in this patient, remains unclear. Salome's study in Italy indicated that when syphilis treatment is given in the third trimester, there is limited time for nontreponemal titers to decrease before delivery.[5, 17] Managing early latent syphilis in the mother is crucial to reduce the transmission of maternal syphilis to the fetus by 98%.

The prognosis in this patient has not been determined. It depends on the adequacy of the therapy, whether the jaundice lasts for a long time and leads to decreased consciousness (kernicterus), and whether the biopsy examination shows massive

inflammation. According to the study by Yang et al, the liver function test significantly improved and decreased gradually compared to before treatment.[7, 14] From this case, we can learn that we must evaluate liver function every two weeks to maintain the adequacy of post-treatment antibiotics.[7]

Clinical implication for this case is that it can be a lesson learn for clinicians, mainly for the condition of syphilitic hepatitis, which is diagnosed at a late stage, because in the early phase, it is asymptomatic. Syphilitic hepatitis in many recent studies manifested with a multiorgan involvement until a fatal outcome. Today, the incidence of syphilitic hepatitis is still increasing because of the lack of antenatal screening with various and unspecified clinical manifestations. It's necessary for early recognition of an infant with probable congenital syphilis.

The key limitation of this case report is that the diagnosis of syphilitic hepatitis is still a presumptive diagnosis. Diagnostic tools for supporting diagnosis and the absence of follow-up measurements of bilirubin, ALT, and AST levels after therapy limited the ability to assess treatment response. This case report also did not perform GGT, CMV-PCR, or thyroid-stimulating hormone (TSH). Additionally, a liver biopsy could not be performed due to restricted resources. However, several literatures indicate that liver biopsy in similar cases may reveal microscopic findings such as localized leukocyte infiltration, lobular inflammation, and hepatocellular necrosis.[7, 15 11,14] The patient was referred to the referral hospital for further examination and comprehensive management by a pediatric gastroenterohepatologist.

Conclusion

This is a rare case of infant syphilitic hepatitis that was initially confounded with biliary atresia in a resource-limited setting. Syphilitic hepatitis should be considered as a differential diagnosis in neonatal cholestasis born to mothers with syphilis. The liver function should be monitored regularly in a patient with a history of syphilis treatment. Syphilis hepatitis is rarely diagnosed and often overlooked by clinicians. Its manifestations may mimic other causes of neonatal jaundice, leading to delays in appropriate management. As syphilis is a re-emerging but preventable and treatable disease, it is important to increase awareness and adherence to antenatal screening protocols, as outlined by the Indonesia Ministry of Health.

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Conflict of Interest

None declared

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Literature Review

Climate Change and Its Emerging Impact on Pediatric Gastrointestinal Infections in Indonesia – A Review Article

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Abstract:

Background: Pediatric gastrointestinal (GI) infections remain a major public health issue in Indonesia, particularly among children under five. These infections are closely linked to poor sanitation, unsafe water, malnutrition, and inadequate healthcare access. Climate change has intensified these challenges, with rising temperatures, floods, and droughts increasingly influencing disease patterns. Despite this growing threat, limited research has explored how environmental changes specifically impact pediatric GI infections in Indonesia.

Discussion: Climate change acts as a multiplier of risk for GI infections by disrupting water and sanitation systems, affecting food safety, and limiting hygiene practices. Floods often contaminate drinking water, while extreme heat enhances pathogen survival in food and water. Droughts reduce water availability, limiting handwashing and sanitation. These environmental stressors disproportionately affect vulnerable populations, especially children living in poverty or disaster-prone areas. In addition, climate-related events often disrupt healthcare services and contribute to malnutrition, further increasing children's susceptibility to infections. However, Indonesia's health and climate policies remain fragmented. There is a lack of integrated research, limited disease surveillance, and insufficient public health preparedness that specifically addresses pediatric needs in a changing climate.

Conclusion: To address the growing threat of climate-sensitive pediatric GI infections, Indonesia must strengthen its surveillance systems, invest in climate-resilient health infrastructure, and integrate environmental risks into child health strategies. A coordinated, multisectoral response that prioritizes vulnerable children is essential to reduce disease burden and improve health outcomes in the face of climate change.

Keywords: climate change, gastrointestinal infection, indonesia, surveillance

Introduction

Pediatric GI infections, including diarrhea, typhoid fever, cholera, and hepatitis A, remain leading causes of morbidity and mortality among children in Indonesia, particularly in children under five.[1, 2] These infections are closely linked to poor sanitation, unsafe water, and limited access to healthcare, conditions that are prevalent in many parts of the country.[3, 4] According to the Indonesian Ministry of Health, diarrhea accounts for a significant proportion of childhood hospitalizations and deaths, up to 3.9% under one and 5,2% under four.[5] Importantly, the prevalence of these diseases tends to rise following extreme weather events, such as floods and prolonged droughts, or other natural hazards,[6] suggesting a potential link between climate variability and infectious disease outbreaks.[3]

Indonesia is one of the world's most climate-vulnerable countries, with its extensive coastline, high population density, and diverse ecosystems making it particularly susceptible to the effects of climate change.[7] In recent years, the country has experienced an increase in the frequency and intensity of natural disasters, including floods, droughts, and tropical storms.[6] These events can directly impact water quality, sanitation infrastructure, and food security, conditions that are strongly associated with increased risk of GI infections in children. For example, flooding often leads to contamination of drinking water sources,[8] while drought limits water availability for hygiene practices, both of which can elevate disease transmission in pediatric populations.[9]

Understanding how climate change affects pediatric gastrointestinal infections is crucial for informing health policy, enhancing healthcare systems, and developing early warning strategies in Indonesia. Children are especially vulnerable due to their developing immune systems and reliance on adults for care and hygiene.[10] This literature review aims to explore the emerging connections between climate change and the burden of pediatric GI infections in Indonesia, identify knowledge gaps, and highlight opportunities for targeted interventions in public health and climate adaptation planning.

Methodolgy

This narrative review synthesized literature published between 2020 and 2025 on the impact of climate change on pediatric GI infections in Indonesia. Relevant articles were identified through searches in PubMed, Scopus, Google Scholar, and direct searches via Google, as well as national data sources such as Ministry of Health reports, WHO publications, and disaster databases. Eligible sources included studies or reports focusing on pediatric populations in Indonesia that addressed GI infections in relation to climate variability or environmental change. Articles unrelated to Indonesia, focusing solely on adults, or lacking relevant epidemiological or

environmental context were excluded. The selected literature was narratively synthesized to describe epidemiological patterns, climate-related transmission pathways, and research and policy gaps.

Pediatric Gastrointestinal Infections in Indonesia

In the Indonesian context, pediatric GI infections exhibit marked seasonal and geographic variation, with higher incidence rates commonly observed during the rainy season and in flood-prone or low-income regions. For example, a study in South Kalimantan found statistically significant associations between rainfall, temperature, and diarrhea incidence in children under five.[11] Surveillance data show a consistent rise in outpatient visits and hospitalizations for acute diarrhea, particularly in provinces with limited access to piped water and poor sanitation coverage.[12, 13] Urban slums and rural communities face overlapping risk factors, including unsafe drinking water, poor food hygiene, and overcrowded living conditions, which facilitate the transmission of GI pathogens.[2]

Rotavirus remains one of the most frequently detected viruses in stool specimens from children with diarrhea, despite the availability of a vaccine.[14, 15] Meanwhile, bacterial infections caused by *Enterotoxigenic E. coli* (ETEC), *Shigella*, and *Salmonella* continue to be reported across healthcare facilities.[15] A study by Puspandari et al. found that around 68% diarrhea cases are viral infection, with 54% cases are due to Rotavirus, followed by less than 10% cases caused by ETEC, *Shigella*, and *Campylobacter jejuni*.[15] In some coastal areas, outbreaks of cholera and hepatitis A have been linked to contaminated water following extreme weather events, highlighting the environmental sensitivity of these diseases.[16]

Socio-economic determinants also shape the persistence of these infections. Household-level practices such as improper food handling, inadequate handwashing, and reliance on non-treated water sources remain prevalent.[17, 18] Moreover, fragmented health service delivery, vaccine hesitancy, and limited laboratory capacity for pathogen-specific diagnostics pose significant barriers to timely diagnosis and treatment.[19] Malnutrition, particularly among children under five, further complicates disease management by increasing susceptibility and prolonging recovery.[18]

When considered alongside the intensifying effects of climate change, these conditions reinforce the need for a targeted, multisectoral approach to control and prevent pediatric GI infections across Indonesia's diverse regions.

Climate-Driven Pathways of Infection

Climate change is increasingly influencing the transmission patterns of pediatric GI infections in Indonesia. Rising temperatures, unpredictable rainfall, floods, and prolonged droughts directly impact water quality, sanitation, and hygiene, critical

factors in the spread of GI diseases. Children are especially vulnerable due to their developing immune systems and frequent contact with contaminated environments such as floodwater, unclean food, or poor sanitation facilities.[3, 8, 9] A study by Dharmayanti et al. found that climate variables play a significant role in children's diarrhea incidence.[11]

Flooding, which has become more frequent in lowland and urban areas, often overwhelms sanitation systems and contaminates drinking water supplies. This leads to increased exposure to pathogens such as *E. coli*, *Shigella*, and *Salmonella*, especially in children who are more likely to play in or consume unsafe water. In coastal and island communities, saltwater intrusion caused by rising sea levels also compromises freshwater sources, pushing families to rely on unsafe alternatives.[2, 15, 16]

Meanwhile, extreme heat can increase the survival and replication of bacteria and viruses in food and water, particularly in households lacking refrigeration or safe storage. Droughts, on the other hand, limit water availability, reducing hygiene practices like handwashing and food rinsing. These environmental stressors worsen in areas already struggling with poor infrastructure, high poverty, and limited public health services.[3, 17, 18]

Moreover, climate-related disasters often disrupt healthcare access. Post-disaster periods frequently see spikes in diarrhea and other GI diseases, but health systems may be ill-prepared to handle such outbreaks. Temporary shelters often lack adequate sanitation, clean water, and child-specific care, creating hotspots for disease transmission. Surveillance systems may miss early signs due to weak coordination between the environmental and health sectors.[2, 20]

Additionally, climate change impacts food security, which in turn contributes to a higher risk of infection. Malnutrition compromises immune function, making children more susceptible to infections and slowing recovery. Studies in Indonesia have shown that undernourished children are more likely to suffer severe and prolonged bouts of diarrhea following exposure to waterborne pathogens.[21]

Despite the growing evidence, climate-health links in Indonesia are not yet fully incorporated into pediatric infection control programs. Most responses remain reactive rather than preventive. Understanding these pathways is crucial not just for responding to outbreaks but also for planning climate-resilient health systems that protect vulnerable children amid a changing environment.

Research and Policy Gap

Indonesia still lacks integrated research and policy frameworks that connect environmental risks with child health outcomes. Most surveillance systems are

fragmented and reactive, making it difficult to predict or prevent outbreaks.[22] Few studies specifically examine how climate-related events, like floods or droughts, affect GI infection patterns in children.[3, 8, 9, 20, 21] Existing research often focuses on adults, overlooks regional disparities, or lacks long-term data. As a result, children's unique vulnerabilities—such as weaker immunity and high exposure to contaminated environments—remain underrepresented in national health strategies. On the policy side, health and climate programs are still treated as separate domains. Initiatives like the *Rencana Aksi Nasional Adaptasi Perubahan Iklim*/National Action Plan for Climate Change Adaptation (RAN-API) rarely address pediatric-specific health threats.[23] Meanwhile, public health measures such as rotavirus vaccination, clean water infrastructure, and hygiene promotion remain inconsistently implemented across provinces. Limited investment in laboratory diagnostics, behavior change programs, and early warning systems further hinders a timely response.

Addressing these gaps requires a coordinated approach that integrates health, environmental, and disaster management policies while placing children's needs at the center of climate adaptation and public health planning. Policy priorities should include incorporating pediatric-specific climate–health risk assessments into national adaptation strategies such as the RAN-API, mandating climate-resilient Water, Sanitation, and Hygiene (WASH) infrastructure in schools, health centers, and community shelters, and expanding rotavirus vaccination coverage with priority for flood-prone and high-incidence provinces. On the research front, longitudinal surveillance linking district-level climate variables with pediatric GI infection trends is essential to enable earlier detection and targeted interventions. Operational research on affordable, climate-resilient water purification and storage systems suitable for rural and peri-urban households, as well as the development of predictive models that combine meteorological forecasts with health surveillance data, will further strengthen the country's capacity to prevent climate-triggered outbreaks. These efforts, if implemented in a coordinated manner, can help reduce the burden of pediatric GI infections and build long-term resilience against the health impacts of climate change in Indonesia.

Conclusion

Pediatric gastrointestinal infections in Indonesia remain a significant public health concern, increasingly shaped by climate-related factors such as floods, heat waves, and poor water quality. Children are especially vulnerable due to their biology, environment, and nutritional status. Yet, existing research and policy frameworks often overlook the intersection of climate change and child health. To reduce disease burden, Indonesia must strengthen surveillance systems, invest in climate-resilient infrastructure, and integrate health with environmental planning. A multisectoral

approach that prioritizes children's needs is essential to build long-term resilience and ensure healthier outcomes in an era of growing climate uncertainty.

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Conflict of Interest

None declared.

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