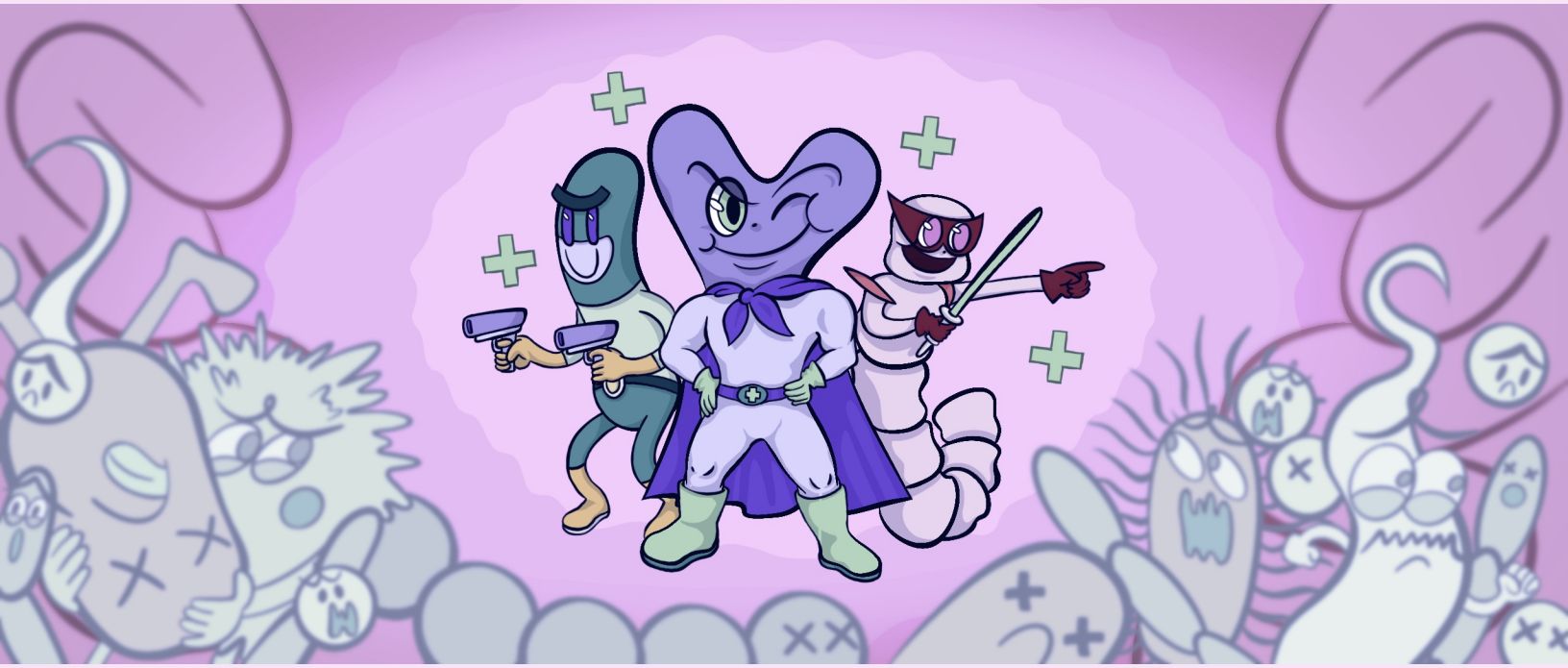
e-ISSN 2830 5442

APGHN

Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Volume 4 / No. 2

May 2025



www.apghn.com

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

e-ISSN 2830 5442

Volume 4, No. 2, May 2025

APGHN

Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

EDITORIAL BOARD

COVER ILLUSTRATION

Tamara Dhannisa

Archives of Pediatric Gastroenterology, Hepatology, and Nutrition (APGHN) is the official journal issued by the Indonesian Society of Pediatric Gastroenterology, Hepatology, and Nutrition.
Contact us: apghnjgai@gmail.com

e-ISSN 2830 5442

Volume 4, No. 2, May 2025

APGHN

Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

TABLE OF CONTENT

Archives of Pediatric Gastroenterology, Hepatology, and Nutrition (APGHN) is the official journal issued by the Indonesian Society of Pediatric Gastroenterology, Hepatology, and Nutrition.
Contact us: apghnjgai@gmail.com

APGHN
Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Original Article

Risk Factors of Stunted Children Aged 0-23 Months at Jatibaru Public Health Center Bima, West Nusa Tenggara: A Case Control Study

Khafifah Puja Atmalia[1,2], Rania Reiza Faris Balfas[1], Nurfathonah Aryana[1], Wulandari Hidayat[3], Nina Dwi Putri[2]

[1]Jatibaru Public Health Center, Bima, West Nusa Tenggara

[2]Department of Child Health, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

[3]Bima Regional Public Hospital, Bima, West Nusa Tenggara

e-ISSN: 2830-5442

Corresponding author:
Khafifah Puja Atmalia
khafifahpuja08@gmail.com

Published:
31st May 2025

DOI:
https://doi.org/10.58427/apghn.4.2.2025.51-61

Citation:
Atmalia KP, Balfas RRF, Aryana N,Hidayat W, Putri ND. Risk factors of stunted children aged 0-23 months at Jatibaru Public Health Center, Bima, West Nusa Tenggara: a case-control study. *Arch Pediatr Gastr Hepatol Nutr.* 2025;4(2).51-61

Abstract:

Background: Nutritional status in children under-five profoundly affects linear growth, cognitive development, and long-term disease. Stunting, defined as a child being too short for their age, results from prolonged malnutrition, particularly in the first 1000 days. In West Nusa Tenggara (NTB), stunting prevalence is the fourth highest at 32.7%, with 31.2% affected in Bima. This study aims to compare previous exposure between stunted children and non - stunted children in primary health care settings in Bima.

Methods: A case-control study was conducted involving children aged 0–23 months who accessed integrated health services, bring a Maternal and Child Health Book (MCH), and had recorded health data at the Jatibaru Primary Health Center. Children with congenital anomalies were excluded. Maternal and child-related risk factors were assessed through anthropometric measurements (WHO standards) and structured interviews with validated questionnaire. Bivariate analysis (Chi-square, $p < 0.25$) was followed by multivariate logistic regression ($p < 0.05$).

Result: A total of 124 participants were included (62 cases, 62 controls). Multivariate analysis revealed that maternal factors significantly associated with stunted growth in children were poor nutritional status (AOR 7.519, $p = 0.000$) and low nutrition knowledge (AOR 6.930, $p = 0.000$). Among child-related factors, stunted children were significantly associated with low birth weight (AOR 17.013, $p = 0.000$) and inadequate breastfeeding (AOR 7.434, $p = 0.006$).

Conclusion: The mother's nutritional status and children's birth weight are the main risk factors of stunted children. Targeted interventions addressing maternal education and perinatal care are recommended to reduce stunting prevalence.

Keyword: children, mothers, risk factors, stunting

Introduction

Stunting is a condition of failure to thrive in children under five years of age due to chronic malnutrition and recurrent infections, especially in the first 1,000 days of life, from fetus to 23 months of age.[1] One of the most critical risk factor is maternal nutritional status during pregnancy; mothers suffering from chronic energy deficiency or micronutrient deficiencies (such as iron, folate, and iodine) are more likely to give birth to low birth weight (LBW) infants, who are at significantly higher risk of experiencing linear growth faltering.[2] This risk is further compounded by inadequate exclusive breastfeeding, suboptimal complementary feeding practices, recurrent infections, poor parental knowledge on nutrition, limited access to health services, and insufficient sanitation. The synergistic effects of these factors often create a vicious cycle of undernutrition and illness, making it difficult for affected children to achieve optimal growth without targeted and sustained interventions.[3]

The national prevalence of stunting in 34 provinces in Indonesia from 2021 to 2022 decreased from 24.4% to 21.6%. However, according to World Health Organization (WHO), this incidence rate is still classified as high (>20%).[4] West Nusa Tenggara (NTB) Province in 2022 ranks fourth highest in Indonesia for the prevalence of stunting toddlers at 32.7%. In 2022, there were 9 clinically diagnosed cases of severe malnutrition with comorbidities requiring hospitalization, and 23 cases (1.12%) of severe malnutrition based on weight-for-height (WHZ), along with 173 children (8.62%) categorized as moderately undernourished. According to data from the 2022 EPPGBM (Electronic Community-Based Nutrition Recording and Reporting System), 253 children under five (12.34%) were identified as stunting out of 2,051 children assessed. Jatibaru Health Center serves the largest population among all primary health care facilities in Bima. Based on the latest data from May 2024, Jatibaru Health Centre has 243 (14.86%) stunting children under five.[4] This highlights stunting as a health problem in Jatibaru that still requires close attention.

The government is targeting 14% reduction in stunting rates by 2024 through the National Strategy (Stranas) program. The program is divided into two, namely specific and sensitive nutrition services. Specific nutrition services are nutrition interventions across health programs that target the direct causes of stunting, including lack of food and nutrient intake and infectious diseases. While sensitive nutrition interventions are interventions implemented by cross-sectoral non-governmental organization (NGO) health programs.[5]

Diagnosis of stunting was confirmed by history taking, physical examination, and anthropometric measurements (based on the index of body length or height according to age and sex (PB/U or TB/U) <-2 SD according to the WHO 2006 growth chart for children aged 0-5 years).[6] The purpose of this study was to determine the risk factors that influence the occurrence of stunting in toddlers in the Jatibaru Health

Centre working area. In order to support the achievement of the Stranas for the Acceleration of Stunting Prevention 2018-2024 and National Medium-Term Development Plan 2020-2024, Puskesmas Jatibaru as a primary healthcare facility must know the factors that cause stunting in toddlers in the working area in order to prepare quality and specific nutrition intervention programs and in accordance with the problems that occur.[5] This study identified several maternal and child-related factors that were significantly associated with the incidence of stunted growth, which is key factor of stunting.

Method

This analytical study used a case control approach that examines the relationship between certain effects (stunted and non-stunted) and certain risk factors (with risk factor and without risk factor). Data collection was carried out at the Jatibaru Health Centre Hall from 1 to 26 June 2024 and has received approval from from Jatibaru Public Health Center. Inclusion of this study were all infants aged 0 - 23 months who took anthropometric measurements, had data recorded at Health Centre Hall Jatibaru, Bima City, had a maternal and child health book (MCH), lived in the study area, and parents were willing to participate by filling out informed consent. Toddlers whose parents were not willing to participate or had congenital abnormalities were excluded. The data was aggregated to be in case with stunted and control group without stunted. Stunted definition based on Z-score of PB/U or TB/U <-2 SD on the WHO growth chart.

The sample size and sampling technique used total sampling, with case-to-control ratio of 1:1. Risk factors were categorized into two groups: maternal and child-related factors. Maternal risk factors included maternal education, socioeconomic status, pregnancy nutritional status, nutritional knowledge, and employment status. Child-related risk factors comprised birth weight, breastfeeding practices, history of infections, and immunization status. All of data was obtained directly from the field by taking anthropometric measurements who were conducted by trained health personnel using calibrated equipment following WHO standards. The Health Department supplied the GEA brand anthropometric tools. Maternal nutritional knowledge was evaluated using a questionnaire consisting of 14 yes-or-no questions. Participants who answered "no" to more than 7 questions were classified as having poor nutritional knowledge.[7] Pregnancy nutritional status was determined from data recorded in the MCH book. Mothers are classified as having chronic energy deficiency (CED) if their mid-upper arm circumference (MUAC) is less than 23.5 cm. For child-related risk factors, birth weight and immunization status were also obtained from the MCH book. Other risk factor data was gathered through structured interviews.

Data analysis used univariate, bivariate (Chi-square), and multivariate (Multivariate logistic regression analysis) methods. Before analysis, a completeness check was carried out on the collected data, coding, and data tabulation with the SPSS v.26.0.

Result

Study Characteristic

This study involved 124 pairs of mother and child, consisting of 62 cases and 62 controls. From the analysis of the characteristics of mothers and children in this study, 41.9% of mothers had Chronic Energy Deficiency (CED). Most mothers (84.7%) were unemployed, which may affect social and economic support in child care. 73.4% of mothers had a high level of education. However, 74.2% came from low socio-economic backgrounds, which risks hindering access to health and nutrition services. 29.8% of children were born with low birth weight (LBW), 75.8% were breastfed, but 62.9% had infections, and 33.1% were not fully immunized.

Maternal and Child-Related Risk Factors of Stunted

In the bivariate analysis, maternal factors such as nutrition knowledge, nutritional status, and employment status showed significant differences between the two groups. In the stunted group, chronic energy deficiency (CED) was more common (67.7%) compared to the non-stunted group (16.1). Additionally, employed mothers were more frequently found in the stunted group (14% vs 5%).

Regarding child-related factors, birth weight, breastfeeding status, and history of infections also showed significant differences between the groups. Low birth weight was more prevalent in the stunted group (51.6) than in the non-stunted group (8%). Furthermore, children in the stunted group were less likely to be breastfed (59.6%) compared to those in the non-stunted group (91.9%). The results of the bivariate analysis are presented in **Table 1**.

Based on the multivariate analysis, several maternal factors were significantly associated with the outcome. The most influential was the nutritional status of the mother **(**AOR = 7.519; 95% CI: 2.728–20.729; p = 0.000), indicating that poor maternal nutrition greatly increases the risk. This was followed by maternal knowledge (AOR = 6.930; 95% CI: 2.375–20.216; p = 0.000), showing that mothers with better knowledge had a significantly lower risk. Meanwhile, maternal employment (AOR = 0.303; 95% CI: 0.046–2.005; p = 0.216), education (AOR = 0.957; 95% CI: 0.298–3.081; p = 0.942), and socioeconomic status (AOR = 0.580; 95% CI: 0.161–2.094; p = 0.406) were not significantly associated with the outcome.

Among child-related factors, the most significant was birth weight (AOR = 17.013; 95% CI: 3.318–29.112; p = 0.000), where low birth weight dramatically increased the risk. Breastfeeding also showed a significant association (AOR = 7.434; 95% CI:

0.063–0.637; p = 0.006), suggesting a strong protective effect. However, infection (AOR = 0.825; 95% CI: 0.264–1.630; p = 0.364) and immunization (AOR = 0.912; 95% CI: 0.253–1.605; p = 0.340) were not found to be significantly associated. The multivariate analysis is summarized in **Table 2.**

Table 1. Association Between Maternal and Child Characteristics with Stunted Children Prevalence

Characteristics	Stunted (Yes) n (%)	Stunted (No) n (%)	P-value
Mother			
Maternal Education			
- Low	17 (27.4)	16 (25.8)	0.825
- High	45 (72.5.3)	46 (74.1)	
Socioeconomic Status			
- Low Income	41 (66.1)	51 (82.2)	0.149
- Middle Income	21 (33.8)	11 (17.7)	
Maternal Nutrition Knowledge			
- Poor Knowledge	40 (64.5)	62 (100.0)	0.000
- Good Knowledge	22 (35.4)	0 (0.0)	
Maternal Nutrition			
- Chronic Energy Deficiency	42 (67.7)	10 (16.1)	0.000
- Normal	20 (32.2)	52 (83.8)	
Maternal Employment			
- Unemployed	48 (77.4)	57 (91.9)	0.007
- Employed	14 (22.5)	5 (8.0)	
Child			
Birth Weight			
- Low Birth Weight (LBW)	32 (51.68)	5 (8.0)	0.000
- Normal Birth Weight	30 (48.3)	57 (91.9)	
Breastfeeding			
- Not Breastfed	25 (40.3)	5 (8.0)	0.000
- Breastfed	37 (59.6)	57 (91.9)	
Infections			
- Yes	33 (53.2)	45 (72.5)	0.026
- No	29 (46.7)	17 (27.4)	
Immunization Status			
- Incomplete	25 (40.3)	16 (25.8)	0.086
- Complete	37 (59.6)	46 (74.1)	

Table 2. Multivariate analysis of risk factors of stunted children

Variable	AOR	Confidence Interval		p-value
		under 95%	above 95%	
Mother				
Nutritional status	7.519	2.728	20.729	0.000
Nutrition knowledge	6.930	2.375	20.21	0.000
Maternal education	0.957	0.298	3.081	0.942
Employment status	0.303	0.046	2.005	0.216
Socioeconomic Status	0.580	0.160	2.094	0.406
Child				
Birth weight	17.013	3.318	29.11	0.000
Breastfeeding	7.434	0.063	0.067	0.006
History of infection	0.825	0.264	1.630	0.364
Immunization status	0.912	0.253	1.605	0.340

Discussion

Stunting in children under-five is a complex and multidimensional chronic nutritional problem, involving various interacting factors that affect children's growth and development. Key factors contributing to stunting include maternal nutritional status, exclusive breastfeeding and complementary feeding, recurrent infections, family socio-economic conditions, and access to adequate health and sanitation services. Each of these factors can exacerbate the child's condition, creating a cycle that is difficult to break without effective intervention.[8]

This study identified several maternal and child-related factors that were significantly associated with the incidence of stunted. The most dominant maternal factor was nutritional status (AOR = 7.519; 95% CI: 2.728–20.729; p = 0.000), confirming that inadequate maternal nutrition significantly increases the risk of stunted children. Poor intake of macronutrients (protein, fat, total energy) and essential micronutrients (iron, folic acid, zinc, calcium) during pregnancy can impair intrauterine growth, leading to low birth weight (LBW), stunting, and higher perinatal mortality rates. Nutritional status can be assessed through mid-upper arm circumference (MUAC), where values below 23.5 cm indicate chronic energy deficiency (CED), increasing the risk of fetal growth restriction and poor postnatal development.[9, 10] A study in Ethiopia also reported that maternal undernutrition was a key determinant of stunting, highlighting the intergenerational cycle of malnutrition.[11]

The second strongest maternal factor was nutritional knowledge (AOR = 6.930; 95% CI: 2.375–20.216; p = 0.000), showing that mothers with better knowledge of nutrition were significantly less likely to have stunted children. Similarly, research in Indonesia found that lack of knowledge on child feeding practices increased the likelihood of stunting in children.[12] Interestingly, this study found no significant

association between maternal education and stunted children (AOR = 0.957; p = 0.942), contrasting with studies that link lower education to higher risk.[13] This may suggest that knowledge-based interventions may be more effective than solely improving educational attainment.[14] This supports previous findings that adequate maternal knowledge—regardless of formal education level—improves child-feeding practices and care behaviors, ultimately reducing stunting risk.[14, 15]

Additionally, in multivariate analysis maternal employment did not show a significant association (AOR = 0.303; p = 0.216), differing from earlier research that suggested employment, particularly in low-income or rural settings, reduces time available for child care, increasing stunting risk.[15] Socioeconomic status significantly affects a family's capacity to meet the nutritional needs of children under five. It also influences decisions regarding supplementary food choices, meal schedules, and adherence to healthy lifestyle practices. Children from low-income households with working mothers have a higher risk of stunting compared to those from high-income households.[16, 17] However, this study showed no significant correlation between socioeconomic status and the occurrence of stunted growth in children (AOR = 0.580; p = 0.406), in line with the study by Aida et al.,[18] which found that there was no correlation between socioeconomic status and the occurrence of stunting. Socioeconomic status was not significantly associated with stunted in this study, potentially due to sample homogeneity or stronger effects from biological and behavioral factors.[19]

From the child-related variables, low birth weight was the strongest predictor of stunted growth in children (AOR = 17.013; 95% CI: 3.318–29.112; p = 0.000). Inadequate fetal growth due to maternal malnutrition is a primary contributor to LBW, which significantly impairs early linear growth.[9, 10] Exclusive breastfeeding was also significantly associated with reduced stunted growth in children (AOR = 7.434; 95% CI: 0.063–0.637; p = 0.006), reinforcing global recommendations for optimal infant feeding during the first six months of life.[20] In contrast, infection and immunization were not significantly associated with stunted children in this study, although both factors remain important for overall child health and resilience.

This study revealed that birth weight is the most significant factor associated with stunted growth in children (AOR = 17.013; 95% CI: 3.318–29.112; p = 0.000). Aryastami et al.[21] revealed that infants born with low birth weight are highly vulnerable and face increased health risks, including morbidity, mortality, infectious diseases, underweight status, and are 1.74 times more likely to be stunting during the neonatal period and early childhood compared to infants born with normal weight, which is in line with the results of this study. Child stunting is often the result of growth delays that occur in utero, known as intrauterine growth retardation (IUGR).[9] Study

conducted in India, indicated that children with low birth weight were almost four times more likely to be stunted. [22]

This study showed a breastfeeding practice as a significant risk factor (AOR = 7.434; 95% CI: 0.063–0.637; p = 0.006). Low nutrient density and poor-quality complementary foods contribute to nutrient deficiencies and illness in children, leading to early malnutrition. The results of this study are consistent with those of Wicaksono[13] that non-exclusive breastfeeding is associated with higher rates of stunting. Some studies have suggested that exclusive breastfeeding for the first six months of life may have a protective effect against stunting, as breast milk provides essential nutrients, antibodies and bioactive components that support optimal growth and development, and early initiation of breastfeeding may contribute to this protective effect.[23, 24] However, other studies have found no direct association or even a positive correlation between prolonged breastfeeding and increased risk of stunting.[8] These contradictory findings may be influenced by factors such as maternal nutritional status, complementary feeding, and the presence of underlying health conditions or environmental factors that may affect child growth.[25]

During the first 1000 days of life, the absence of immunization is known to increase the risk of stunting; however, in this study, no significant association was found (p-value = 0.086), which is consistent with findings from studies conducted in West Sumatra and by Sutriyawan et al.[26, 27] As the child does not gain passive immunity, is more susceptible to infections, has a decreased appetite, and may have impaired nutrient absorption leading to stunting. There is also a reciprocal relationship between infection and malnutrition. Children with frequent infections are more likely to be malnourished, while malnourished children are more susceptible to infections. These findings are consistent with previous studies conducted in Bangladesh,[28] which showed that inadequate sanitation leads to excess bacterial proliferation in the gut, decreasing probiotic levels, thus causing inflammation and malabsorption of nutrients, ultimately contributing to stunting.[16, 17] Similarly, this study found a significant association between infections and stunted growth (p = 0.026). In the multivariate analysis, interestingly the presence of childhood infections (OR 0.825; 95% CI 0.264–1.630; P = 0.364) was not a significant risk factor for stunted growth in this study, although other literature often points to recurrent infections—particularly diarrheal diseases—as contributors to poor nutrient absorption and growth delays.[29] Likewise, immunization history (OR 0.912; 95% CI 0.253–1.605; P = 0.340) showed no significant association with stunted children, contrasting with evidence from other studies where complete immunization was correlated with improved child health outcomes and reduced stunting prevalence.[30] These differences may be attributed to variations in population characteristics, sample sizes, or public health infrastructure between study areas. Nonetheless, the current findings underscore the critical role of

maternal factors in preventing child stunting and support ongoing efforts to improve maternal nutrition, knowledge, and support for early childcare practices.

Although the analysis of risk factors of stunted growth has been widely conducted in various regions, such data remain unavailable specifically for the Bima region. Nevertheless, such data are essential to guide targeted and effective stunting prevention interventions for children in Bima. In summary, maternal nutritional status, maternal knowledge, birth weight, and exclusive breastfeeding were the most significant determinants of stunted growth in this population. These findings emphasize the urgent need to enhance maternal nutritional support and health literacy —especially during the preconception and pregnancy periods—through integrated public health programs.[9, 14, 15] Future studies are recommended to explore a broader range of risk factors with larger sample sizes. Additionally, implementing intervention studies that assess outcomes before and after the intervention would provide valuable evidence on the effectiveness of specific strategies to prevent stunting.

Conclusion

This study identified several significant maternal and child-related factors associated with stunted. Poor maternal nutrition knowledge, chronic energy deficiency, and maternal status employment were significant risk factors, with poor maternal nutritional presenting the highest risk. Among child-related factors, low birth weight, inadequate breastfeeding, and a history of infections were significantly associated with increased stunted prevalence, with low birth weight emerging as the strongest predictor. These findings underscore the need for targeted maternal nutritional support and preventive child health strategies to reduce the risk of stunted, which, if not addressed early, can result in stunting.

Acknowledgement

Thank you for the participant and community health volunteers from the primary health center who assisted with data collection in the field.

Conflict of Interest

None declared

Funding Statement

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

References

1. Tim Nasional Percepatan Penanggulangan Kemiskinan. Strategi nasional percepatan pencegahan anak kerdil (stunting) periode 2018–2024. Jakarta: Kemeterian Koordinator Bidang Pembangunan Manusai dan Kebudayaan; 2018.
2. Sana, Sajid I, Khan SA, Hussain S, Masood Ur R, Adnan MS. Maternal nutrition and its impact on low birth weight in newborns. Indus Journal of Bioscience Research. 2025;3(1):236-44. https://doi.org/10.70749/ijbr.v3i1.482
3. Saaka M, Saapiire FN, Dogoli RN. Independent and joint contribution of inappropriate complementary feeding and poor water, sanitation and hygiene (wash) practices to stunted child growth. J Nutr Sci. 2021;10:e109. https://doi.org/10.1017/jns.2021.103
4. Kementrian Kesehatan Republik Indonesia. Buku saku hasil survei status gizi Indonesia (SSGI) 2022. Jakarta: Kemenkes RI; 2022.
5. Kementrian Kesehatan Republik Indonesia. Pedoman manajemen pelayanan gizi spesifik di Puskesmas untuk percepatan penurunan stunting di Indonesia. Jakarta: Kemenkes RI; 2021.
6. Kementrian Kesehatan Republik Indonesia. Keputusan Menteri Kesehatan Republik Indonesia Nomor HK.01.07/Menkes/1928/2022 tentang Pedoman Nasional Pelayanan Kedokteran Tata Laksana Stunting. Jakarta: Kemenkes RI; 2022.
7. Sukiman M, Bamahry A, Irwan A, Laddo N, Arifin A. Faktor-faktor risiko terjadinya stunting pada balita di Puskesmas Kassi-Kassi Kota Makassar periode Januari 2022. Fakumi Medical Journal: Jurnal Mahasiswa Kedokteran. 2022;2:656-67. https://doi.org/10.33096/fmj.v2i9.121
8. Alifariki L, Haryati H, Rahmawati R, Sukurni S, Salma W. Risk factors of stunting in children age 24-59 months old. Media Keperawatan Indonesia. 2020;3:10. https://doi.org/10.26714/mki.3.1.2020.10-16
9. Sjarif DR, Yuliarti K. Petunjuk teknis berbasis bukti: diagnosis dan tata laksana stunting secara komprehensif untuk dokter spesialis anak. Jakarta: Ikatan Dokter Anak Indonesia; 2024.
10. Young MF, Nguyen PH, Gonzalez Casanova I, Addo OY, Tran LM, Nguyen S, et al. Role of maternal preconception nutrition on offspring growth and risk of stunting across the first 1000 days in vietnam: a prospective cohort study. PLoS One. 2018;13(8):e0203201. https://doi.org/10.1371/journal.pone.0203201
11. Anato A, Baye K, Tafese Z, Stoecker BJ. Maternal depression is associated with child undernutrition: a cross-sectional study in Ethiopia. Matern Child Nutr. 2020;16(3):e12934. https://doi.org/10.1111/mcn.12934
12. Sari M, Pee S, Bloem M, Sun K, Thorne-Lyman A, Moench-Pfanner R, et al. Higher household expenditure on animal-source and nongrain foods lowers the risk of stunting among children 0-59 months old in Indonesia: implications of rising food prices. The Journal of nutrition. 2009;140:195S-200S. https://doi.org/10.3945/jn.109.110858
13. Wicaksono RA, Arto KS, Mutiara E, Deliana M, Lubis M, Batubara JRL. Risk factors of stunting in Indonesian children aged 1 to 60 months. Paediatrica Indonesiana. 2021;61(1):12-9. https://doi.org/10.14238/pi61.1.2021.12-9
14. Nirmalasari NO. Stunting pada anak: penyebab dan faktor risiko stunting di Indonesia. QAWWAM : Journal for gender mainstreaming. 2020;14(1):19-28. https://doi.org/10.20414/qawwam.v14i1.2372
15. Rufaida F, Raharjo A, Handoko A. The correlation of family and household factors on the incidence of stunting on toddlers in three villages Sumberbaru Health Center Work Area of Jember. Journal of Agromedicine and Medical Sciences. 2020;6:1. https://doi.org/10.19184/ams.v6i1.9541
16. Nurkomala S, Nuryanto N, Panunggal B. Praktik pemberian mpasi (makanan pendamping air susu ibu) pada anak stunting dan tidak stunting usia 6-24 bulan. Journal of Nutrition College. 2018;7:45. https://doi.org/10.14710/jnc.v7i2.20822
17. Nurdin SS, Katili D, Fikar Z. Faktor ibu, pola asuh anak, dan mpasi terhadap kejadian stunting di Kabupaten Gorontalo. Jurnal Riset Kebidanan Indonesia. 2019;3:19. https://doi.org/10.32536/jrki.v3i2.57
18. Aida AN. Pengaruh kondisi sosial ekonomi terhadap kejadian stunting di Indonesia. Jurnal Budget: Isu dan Masalah Keuangan Negara. 2019;4(2):1250140.
19. Suhaerudin S, Sumardi A, juliane C. Linear regression analysis to measure the correlation between poverty rate and stunting rate. sinkron. 2023;8:2635-40. https://doi.org/10.33395/sinkron.v8i4.13007
20. Purwaningsih D, Sudarmi S. Analysis of determinants of exclusive breastfeeding in breastfeeding mothers. Jurnal Kesehatan. 2024;15:472-8. https://doi.org/10.26630/jk.v15i3.4799
21. Aryastami NK, Shankar A, Kusumawardani N, Besral B, Jahari AB, Achadi E. Low birth weight was the most dominant predictor associated with stunting among children aged 12–23 months in Indonesia. BMC Nutrition. 2017;3(1):16. https://doi.org/10.1186/s40795-017-0130-x
22. Halli SS, Biradar RA, Prasad JB. Low birth weight, the differentiating risk factor for stunting among preschool children in India. Int J Environ Res Public Health. 2022;19(7). https://doi.org/10.3390/ijerph19073751

23. Utami AR, Nurhaeni N. Factors contributing to catch-up growth of child with stunting: a literature review. STRADA: Jurnal Ilmiah Kesehatan. 2021;10(1):350-9. https://doi.org/https://doi.org/10.30994/sjik.v10i1.638
24. Scheffler C, Bogin B, Hermanussen M. Catch-up growth is a better indicator of undernutrition than thresholds for stunting. Public Health Nutr. 2021;24(1):52-61. https://doi.org/10.1017/s1368980020003067
25. Saadah N, Yumni H, Mugianti S, Yulianto B. Analysis of stunting risk factors in children in the Magetan district. Jurnal Berkala Epidemiologi. 2022;10:265-73. https://doi.org/10.20473/jbe.V10I32022.265-273
26. Vasera RA, Kurniawan B. Hubungan pemberian imunisasi dengan kejadian anak stunting di Puskesmas Sungai Aur Pasaman Barat tahun 2021. Jurnal Kedokteran STM (Sains dan Teknologi Medik). 2023;6(1):82-90. https://doi.org/10.30743/stm.v6i1.376
27. Sutriyawan A, Kurniawati RD, Rahayu S, Habibi J. Hubungan status imunisasi dan riwayat penyakit infeksi dengan kejadian stunting pada balita: studi retrospektif. Journal of Midwifery. 2020;8(2):1-9. https://doi.org/10.37676/jm.v8i2.1197
28. Tjandrawinata RR, Amalia N, Tandi YYP, Athallah AF, Afif Wibowo C, Aditya MR, et al. The forgotten link: how the oral microbiome shapes childhood growth and development. Frontiers in Oral Health. 2025;Volume 6 - 2025. https://doi.org/10.3389/froh.2025.1547099
29. Checkley W, Buckley G, Gilman RH, Assis AM, Guerrant RL, Morris SS, et al. Multi-country analysis of the effects of diarrhoea on childhood stunting. Int J Epidemiol. 2008;37(4):816-30. https://doi.org/10.1093/ije/dyn099
30. Machado AA, Edwards SA, Mueller M, Saini V. Effective interventions to increase routine childhood immunization coverage in low socioeconomic status communities in developed countries: a systematic review and critical appraisal of peer-reviewed literature. Vaccine. 2021;39(22):2938-64. https://doi.org/10.1016/j.vaccine.2021.03.088

APGHN
Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Original Article

The Effect of Giving One Egg Per Day on Stunted Children Aged 2-5 Years in Buton Regency on Zinc Levels

Alvreyna Charienda Laviashna Saputro[1], Dwirini Retno Gunarti[2]
[1]Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[2]Department of Biochemistry and Molecular Biology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

e-ISSN: 2830-5442

Corresponding author:
Dwirini Retno Gunarti
drg.yellow@gmail.com

Published:
31st May 2025

DOI:
https://doi.org/10.58427/apghn.4.2.2025.62-72

Citation:
Saputro ACL, Gunarti DR. The effect of giving one egg per day on stunted children aged 2-5 years in Buton Regency on zinc levels. *Arch Pediatr Gastr Hepatol Nutr.* 2025;4(2).62-72

Abstract:

Background: Despite can be prevented with good nutrition, average prevalence of stunting in Indonesia remains high at 30.8%. The effects of stunting are detrimental to the individual and Indonesia's human resources. Stunted children had low blood zinc levels which disrupted enzyme and antioxidant activity, as well as bone growth processes and bone homeostasis. Eggs that contain zinc and have high bioavailability are expected to be able to increase low blood zinc levels. This study was designed to examine the impact of routine egg consumption on zinc levels in stunted children.

Methods: This experimental quantitative study was conducted in the Siontapina Health Center, Buton Regency, Southeast Sulawesi. and included 22 participants which divided into intervention and control groups. The intervention was carried out by health workers giving one egg per day for 30 days with the same type of cooking per day to the participants. Zinc levels were assessed using a spectrophotometer and analyzed using statistical software.

Result: The results showed a significant difference between the two groups ($p < 0.05$). The average zinc level in the intervention group was 718.8133 ug/dL, which was higher than the control group (143.4536 ug/dL). Thus, giving 1 egg a day for 30 days caused a significant change in blood zinc levels in stunted children aged 2-5 years in Buton Regency.

Conclusion: Stunted children supplemented with one egg daily for 30 days had significantly higher zinc levels than unsupplemented children.

Keyword: children, egg supplementation, nutrition, stunting, zinc level

Introduction

Stunting is caused by chronic malnutrition and is clinically manifested as children with short stature (z-score of height/length per age <-2 SD).[1] Indonesia has one of the highest stunting rates globally, with Buton Regency among the regions most affected. In Buton Regency, the stunting prevalence is reported at 32.6%, with children aged 2 to 5 years being the most affected age group.[2, 3] Stunting leads to multiple issues in children's growth and development, including impaired learning concentration, reduced productivity, and compromised reproductive health. In adulthood, individuals who experienced stunting are more likely to have lower educational level, poorer health outcomes, and higher risk of non-communicable diseases and poverty.[4]

The poorer outcomes observed in stunted children are thought to be partly caused by the increase of oxidative stress and cell injury. Study has demonstrated that children with stunting exhibit significantly lower levels of antioxidant markers—including catalase (CAT), plasma glutathione, total plasma protein, superoxide dismutase (SOD), total antioxidant capacity (TAC), copper (Cu), zinc (Zn), and vitamin C—compared to their non-stunted peers.8 This reduction in antioxidant defenses contributes to the accumulation of oxidative stress, which may exacerbate infections, inflammation, and cellular injury.[5-7] Zinc, in particular, is an essential micronutrient with a vital role in protection against oxidative stress. Specifically, zinc acts as a cofactor of antioxidant enzymes like superoxide dismutase (SOD) that neutralize harmful free radicals. Zinc also contributes to the regulation of Nrf2, a key transcription factor involved in the cellular antioxidant response.[5, 8-11] Furthermore, zinc protects DNA from oxidative damage and aids in cellular repair processes. It also regulates immune function by supporting both innate and adaptive responses, reduces inflammation, and promotes skin and tissue repair.[6, 11] Crucially, zinc is involved in bone growth and development by supporting osteoblast and chondrocyte activity, which are essential for linear growth.[12] Given these roles, zinc deficiency contributes directly to the impaired growth and increased vulnerability seen in stunted children, making it a key target for nutritional interventions.

Given the critical role of zinc in antioxidant defense, immune regulation, and linear growth, ensuring adequate zinc intake is essential in addressing stunting. Eggs are a practical source of animal protein that are rich in essential nutrients, including zinc—most of which is concentrated in the yolk.[13] Furthermore, a study by Lonnerdal et al had reported that the consumption of zinc along with high level of protein also increase zinc absorption.[14] Eggs are also widely accessible and affordable, making them a promising intervention for improving zinc status.[15] Based on these knowledge, egg can be considered as both method of intervention by increasing zinc consumption as well as adjuvant to increaset the absorption of zinc. While previous studies have shown that daily egg consumption may support growth and reduce stunting rates[7, 16, 17], its

direct impact on zinc levels in stunted children remains unexplored. Therefore, the purpose of this study was to examine the effect of one egg consumption on the zinc level in children with stunting.

Method

Study Design

This study is an experimental quantitative study conducted between Januari – September 2024. This study divided the participants into 2 groups: intervention and control groups. The intervention group received one egg per day as a source of animal protein for a duration of 30 days The eggs were provided by the researchers, and consumption was closely supervised and documented to ensure that participants consumed them. This study was approved by the Ethics Committee (Approval No. KET1501/UN.2F1/ETIK/PPM.00.02/2023).

Sample Criteria

Participants included in this study were stunted children aged 2-5 years who were registered at the Siontapina Health Center, Buton Regency, Southeast Sulawesi. Stunting was defined as a height-for-age z-score below −2 standard deviations (SD) based on the WHO growth chart. Children were excluded if they had a known egg allergy, were acutely ill due to infection, had a malignant disease, or suffered from congenital or hereditary conditions. Furthermore, parents or guardians were required to be literate and free from communication barriers (e.g., speech or hearing impairments) to ensure their capability to comply with the study protocol. Informed consent was also obtained from parents or guardians prior to the enrollment of patients in the study. Participants were classified as dropouts if their parents or guardians opted to withdraw from the study, if allergic reactions or clinical deterioration occurred (such as rash, diarrhea, fever, cough, itching, or respiratory symptoms), or if the intervention protocol was not followed accordingly. Due to the requirement for post-intervention blood sample collections, children who missed the post-intervention visit and were unreachable (i.e., lost to follow-up) were also classified as dropouts.

Sample Size Calculation and Randomization

Due to limitations in prior data, the sample size was calculated based on zinc levels in stunted children reported in a previous study, using a 95% confidence interval and 80% statistical power. This calculation yielded a total required sample size of 20 participants (10 per group). Furthermore, accounting for an anticipated 10% non-response rate, the minimum total sample size was adjusted to 22 participants.

Participant selection was conducted using simple random sampling method from a the total of 50 eligible participants. Once the required number of samples (11 per

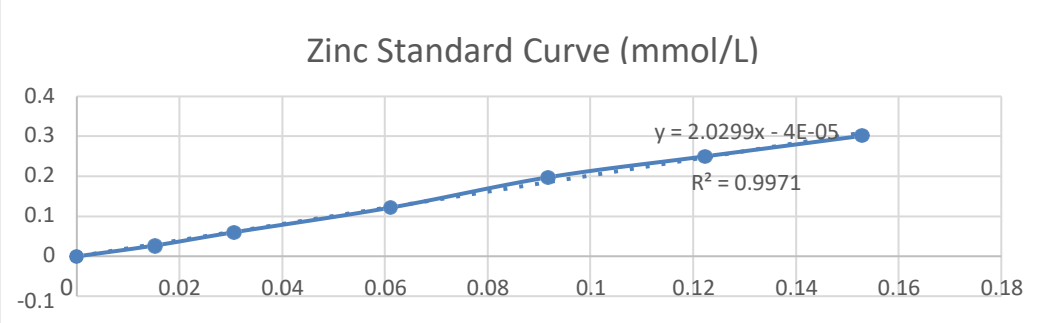
group) was selected, the randomization process was concluded, and the study proceeded to the next stage.

Sample Collection, Storage, and Processing

The biological samples used in this study was obtained from the umbrella study "The Effect of Egg Administration on Digestive Enzyme Biomarkers, Oxidative Stress Biomarkers and Inflammatory Biomarkers in Stunted Children in Buton Regency" which had similar eligibility criteria. Sample collection was carried out between January and February 2024. The samples were then stored in the Laboratory of the Department of Biochemistry, Faculty of Medicine, Universitas Indonesia, until zinc level analysis was conducted between July and September 2024.

Measurement of zinc levels began by preparing a standard zinc solution with varying concentrations to form a standard dilution curve. Firstly, working reagent was prepared by mixing 20 mL of pH.10 chloride buffer solution with 190 mL of dissolving and magnesium masking solution as well as 4 mL of 1-(2-pirodilazo)-2-napthol (PAN) solution.

A total of 100 µL of each sample was then mixed with 750 µL of working reagent, vortexed thoroughly, and incubated for 10 minutes at room temperature. The resulting mixture produced a colored complex. The intensity was measured by spectrophotometry at a wavelength (λ) of 550 nm. To convert absorbance values (color intensity) into actual zinc concentrations, a zinc standard curve was used. The relationship between absorbance and zinc concentration is illustrated in **Figure 1.**



a = SLOPE(B2:B8;A2:A8) b=INTERCEPT(B2:B8;A2:A8)

Figure 1. Zinc Standard Curve

From the slope obtained in the following graph, the values of a and b are calculated. The following is the formula used with B2 (0), B8 (0.3025), A2 (0), and A8 (0.153). The equation obtained is y = 2.0299x – 4E-05 with an R^2 value of 0.9971.

Data Analysis

Data were analyzed using SPSS version 26. The Shapiro-Wilk test was employed to assess data normality. Subsequently, independent sample t-test was used to analyze

data that met the assumptions of normality (parametric data). Categorical data was analysed using Fisher Exact test.

Result

The characteristics of the participants are presented in **Table 1**. From the following analysis, it was found that the p-value of each variable was above 0.05, so indicating that there was no significant difference between the characteristics of the intervention and control group.

Table 1. Characteristics of Participants

Characteristics	Intervention Group	Control Group	P-value
Age			
2-3 years old	10 (90.91)	9 (81.8)	>0.05
4-5 years old	1 (9.09)	2 (18.1)	
Gender			
Male	5 (45.4)	6 (54.5)	>0.05
Female	6 (54.5)	5 (45.4)	
Guardian Education Level			
Low	5 (45.5)	3 (27.3)	
Moderate	5 (45.5)	5 (45.5)	>0.05
High	0	1 (9.1)	
Family Income Level			
Low income	6 (54.5)	5 (45.4)	>0.05
Moderate – high income	4 (36.4)	4 (36.4)	
Height/Age			
Stunted	10 (90.9)	9 (81.8)	>0.05
Severely stunted	1 (9.1)	2 (18.2)	
Weight/Age			
Normal	3 (27.3)	3 (27.3)	
Underweight	7 (63.6)	6 (54.5)	>0.05
Severely underweight	1 (9.1)	2 (18.2)	

Using the standard zinc curve (**Figure.1**), the zinc concentration is obtained and presented in **Table 2.** In the intervention group, zinc levels ranged from 318.996 to 1,515.522 µg/dL. In contrast, the control group exhibited considerably lower values, with zinc levels ranging from 69.381 to 299.671 µg/dL. Notably, the highest zinc concentration in the control group was still lower than the lowest value observed in the intervention group. The data samples were tested for homogeneity and were found to be normally distributed.

Table 3. demonstrates that zinc concentrations were significantly higher in the intervention group than in controls with $p < 0.000$. The different values of the two group is illustrated in Figure 1, showing intervention values clustered at higher levels and a wider range compared with control group, indicating the significant difference.

Table 2. Zinc Levels after Intervention in Each Sample

Intervention Group	Zn Level (ug/dL)	Control Group	Zn Level (ug/dL)
A1	879,413	C2	108,034
A5	378,583	C5	72,605
A8	552,500	C6	127,360
A9	575,050	C7	182,110
A11	1.515,522	C8	125,745
A14	641,077	C10	141,855
A25	436,555	C11	69,381
A20	802,115	C12	206,267
A21	1.203,103	C20	117,697
A23	604,033	C23	127,360
A7	318,996	C22	299,671

Table 3. Analysis of The Zinc Level in the Intervention Group and Control Group After Intervention

	Intervention Group (n=11)	Control Group (n=11)	P value
Zinc levels (µg/dL)	718.8 ± 363.9	143.4 ± 65.6	0.000

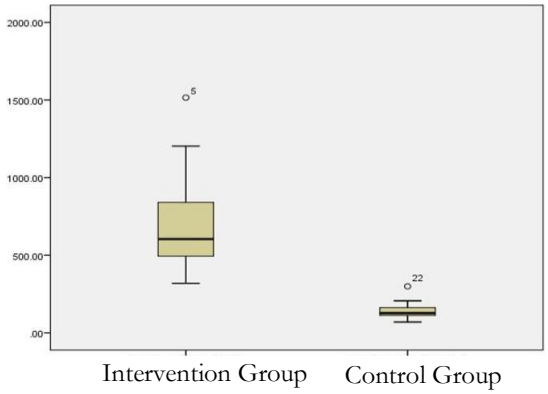


Figure 2. Boxplot of Zinc Levels in Intervention Group and Control Group

Discussion

National data show that the highest prevalence of stunting occurs in children aged 24 to 35 months, aligning with the age characteristics of participants in this study.[2] According to a cross-sectional study by Karlsson et al., the prevalence of stunted toddlers in low- to middle-income countries is estimated to be 32% among children aged 0 to 59 months, with a higher prevalence observed in toddlers around 28 months (2.3 years) of age. This is likely due to the effects of prolonged exposure to malnutrition and infections at this age.[18]

The number of male and female participants in this study has a percentage that is close to each other. This is in accordance with the data in the SSGI where gender is not one of the factors that influences the possibility of a child experiencing stunting.[2] This is proven by research by Priyantini et al. where it was found that the height per age (H/U) score was not related to gender.[19] This finding contrasts with the study by Karlsson et al., which reported that boys tend to have a higher prevalence of stunting, with the peak occurring at a younger age compared to girls. However, the prevalence rates between boys and girls converge at approximately 45 months (3.7 years), becoming relatively similar thereafter.[18] No research was found that compared or compiled the relationship between toddler gender and blood zinc levels or zinc intake.

In this study, all guardians of the participants were the participants' mothers. When discussing the level of education with the participant's guardian, it was found that only 1 out of 22 participants had a guardian who had attended higher education. The majority of the participants had guardians who graduated from junior high school/high school. From a study conducted by Rahmah et al. it was found that the mother's education level affects the possibility of a child being stunted or not because the mother's knowledge will determine the attitude in maintaining and meeting the child's nutritional needs.[20] On the other hand, a study by Priyantini et al. found that the mother's education level was not related to the child's height-for-age (H/A) score.[19]

In this study, the proportion of participants from low-income and moderate-to-high-income between the two groups was relatively similar, 76% of families with stunted toddlers had incomes below the regional minimum wage. A study by Lia et al. found that family income level is associated with the risk of stunting in children, identifying it as one of the contributing factors. The risk factors mentioned in this study include lack of nutritional intake, per capita income and inadequate environmental sanitation.[21] However, research by Priyantini et al. stated that socioeconomics is not related to the height per age (H/U) score of their children.[19] No research was found that compared the relationship between family income and blood zinc levels or zinc intake.

All children in this study were classified as stunted, with three falling into the severely stunted category. In terms of weight-for-age, most participants were underweight,

including three who were severely underweight. These similarities between the intervention and control groups indicate no significant baseline differences, helping to minimize potential confounding factors.

Serum zinc levels can serve as one of the markers of oxidative stress, as zinc—along with other antioxidants and antioxidant enzymes—has a synergistic effect in scavenging free radicals, whose increase can lead to oxidative stress. It has been found that in stunted children, serum zinc levels are lower and oxidative stress levels are higher, whereas in non-stunted children, serum zinc levels are higher and oxidative stress levels are lower. This suggests that the condition of stunted children may be considered improving when there is an increase in serum zinc levels, indicating a reduction in oxidative stress.[5, 22]

The present study analyzed serum zinc level data from stunted children aged 2 to 5 years residing in Buton Regency. The results showed a significant difference in zinc levels between stunted children in the intervention group (718.8 ± 363.9 µg/dL) and those in the control group (143.4 ± 65.6 µg/dL), with a p-value of 0.000. A previous randomized controlled trial conducted among children aged 8 to 12 years found that zinc levels increased more in the intervention group receiving egg supplementation than in the control group.[23] Our study focused specifically on stunted children, most of whom were affected by chronic malnutrition. These findings suggest that even in a malnourished population, egg supplementation can significantly affect serum zinc levels.

A study by Caswell et al. involving toddlers aged 6 to 9 months who received a daily egg intervention for six months found that children in the intervention group had higher zinc levels after the intervention compared to the control group, although the difference was not statistically significant.[24] The difference from our study is that Caswell's study involved younger children aged 6 to 9 months. This raises the hypothesis that egg consumption may be more effective in improving zinc levels among older children. This hypothesis is supported by a study by Amenya, which found that older children still showed significantly higher zinc levels even when the intervention was administered only three times a week—compared to our study, in which younger children received eggs daily.[23]

Increased zinc levels provide essential materials for the function of zinc-dependent enzymes, such as superoxide dismutase (SOD), which catalyzes the dismutation of superoxide radicals (a type of free radical) and plays a role in regulating Nrf2. Without adequate zinc, the accumulation of reactive oxygen species (ROS) may increase, exacerbating oxidative stress and worsening the condition of stunted children by making them more susceptible to infections and further impairing various physiological processes. Zinc is closely associated with appetite regulation, and

maintaining adequate zinc levels is important to facilitate nutritional interventions. Low blood zinc levels contribute to reduced appetite, which is particularly concerning since nutritional intake is critical for the recovery of stunted children. Moreover, increasing zinc levels can enhance a compromised immune system and support catch-up growth, including proper bone development.[19, 25]

On average, eggs contain approximately 1.29 mg of zinc per 100 grams, along with a variety of other essential macro- and micronutrients. Children who are stunted also tend to have difficulty absorbing food content so that the nature of eggs as a food with high bioavailability can help the absorption of various nutrients, including zinc in eggs and other foods eaten by children. Improvement in zinc levels is known to repair or reverse damage caused by zinc deficiency, such as intracellular DNA damage, and also supports bone growth and development. Therefore, it is hoped that this intervention may help reverse some of the damage resulting from chronic malnutrition.

A study by Abdollahi et al., conducted in one of the most malnutrition-prevalent areas of Iran, reported that zinc supplementation in children aged 6 to 24 months resulted in a 0.5 cm greater increase in height in the intervention group compared to the control group.[26] In contrast, a study by Priyantini et al., which was conducted predominantly among healthy children, found no significant correlation between zinc intake and child growth when comparing body length from birth to age three.[19] This may suggest that the effect of zinc is more apparent in children with nutritional problems. The World Health Organization (WHO) has stated that although the available evidence remains inconsistent, zinc supplementation may help improve linear growth in children under five years of age.[27] However, no studies to date have specifically used eggs as a source of zinc supplementation to evaluate their effect on children's height. This presents an opportunity for future research.

A limitation of this study is the absence of baseline zinc level measurements prior to the intervention, which limits the ability to rule out the potential bias of pre-existing high zinc levels in the intervention group and highlights the need for future studies in more controlled settings. Nevertheless, this study serves as an initial investigation demonstrating the potential of eggs as a zinc source for stunted children. Additionally, this study did not account for variations in the nutritional content of eggs, which can fluctuate depending on the season and the source. There is also potential bias due to the widespread perception of eggs as a healthy protein source, possibly influencing both participants and researchers. Future studies should consider examining the impact of these nutritional variations and employ blinded methodologies to minimize bias and improve the reliability of the results.

Conclusion

In stunted children aged 2 to 5 years, serum zinc levels were significantly higher following 30 days of daily supplementation with one egg per day, supporting the potential of eggs as a practical nutritional intervention to address micronutrient deficiencies.

Acknowledgement

We would like to thank the laboratory assistant for their assistance in processing the samples.

Conflict of Interest

None declared

Funding Statement

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

References

1. Kementerian Kesehatan. Keputusan Menteri Kesehatan Republik Indonesia Nomor HK.01.07/Menkes/1928/ 2022 tentang Pedoman Nasional Pelayanan Kedokteran Tata Laksana Stunting. Jakarta: Kementerian Kesehatan; 2022.
2. Badan Kebijakan Pembangunan Kesehatan Kementerian Kesehatan. Buku saku hasil survei status gizi Indonesia (SSGI) 2022. Jakarta: Kementerian Kesehatan; 2022.
3. United Nations Children's Fund (UNICEF), World Health Organization (WHO), Bank IBfRaDTW. Levels and trends in child malnutrition: Unicef / who / world bank group joint child malnutrition estimates: Key findings of the 2023 edition New York: UNICEF and WHO; 2023 [28 April 2024]. Available from: https://data.unicef.org/wp-content/uploads/2023/05/ JME-2023-Levels-and-trends-in-child-malnutrition.pdf.
4. Suratri MAL, Putro G, Rachmat B, Nurhayati, Ristrini, Pracoyo NE, et al. Risk factors for stunting among children under five years in the province of east nusa tenggara (ntt), indonesia. Int J Environ Res Public Health. 2023;20(2). https://doi.org/10.3390/ijerph20021640
5. Aly GS, Shaalan AH, Mattar MK, Ahmed HH, Zaki ME, Abdallah HR. Oxidative stress status in nutritionally stunted children. Egyptian Pediatric Association Gazette. 2014;62(1):28-33. https://doi.org/10.1016/j.epag.2014. 02.003
6. Maxfield L, Shukla S, Crane JS. Zinc deficiency. Treasure Island (FL): StatPearls Publishing; 2023.
7. Sartikah. Efektivitas pemberian saluri (satu telur satu hari) terhadap tinggi badan pada balita stunting di Puskesmas Pakuhaji Kabupaten Tangerang Banten tahun 2022. Indonesian Scholar Journal of Nursing and Midwifery Science (ISJNMS). 2023;2(10):910-8. https://doi.org/10. 54402/isjnms.v2i10.361
8. Eide DJ. The oxidative stress of zinc deficiency. Metallomics. 2011;3(11):1124-9. https://doi.org/10.103 9/c1mt00064k
9. Olechnowicz J, Tinkov A, Skalny A, Suliburska J. Zinc status is associated with inflammation, oxidative stress, lipid, and glucose metabolism. J Physiol Sci. 2018;68(1):19-31. https://doi.org/10.1007/s12576-017-0571-7
10. Šulinskienė J, Bernotienė R, Baranauskienė D, Naginienė R, Stanevičienė I, Kašauskas A, Ivanov L. Effect of zinc on the oxidative stress biomarkers in the brain of nickel-treated mice. Oxid Med Cell Longev. 2019;2019:8549727. https://doi.org/10.1155/2019/8549727
11. National Institute of Health Office of Dietary Supplements. Zinc fact sheet for customer: NIH; 2022.
12. O'Connor JP, Kanjilal D, Teitelbaum M, Lin SS, Cottrell JA. Zinc as a therapeutic agent in bone regeneration. Materials (Basel). 2020;13(10). https://doi.org/10.3390 /ma13102211
13. Réhault-Godbert S, Guyot N, Nys Y. The golden egg: Nutritional value, bioactivities, and emerging benefits for human health. Nutrients. 2019;11(3). https://doi.org/10. 3390/nu11030684

14. Lonnerdal B. Dietary factors influencing zinc absorption. J Nutr. 2000;130(5S Suppl):1378S-83S. https://doi.org/10.1093/jn/130.5.1378S
15. Hafifah C. Telur mentah atau setengah matang: Bolehkah diberikan pada bayi anda? : IDAI; 2016 [28 April 2024]. Available from: https://www.idai.or.id/artikel/seputar-kesehatan-anak/telur-mentah-atau-setengah-matang-bolehkah-diberikan-pada-bayi-anda#:~:text=Hindari%20mengonsumsi%20telur%20mentah%20atau,telur%20harus%20dimasak%20hingga%20mengeras.
16. Headey D, Hirvonen K, Hoddinott J. Animal sourced foods and child stunting. Am J Agric Econ. 2018;100(5):1302-19. https://doi.org/10.1093/ajae/aay053
17. Iannotti LL, Lutter CK, Stewart CP, Gallegos Riofrío CA, Malo C, Reinhart G, et al. Eggs in early complementary feeding and child growth: a randomized controlled trial. Pediatrics. 2017;140(1). https://doi.org/10.1542/peds.2016-3459
18. Karlsson O, Kim R, Moloney GM, Hasman A, Subramanian SV. Patterns in child stunting by age: a cross-sectional study of 94 low- and middle-income countries. Matern Child Nutr. 2023;19(4):e13537. https://doi.org/10.1111/mcn.13537
19. Priyantini S, Nurmalitasari A, Am M. Zinc intake affects toddler stunting: a cross-sectional study on toddlers aged 3 years. Amerta Nutrition. 2023;7:20-6. https://doi.org/10.20473/amnt.v7i1.2023.20-26
20. Rahmah A, Yani D, Eriyani T, Rahayuwati L. Correlation mother's eduaction and received stunting information with mother's stunting knowledge. Journal of Nursing Care. 2023;6. https://doi.org/10.24198/jnc.v6i1.44395
21. Agustin L, Rahmawati D. Hubungan pendapatan keluarga dengan kejadian stunting. Indonesian Journal of Midwifery (IJM). 2021;4:30. https://doi.org/10.35473/ijm.v4i1.715
22. De Sanctis V, Soliman A, Alaaraj N, Ahmed S, Alyafei F, Hamed N. Early and long-term consequences of nutritional stunting: from childhood to adulthood. Acta Biomed. 2021;92(1):e2021168. https://doi.org/10.23750/abm.v92i1.11346
23. Amenya PCA, Annan RA, Apprey C, Kpewou DE, Annor IA. The effectiveness of egg supplementation on nutritional status, physical fitness and cognition of school-aged children (8–12 years) in Ho Municipality, Ghana. Human Nutrition & Metabolism. 2024;35:200246.https://doi.org/10.1016/j.hnm.2024.200246
24. Caswell BL, Arnold CD, Lutter CK, Iannotti LL, Chipatala R, Werner ER, et al. Impacts of an egg intervention on nutrient adequacy among young malawian children. Matern Child Nutr. 2021;17(3):e13196. https://doi.org/10.1111/mcn.13196
25. Maxfield L, Shukla S, Crane JS. Zinc deficiency. Treasure Island: StarPearls; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493231/.
26. Abdollahi M, Abdollahi Z, Fozouni F, Bondarianzadeh D. Oral zinc supplementation positively affects linear growth, but not weight, in children 6-24 months of age. Int J Prev Med. 2014;5(3):280-6.
27. World Health Organization (WHO). Zinc supplementation and growth in children [Internet]. WHO; 2023 [cited 1 April 2025]. Available from: https://www.who.int/tools/elena/interventions/zinc-stunting.

APGHN
Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Case Report

Endoscopic Management of a Distal Ileal Foreign Body in a Child with Developmental Delay – A Case Report

Anuradha Lenagala[1,2], Jeewan Samarasena[1,2]
[1]Post Graduate Institute of Medicine, University of Colombo, Colombo, Sri Lanka
[2]Lady Ridgeway Hospital for Children, Colombo, Sri Lanka

e-ISSN: 2830-5442

Corresponding author:
Anuradha Lenagala
anuradhalenagala@gmail.com

Published:
31st May 2025

DOI:
https://doi.org/10.58427/apghn.4.2.2025.73-77

Citation:
Lenagala A, Samarasena J. Endoscopic management of distal ileal foreign body in a child with developmental delay-a case report. *Arch Pediatr Gastr Hepatol Nutr.* 2025;4(2): 73-77

Abstract:

Background: Foreign body ingestion is a common problem in the paediatric age group, with most cases involving the upper gastrointestinal tract. Foreign bodies that pass through the oesophagus can be safely observed. Impaction in the bowel can cause intestinal obstruction or perforation. Complicated foreign bodies can be retrieved either surgically or endoscopically.

***Case*:** A 4-year-and-6-month-old girl with multiple medical conditions presented four days after the ingestion of two foreign bodies (Hair pins). The child was irritable and experienced a vague lower abdominal pain, which was more pronounced in the right iliac fossa (RIF). With conservative management and a rectal enema one foreign body passed with stool. Over the next day she exhibited increasing distress and worsening RIF tenderness. Colonoscopy without air insufflation revealed an impacted foreign body in the distal ileum about 10cm from the ileocecal valve. Successful retrieval improved her clinical status, and she was discharged two days later.

***Discussion*:** Blunt foreign bodies that passed beyond the duodenum require intervention only if they fail to pass in a standard time frame or if a complication arises. Initial conservative management was attempted as she did not have features of generalized peritonism. However, colonoscopy was performed due to worsening distress and localized peritoneal signs, especially given her complex medical background. The procedure was conducted without gas insufflation to avoid pneumoperitoneum in the event of a potential intestinal perforation. Successful retrieval alleviated her clinical symptoms.

Conclusion: Colonoscopy with ileal intubation is an effective method for retrieving impacted distal ileal foreign bodies in patients with localized peritoneal signs.

Keywords: colonoscopy, foreign body, ileal intubation, peritonism

Introduction

Foreign body ingestion is a common problem in the paediatric age group. The upper third of the oesophagus is the most common site of impaction.1 Most of the foreign bodies that pass through the oesophagus can be safely observed.[1, 2] Clinical presentation and examination findings may suggest complications related to a foreign body, such as features of intestinal obstruction or perforation.[3]

Evidence of complications or failure to pass the foreign body within an adequate time are indications for retrieval, either endoscopically or surgically.[3-6] In the literature, only a few cases have been documented on the colonoscopic retrieval of ingested foreign bodies from the ileocecal valve. However, there are no reported cases on the endoscopic retrieval of foreign bodies from the distal ileum particularly in the presence of localized peritonism.

Additionally, in previously reported cases the children were previously well, or their past medical history was not mentioned. In this case we report a 4-year-and 6-month-old girl with multiple medical conditions who presented with an ingested foreign body impacted in the distal ileum, accompanied by features of localized peritonism and was successfully retrieved via colonoscopy and ileal intubation.

Case

A 4-year-and-6-month-old girl was transferred to our tertiary care facility from a nearby base hospital for further management after ingesting two foreign bodies (Hair pins) four days earlier, which she failed to pass. She had been diagnosed with microcephaly and global developmental delay since early childhood, but her family had defaulted on follow-up for the past year due to financial constraints. She was able to walk with a limp for short distances and could vocalize one to two words at her current age. However, over the past two days, she had completely refused to walk or talk to her mother.

She did not have a fever, and her hemodynamic parameters were within the normal range. She had a vague lower abdominal tenderness, which was more prominent in the right iliac fossa (RIF). Blood investigations revealed no abnormalities, and the initial X-ray showed two foreign objects in the lower abdomen **(Figure 1)**. A rectal enema was administered, and one foreign body **(Figure 1-Green arrow)** was expelled with stools.

Over the next day she exhibited increasing distress and refused to eat. Her abdominal examination showed a slight increase in tenderness over RIF, though her hemodynamic parameters remained stable.

Colonoscopy with ileal intubation was performed without gas insufflation, and a foreign body was found impacted in the distal ileum about 10 cm from the ileocecal valve **(Figure 2)**. It was successfully retrieved using a wide-angle colonoscopic biopsy forceps **(Figure 3)**. Her clinical status improved over the next two days, and she was discharged on the second post procedure day. She returned two weeks later with complete recovery, and necessary arrangements were made to prevent future incidents and ensure further medical follow-up.

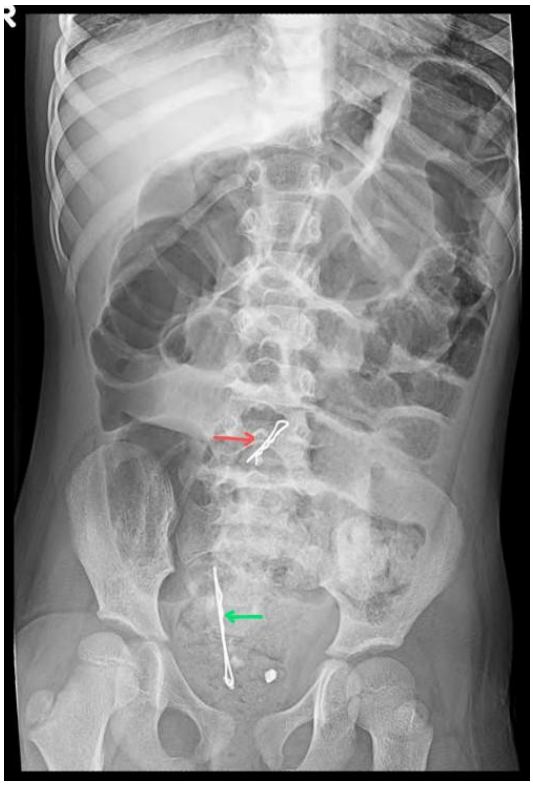


Figure 1. X-ray after admission showing two foreign bodies

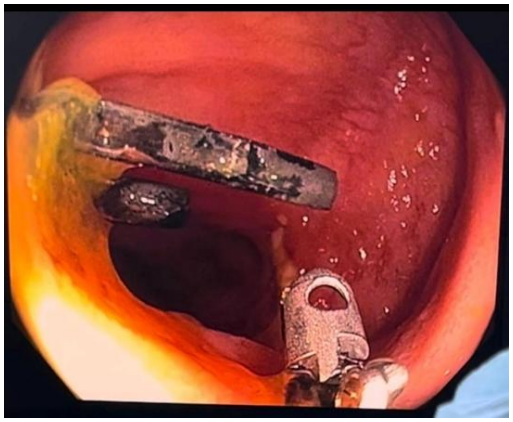


Figure 2. Endoscopic appearance of the impacted foreign body in the distal ileum

Figure 3. Foreign body after retrieval

Discussion

Endoscopic removal of upper gastrointestinal foreign bodies is a well-established and long-practiced technique.[7, 8] However, colonoscopy for removal of impacted foreign bodies is less commonly performed, as many objects that pass through the oesophagus are likely to traverse the bowel without intervention.[1-3] Blunt, small objects beyond the duodenum are extracted only if complications arise or if they fail to pass after an adequate time for spontaneous passage.[3]

In this case the patient was transferred to a tertiary care facility to access paediatric surgical expertise, as she exhibited some signs of localized peritonism. At our institute, initial management was conservative, as there were no obvious signs of peritonism, and she remained hemodynamically stable. A rectal enema was administered to clear distal bowel and relieve a possible distal obstruction.[9] Following the enema, one foreign body was expelled with stools.

On the second day at our institute, she began showing increased distress and worsening RIF tenderness. However, there was still no evidence of generalized peritonism. On the other hand, assessing this child was particularly challenging due to her preexisting medical conditions, and her overall developmental age was closer to one year.[10]

At this stage, a computed tomography (CT) scan could have been ordered to diagnose an intestinal perforation.[11] However, identifying a small perforation in close proximity to a metallic foreign body would have been difficult due to imaging artifacts, and a negative result could have given a false sense of reassurance.[12]

Colonoscopy was preferred over laparoscopy as there was no generalized peritonitis, and the foreign body was located near the RIF, suggesting proximity to the cecum **(Figure 1-Red arrow**). Colonoscopy was performed without gas insufflation, as high-pressure gas could have resulted in pneumoperitoneum if a perforation was present.[13] 13 Successful retrieval of the foreign body led to improvement in her clinical condition.

In retrospect, the vague tenderness in the right lower abdomen may have resulted from foreign body impaction causing local irritation of the bowel and peritoneum. A tiny perforation which sealed off completely is another possibility.

Conclusion

Colonoscopy with ileal intubation is a preferable option to retrieve foreign objects impacted in the distal ileum. Mild localized tenderness is not always indicative of perforation or peritonitis. Care should be taken to avoid excessive gas insufflation to prevent potential catastrophic events.

Acknowledgement

The subject gave informed consent, and patient anonymity was preserved. Authors wish to acknowledge the other medical staff who took care of the patient.

Conflict of Interest

The authors have no conflicts of interest to declare.

Funding Statement

This study was not supported by any external funding.

References

1. Jayachandra S, Eslick GD. A systematic review of paediatric foreign body ingestion: Presentation, complications, and management. International Journal of Pediatric Otorhinolaryngology. 2013;77(3):311-7. https://doi.org/10.1016/j.ijporl.2012.11.025
2. Antoniou D, Christopoulos-Geroulanos G. Management of foreign body ingestion and food bolus impaction in children: A retrospective analysis of 675 cases. Turk J Pediatr. 2011;53(4):381-7.
3. Norris N, Barth B. Foreign body ingestion in children [Internet]. Amsterdam: Elsevier; 2023 [cited 2025 March 18]. Available from: https://www.clinicalkey.com/#!/content/clinical_overview/67-s2.0-V2563.
4. Lone YA, Kanojia RP, Samujh R, Rao KL. Laparoscopic retrieval of unusual intra-abdominal foreign bodies in children. J Indian Assoc Pediatr Surg. 2016;21(4):184-6. https://doi.org/10.4103/0971-9261.186549
5. Doya LJ, Mohammad MF, Mohammad A, Ibrahim A. Colonoscopy for foreign body retrieval in ileocecal valve: A rare case report. Oxf Med Case Reports. 2023;2023(8):omad088. https://doi.org/10.1093/omcr/omad088
6. Lee EJ, Yang HR, Cho JM, Ko JS, Moon JS. Two cases of colonoscopic retrieval of a foreign body in children: A button battery and an open safety pin. Pediatr Gastroenterol Hepatol Nutr. 2017;20(3):204-9. https://doi.org/10.5223/pghn.2017.20.3.204
7. Sugawa C, Ono H, Taleb M, Lucas CE. Endoscopic management of foreign bodies in the upper gastrointestinal tract: A review. World J Gastrointest Endosc. 2014;6(10):475-81. https://doi.org/10.4253/wjge.v6.i10.475
8. Yoo DR, Im CB, Jun BG, Seo HI, Park JK, Lee SJ, et al. Clinical outcomes of endoscopic removal of foreign bodies from the upper gastrointestinal tract. BMC Gastroenterol. 2021;21(1):385. https://doi.org/10.1186/s12876-021-01959-3
9. Bekkali NL, van den Berg MM, Dijkgraaf MG, van Wijk MP, Bongers ME, Liem O, Benninga MA. Rectal fecal impaction treatment in childhood constipation: Enemas versus high doses oral peg. Pediatrics. 2009;124(6):e1108-15. https://doi.org/10.1542/peds.2009-0022
10. Centers for Disease Control and Prevention. Important milestones: Your baby by two months [Internet]. Atlanta: CDC; 2023 [cited 2025 March 18]. Available from: https://www.cdc.gov/ncbddd/actearly/milestones/milestones-2mo.html.
11. Tseng HJ, Hanna TN, Shuaib W, Aized M, Khosa F, Linnau KF. Imaging foreign bodies: Ingested, aspirated, and inserted. Ann Emerg Med. 2015;66(6):570-82.e5. https://doi.org/10.1016/j.annemergmed.2015.07.499
12. Sharma S, Kaushal A, Patel S, Kumar V, Prakash M, Mandeep D. Methods to address metal artifacts in post-processed ct images - a do-it-yourself guide for orthopedic surgeons. J Clin Orthop Trauma. 2021;20:101493. https://doi.org/10.1016/j.jcot.2021.101493
13. Kozarek RA, Earnest DL, Silverstein ME, Smith RG. Air-pressure-induced colon injury during diagnostic colonoscopy. Gastroenterology. 1980;78(1):7-14.

APGHN Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Case Report

Silent Splenic Infarction Following Infectious Mononucleosis Associated with Antiphospholipid Antibodies in a Pediatric Patient: A Case Report

Davide Scarponi[1], Branislava Ćosić[1], Costanza Fiorilli[1], Anna Rita Di Biase[2], Lorenzo Iughetti[1]
[1]University of Modena and Reggio Emilia, Modena, Italy
[2]Azienda Ospedaliero - Universitaria of Modena, Modena, Italy

e-ISSN: 2830-5442

Corresponding author:
Davide Scarponi
davide.scarp93@gmail.com

Published:
31st May 2025

DOI:
https://doi.org/10.58427/apghn.4.2.2025.78-82

Citation:
Scarponi D, Ćosić B, Fiorilli C, Di Biase AR, Iughetti L. Silent splenic infacrtion following infectious mononucleosis associated with antiphospolipid antibodies in a pediatric patient: a case report. *Arch Pediatr Gastr Hepatol Nutr.* 2025;4(2): 78-82

Abstract:

Background: The splenic infarction (SI) is a rare complication of infectious mononucleosis (IM), especially in paediatric population. The clinical presentation of this condition can vary widely, but it is most often symptomatic (e.g. pain in the left upper quadrant).

***Case*:** We report a case of a previously healthy 12 year old female with a silent splenic infarction (SI) following IM by Epstein-Barr virus (EBV), positive for antiphospholipid anti-cardiolipin IgM antibodies (ACA IgM).

***Discussion*:** Numerous pathogenetic mechanisms have been proposed for the SI in the course of IM. The definitive diagnosis of SI is made with CT; in our case, given the lack of urgent clinical indications, the definitive diagnosis was made with MRI. Follow-up was continued using ultrasound and therapeutic management was conservative.

Conclusion: We describe a rare case of asymptomatic splenic infarction, in a girl with no underlying predisposing condition. It is important for a pediatrician to be aware of this possible complication and its correct therapeutic management.

Keywords: antiphospholipid antibodies, epstein-barr virus, mononucleosis, pediatric, splenic infarction

Introduction

Splenic infarction (SI) is a complication of various pediatric pathologies: haematological (10%), cardioembolic (22%), discoagulopathies (22%), sepsis (10%), vascular disease of the spleen or connective tissue disorders. It can also be a rare complication of infectious mononucleosis (IM) and for this reason it is often underdiagnosed and remains unrecognised in the absence of associated symptoms (e.g. pain in the left upper quadrant). The association with IM was found only in 3 out of 49 patients described in the largest case series of SI in the literature.[1] Heo et al. reported between 1961 and 2015 19 cases of splenic infarction following IM by EBV infection 2. There are even fewer cases in the pediatric population.[2]

Case

The 12-year-old girl presented to the Pediatric Emergency Room with asthenia and headache in the course of IM caused by EBV, previously diagnosed by her pediatrician (EBV IgM > 160 S/CO [positive ≥ 40]; IgG 21.1 S/CO [positive ≥ 20]; EBNA negative). Additionally, an abdominal ultrasound (US), performed several days earlier, showed splenomegaly with a bipolar diameter of 15 cm without focal lesions and two accessory spleens measuring 1 cm each. Her medical history was unremarkable. Upon arrival, she presented with fever (40°C), exudative tonsillitis, splenomegaly, and signs of moderate dehydration. Laboratory tests revealed a mild rise in inflammatory biomarkers (CRP 3,1 mg/dl). She was admitted for observation and supportive care. Her clinical course was regular, and she was discharged after four days. Abdominal US follow-up, performed two weeks post-discharge, showed a 2 cm hypoechoic area suggestive of SI. The patient was otherwise well and no abdominal trauma was reported. As a result, she was re-hospitalized for further evaluation. A contrast MRI confirmed the presence of subacute splenic haemorrhagic infarction (**Figure 1.**) with no evidence of splenic rupture, malformations or vascular anomalies. Further diagnostic work-up that included thrombophilia screening, revealed presence of ACA IgM (25 MPL-U/ml [negative < 10 MPL-U/ml]); ACA IgG were negative; PT INR, aPTT ratio, liver and kidney function, ESR, haemoglobin electrophoresis, peripheral blood smear, homocysteinemia, ANA, anti-beta2-glycoprotein antibodies, ANCA, APC resistance, Protein C, Protein S, Factor VIII, Factor V and II mutations, Apolipoprotein A1 and B, C3, C4 were all within range. Additionally, elevated cholesterol levels were noted, due to previously undiagnosed familial hypercholesterolemia (cholesterol 415 mg/dl, HDL 76 mg/dl, LDL 281 mg/dl). Echocardiography and supra-aortic trunk US were normal. The clinical course remained uneventful. The SI was managed conservatively; the patient reported no pain or additional symptoms. She was discharged in good condition after four days. Subsequent follow-up showed complete resolution of the lesion on the US and negativization of ACA after two months.

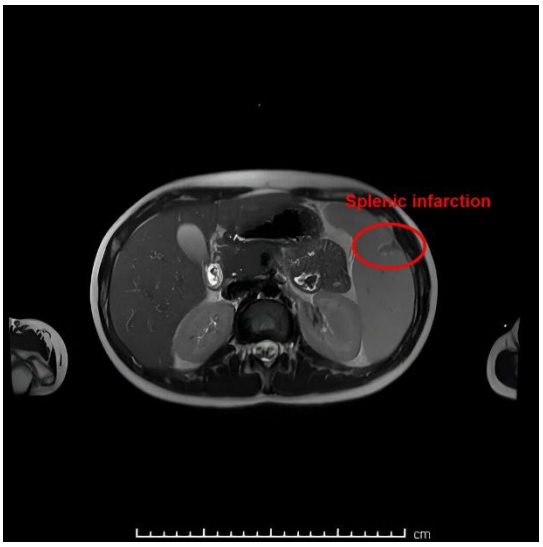


Figure 1. MRI image of splenomegaly and splenic infarction: enlarged spleen with a bipolar diameter of 13.8 cm; in the inferior anterior segment there is a triangular subcapsular area with a base of 2x1 cm and cranio-caudal extension of 1.5 cm, compatible with the early phase subacute haemorrhagic infarct.

Discussion

Splenic rupture is a rare complication of IM affecting 0.5-1% of patients, whilst the incidence of SI is unknown due to the low number of cases reported to date. Numerous pathogenetic mechanisms have been proposed for the SI in the course of IM. Some authors suggest that EBV infection may induce hypoxemia, high level of circulating immune complexes (which promote leucocyte adhesion and aggregation) or transient hypercoagulability state. Others focus on the potential role of transient antiphospholipid antibody (aPLs) production during EBV infection.[3-5] aPLs are a heterogeneous group of autoantibodies targeting phospholipid-binding proteins, such as β2-glycoprotein I (β2GPI) and cardiolipin. Persistent, high titer aPLs are a hallmark of antiphospholipid syndrome (APS) and are linked to thrombotic or obstetric complications.[6] Viral infections, including EBV, induce proliferation of B lymphocytes with a consequent production of various antibodies, including aPLs. These antibodies are typically transient (disappearing within 1-4 years), of low titer, often of the IgM isotype and usually do not corelate with the risk of thrombosis or other manifestations of APS.[7, 8]

Nonetheless, some studies have reported possible association between transient aPL positivity and ischemic events, suggesting that under certain conditions, these antibodies may have pathogenic potential.[9-11] Additionally, temporary reduction in anticoagulation factors such as Protein C or Protein S have been described in the context of acute infections.[12] Splenomegaly may further exacerbate the risk of ischemia

by creating a mismatch between oxygen supply and metabolic demand in splenic tissue.

In our case, we inferred that EBV infection triggered a transient increase of aPLs that could have played a role in pathogenesis of SI, as hypothesized in several articles.[4, 5, 7, 13, 14] Splenomegaly, that may have contributed to SI, was described in almost all cases, including ours. Furthermore, our patient was also found to have previously undiagnosed familial hypercholesterolemia (FH), a known prothrombotic condition, which may have further contributed to the thrombotic risk. Beyond the various hypotheses proposed, the mechanisms underlying SI pathogenesis remain unclear and need further research.

In reported case series it is uncommon for SI following EBV infection to be asymptomatic.[2] The definitive diagnosis of SI is made using CT.[1] However, in our case, considering the lack of urgent indications, the definitive diagnosis was made using MRI, to avoid radiation exposure. Although ultrasound has a low sensitivity in the detecting SI, it is useful for initial assessment and longitudinal monitoring of the lesion. The US follow-up of our patient documented a complete resolution of SI after two months. There is no specific treatment of SI apart from splenectomy, which should be considered only in case of surgical complications or in an unstable patient.[4]

Conclusion

In conclusion, we reported the atypical case of silent SI associated with the presence of ACA, a rare complication of IM, especially in pediatric population and in the absence of significant clinical history. It is important for a pediatrician to be aware of this possible complication and its correct therapeutic management. In case of US suspicion of SI in an asymptomatic, stable pediatric patient, it is possible to use MRI for a definitive diagnosis, when available. Subsequent follow-up can be continued with US. Surgical therapy should be reserved for selected cases with clinical instability.

Acknowledgement

This case report has been published with the consent of the patient parents. The authors would like to thank the patient and their parents.

Conflict of Interest

No potential conflict of interest was reported by the authors.

Funding Statement

This study was not supported by any external funding.

References

1. Antopolsky M, Hiller N, Salameh S, Goldshtein B, Stalnikowicz R. Splenic infarction: 10 years of experience. Am J Emerg Med. 2009;27(3):262-5. https://doi.org/10.1016/j.ajem.2008.02.014
2. Heo DH, Baek DY, Oh SM, Hwang JH, Lee CS, Hwang JH. Splenic infarction associated with acute infectious mononucleosis due to epstein-barr virus infection. J Med Virol. 2017;89(2):332-6. https://doi.org/10.1002/jmv.24618
3. Choi B, Kwon B, Kim GB, Jeon H-Y, Cheon J-E, Bae E, et al. A case of adolescent kawasaki disease with epstein-barr virus-associated infectious mononucleosis complicated by splenic infarction. Korean Journal of Pediatrics. 2009;52:1029. https://doi.org/10.3345/kjp.2009.52.9.1029
4. Naviglio S, Abate MV, Chinello M, Ventura A. Splenic infarction in acute infectious mononucleosis. J Emerg Med. 2016;50(1):e11-3. https://doi.org/10.1016/j.jemermed.2015.09.019
5. van Hal S, Senanayake S, Hardiman R. Splenic infarction due to transient antiphospholipid antibodies induced by acute epstein-barr virus infection. J Clin Virol. 2005;32(3):245-7. https://doi.org/10.1016/j.jcv.2004.07.013
6. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (aps). J Thromb Haemost. 2006;4(2):295-306. https://doi.org/10.1111/j.1538-7836.2006.01753.x
7. Ben-Chetrit E, Wiener-Well Y, Fadeela A, Wolf DG. Antiphospholipid antibodies during infectious mononucleosis and their long term clinical significance. J Clin Virol. 2013;56(4):312-5. https://doi.org/10.1016/j.jcv.2012.12.011
8. von Landenberg P, Döring Y, Modrow S, Lackner KJ. Are antiphospholipid antibodies an essential requirement for an effective immune response to infections? Ann N Y Acad Sci. 2007;1108:578-83. https://doi.org/10.1196/annals.1422.060
9. Carrasco M, Galarza-Maldonado C, Mendoza-Pinto C, Escárcega R, Cervera R. Infections and the antiphospholipid syndrome. Clinical reviews in allergy & immunology. 2009;36:104-8. https://doi.org/10.1007/s12016-008-8103-0
10. Abdel-Wahab N, Lopez-Olivo MA, Pinto-Patarroyo GP, Suarez-Almazor ME. Systematic review of case reports of antiphospholipid syndrome following infection. Lupus. 2016;25(14):1520-31. https://doi.org/10.1177/0961203316640912
11. Serrano M, Espinosa G, Cervera R, Serrano A. Covid-19 coagulopathy and antiphospholipid syndrome. Revista Colombiana de Reumatología. 2022;29:S25-S34. https://doi.org/10.1016/j.rcreu.2021.02.013
12. Gang MH, Kim JY. Splenic infarction in a child with primary epstein-barr virus infection. Pediatr Int. 2013;55(5):e126-8. https://doi.org/10.1111/ped.12143
13. Turrian U. Splenic infarction after epstein-barr virus infection: Case report. Annals of Clinical Case Reports. 2021;6. https://doi.org/10.25107/2474-1655.2045
14. Khan S, Saud S, Khan I, Prabhu S. Epstein barr virus-induced antiphospholipid antibodies resulting in splenic infarct: a case report. Cureus. 2019;11(2):e4119. https://doi.org/10.7759/cureus.4119

APGHN
Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Literature Review

CMV-Positive Biliary Atresia in Infants: A Review of Prognosis and Therapeutic Impact

Qonita Rahmadiena[1], Nailah Rahmah[1], Mulya Rahma Karyanti[2], Himawan Aulia Rahman[3]
[1]Departement of Child Health, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia
[2]Infection and Tropical Disease Division, Departement of Child Health, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia
[3]Gastroenterology and Hepatology Division, Departement of Child Health, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

e-ISSN: 2830-5442

Corresponding author:
Qonita Rahmadiena
qonita.diena@gmail.com

Published:
31st May 2025

DOI:
https://doi.org/10.58427/apghn.4.2.2025.83-96

Citation:
Rahmadiena Q, Rahmah N, Karyanti MR, Rahman HA. CMV-positive biliary atresia in infants: a review of prognosis and therapeutic impact *Arch Pediatr Gastr Hepatol Nutr.* 2025;4(2): 83-96

Abstract:

Background: Biliary atresia (BA) is a progressive cholangiopathy of infancy that can lead to end-stage liver disease and is the leading indication for pediatric liver transplantation. Among various proposed etiologies, cytomegalovirus (CMV) infection has emerged as a significant factor, giving rise to a distinct clinical subset known as CMV-positive BA.

Discussion: CMV-positive BA is frequently associated with delayed diagnosis, increased incidence of postoperative cholangitis, and advanced liver fibrosis at initial presentation. These features contribute to lower rates of jaundice clearance and native liver survival. Mortality is also higher in CMV-positive patients than in their CMV-negative. Diagnostic methods include performing polymerase chain reaction (PCR) tests on saliva, urine, or dried blood spot samples, as well as conducting abdominal ultrasound examinations that focus on identifying specific indicators, such as the triangular cord sign, which is commonly observed in patients with BA. Antiviral therapy, particularly with ganciclovir or valganciclovir, shows promise in improving native liver outcomes in CMV-positive BA patients. Early surgical intervention remains critical, yet CMV-positive BA often presents later, worsening prognosis. Preventive strategies are under investigation, including maternal CMV screening and neonatal testing.

Conclusion: Early identification and tailored antiviral intervention may play a critical role in altering the disease trajectory. Increased awareness of CMV-positive BA is essential for timely diagnosis and optimal management. This review emphasizes the need to recognize CMV-positive BA as a clinically important biliary atresia subset with distinct pathophysiology and worse prognosis, underscoring the importance of early CMV screening and targeted antiviral therapy.

Keywords: biliary atresia, cytomegalovirus infection, prognosis

Introduction

Biliary atresia (BA) is a cholangiopathy affecting the intra- and extrahepatic bile ducts, leading to liver fibrosis, portal hypertension, and eventual liver failure.[1] Viral infections have long been hypothesized to contribute to the development of biliary atresia (BA), with several viruses, including Reovirus 3, Epstein-Barr virus (EBV), Cytomegalovirus (CMV), and human papillomavirus (HPV), detected in the livers of BA patients. Notably, CMV has been identified in 60% of BA cases in China.[2]

The role of viruses in initiating or causing biliary atresia (BA) has been debated for at least 30 years but without a definitive consensus. Of all the possible viruses proposed, CMV appears to have the strongest evidence. Some reports indicate that infections with reovirus 3, rotavirus C, or cytomegalovirus (CMV) could be important. The hypothesis of a viral etiology is further supported by suggestions of an uneven distribution of the birth months in patients with BA.[3]

Cytomegalovirus (CMV) has emerged as one of the most clinically significant potential contributors to biliary atresia (BA). Its involvement was first noted in a Swedish study that detected CMV DNA in around half of BA cases, along with an IgM immune response localized to the canalicular membranes of liver cells. Building on this, Brindley et al. found a CMV-specific T cell response in liver tissue in just over 50% of BA infants in a U.S. study, which was linked to higher plasma CMV IgM levels.[4] This immune response was also associated with a decrease in circulating regulatory T cells (Tregs).[5]

Interestingly, the rate of CMV exposure observed in these studies is significantly higher than in some European populations, such as the 10% reported by the authors and 11% in a German cohort.[6, 7] These higher rates are more aligned with data from China—for instance, Xu et al. detected the CMV-pp65 antigen in 60% (51 out of 85) of liver samples from BA patients, a figure much greater than for other viruses like Reovirus 1.[8]

A meta-analysis study by Mohamed et al, showed that CMV was detected in 25.4% (95% CI 15.9%–38.0%) of the patients with BA. But, in their subgroup analysis, the detection of CMV infection in patients with BA was higher in the Asian studies (37.9%) than in European and American studies (25.5% and 15.3%, respectively).[9]

Congenital cytomegalovirus (CMV) infection occurs in approximately 0.2% to 2.2% of all live births, while perinatal transmission is even more frequent, ranging from 10% to 60% within the first six months of life. Perinatal CMV infection typically occurs through exposure to maternal genital secretions or breastmilk. Although most

perinatal CMV infections are asymptomatic, they can sometimes lead to cholestasis, which may mimic the symptoms of biliary atresia.[10]

Davenport further classified CMV-positive BA as a distinct subgroup of the disease, characterized by the presence of immunoglobulin M (IgM) antibodies against CMV in liver biopsy specimens and onset during the perinatal period.[11] CMV-positive BA is also defined by a positive polymerase chain reaction (PCR) test for CMV in saliva, urine, or dried blood spot (DBS) samples collected within the first three weeks of life.[12] Hereafter, this condition will be referred to as CMV-positive BA throughout this manuscript.

Evidence suggests that active CMV infection is associated with a poorer prognosis in patients with biliary atresia. CMV-positive infants tend to experience delayed jaundice clearance and slower recovery following Kasai portoenterostomy. Additionally, they have a higher incidence of cholangitis, reduced native liver survival, and increased mortality rates compared to CMV-negative patients.[6]

This literature review aims to introduce the entity of biliary atresia associated with CMV infection, explain its impact on infant health, and encourage healthcare professionals—especially doctors—to be more aware of this condition in order to ensure proper management and prevent poor outcome in the future.

Methodolgy

This literature review was conducted using a structured literature search based on the PICO framework, where **P** (Population) refers to perinatal patients with biliary atresia, **I** (Intervention) indicates no specific intervention, **C** (Comparison) involves CMV-positive versus CMV-negative infection status, and **O** (Outcome) focuses on prognosis and therapeutic outcomes in CMV-positive and CMV-negative biliary atresia patients. The search was performed using the PubMed database with several keywords, including *"biliary atresia," "CMV-positive BA," "prognosis,"* and *"antiviral therapy"*.

CMV-positive Biliary Atresia

What is CMV-positive biliary atresia, and how does it differ from other types of biliary atresia?

Diagnosis of CMV infection is confirmed when PCR of CMV is positive within three weeks after birth. Various methods have been explored for diagnosing congenital CMV infection using samples such as saliva, urine, and dried blood spots (DBS) collected from newborns. The heels of neonates were punctured and capillary blood was blotted onto filter paper and dried. Traditionally, culture-based testing of urine

and saliva has been the gold standard for identifying infants with congenital CMV infection. However, these methods are not easily automated, making them unsuitable for large-scale newborn screening. Laboratory tests using easily obtainable clinical samples from infants are essential for timely diagnosis. While viral isolation remains the most reliable method for confirming infection, it is labor-intensive, time-consuming, and impractical for large-scale use. Additionally, collecting urine samples using sterile bags is technically challenging, further limiting its feasibility for widespread screening. Early detection of congenital CMV infection is crucial for effective monitoring and reducing long-term complications. BA diagnosis can also relies on imaging, liver function tests, and liver biopsy.[12]

Patients with biliary atresia who present with cholestasis (reduced bile flow) and persistent jaundice beyond 14 days of age typically show elevated total bilirubin levels in laboratory findings. This is characterized by direct bilirubin exceeding 1 mg/dL (17.1 μmol/L; when total bilirubin is <5 mg/dL [85.5 μmol/L]) or greater than 20% of total bilirubin (when total bilirubin is >5 mg/dL [85.5 μmol/L]).[13]

These results strongly indicate cholestasis. Additionally, elevated liver function tests (AST and ALT) suggest hepatocellular injury.[14] Additionally, a study by Hasohah et al., obtained that jaundice is the most common clinical feature of CMV infection in infancy. Hyperbilirubinemia or cholestasis (100%) and increased level of aminotranferases serum (77%).[15] Similar findings were reported in a study conducted by Reddy et al., most (71.7%) infants with CMV had raised SGPT level. But in their study, gamma-glutamyl transferase (GGT) was higher in only 30% of infants while Hasosah et al. found higher GGT in 77% of cases.[15, 16]

Abdominal ultrasound findings using 2 phase ultrasonography (USG) is also required to diagnose BA, such as parenchymal abnormalities, hepatic vascular system irregularities, spleen abnormalities, or the presence of cysts, further aid in the diagnostic evaluation.[14] Abdominal ultrasonography, as a non-invasive diagnostic tool, plays a pivotal role in confirming biliary atresia, especially as an initial screening method in infants presenting with elevated conjugated bilirubin levels.[17] It allows for early, prompt, and accurate diagnosis, thereby enabling timely surgical intervention when indicated.[17, 18] A recent study by Anindita et al. reported that abdominal ultrasound demonstrated an overall diagnostic accuracy of 73.7%.[17] One of the key ultrasonographic markers is the triangular cord (TC) sign, defined objectively as an echogenic anterior wall of the right portal vein (EARPV) measuring more than 4 mm on longitudinal imaging.[19] Additional sonographic findings include abnormal gallbladder morphology ($p = 0.01$) and the presence of hepatic subcapsular flow ($p = 0.04$).[17] Furthermore, the use of color Doppler ultrasonography has shown sensitivity and specificity of 100% and 86%, respectively, in detecting hepatic subcapsular flow.[20]

Another study by Lee et al. identified abnormal gallbladder morphology and increased triangular cord thickness (greater than 3.4 mm) as the most reliable predictors for diagnosing biliary atresia.[21] In a study involving 188 children with cholestasis who underwent two-phase ultrasonography, the diagnostic accuracy was found to be 86.3% following a 4-hour fasting period and 93.5% in the non-fasting state. The overall diagnostic accuracy for biliary atresia was 88.7% (157 out of 177 patients).[18]

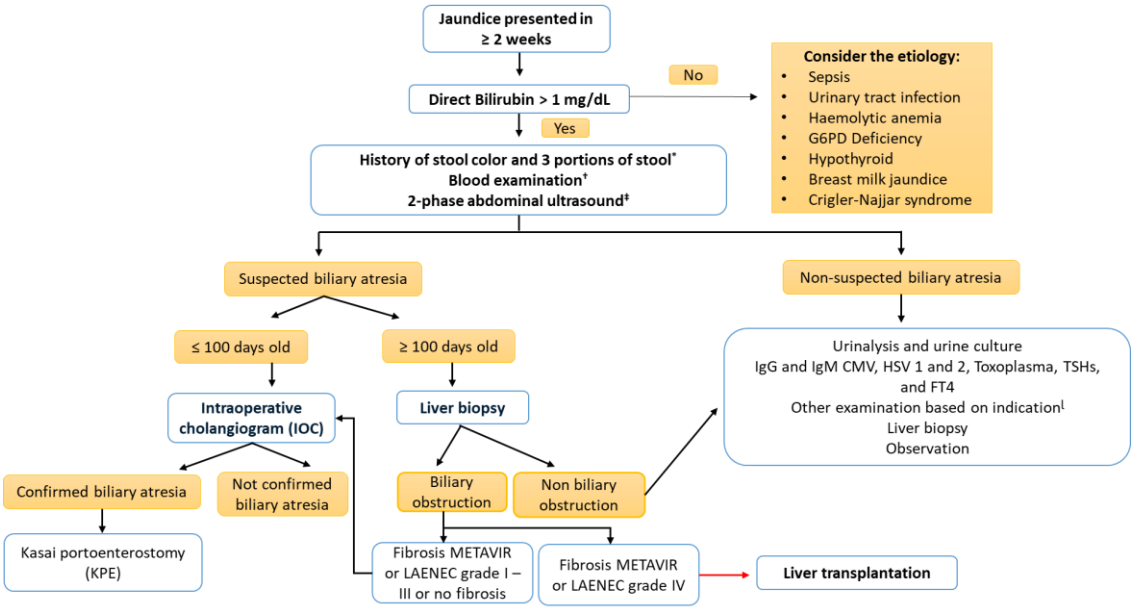
In cases of fetal CMV infection, the presence of specific IgM antibodies to cytomegalovirus (CMV) detected after the fourth week of life may suggest either congenital or perinatal infection. Studies conducted in Brazil have found that positive IgM to CMV prevalence between the second and fourth months of life ranges from 8.1% to 14.7%. When combined with the detection of CMV in urine through viral isolation in cultured cells, the prevalence of infection increases to approximately 30.9% to 38%. Importantly, the majority of these cases are asymptomatic.[22]

Dried blood spots, routinely collected from all newborns, have been investigated as a potential sample for polymerase chain reaction (PCR)-based CMV testing. However, a large-scale newborn screening study by Boppana et al. found that real-time PCR testing of dried blood spots had low sensitivity, failing to detect the majority of CMV-infected infants when compared to the standard saliva rapid culture method. This highlights the ongoing challenges in achieving sufficient sensitivity with dried blood spot testing for effective newborn CMV screening.[23]

CMV-positive BA is one of the theories underlying the pathogenesis of biliary atresia. [5] However, it is important for clinicians to be aware of other potential causes. Approximately 3% to 20% of children with biliary atresia present with an associated syndrome or other congenital abnormalities.[5, 24] Another proposed pathogenesis, aside from CMV-positive biliary atresia, is the Biliary Atresia Splenic Malformation (BASM) syndrome. Infants with BASM often present with unusual anomalies such as polysplenia (or occasionally asplenia), vascular abnormalities (including a preduodenal portal vein or absence of the inferior vena cava), situs inversus, and congenital heart defects. A case report by Allotey et al. described additional congenital anomalies such as esophageal atresia, jejunal atresia, and cat eye syndrome.[5, 25]

[26]Cystic biliary atresia (CBA) is the third form, which can be detected prenatally through fetal sonography.[5] Caponcelli et al. found that out of 270 infants with biliary atresia, 29 (9 males) were diagnosed with the cystic form. Antenatal ultrasonography detected abnormalities in 12 (41%) of these infants at a median gestational age of 22 weeks (ranging from 17 to 34 weeks). All infants exhibited conjugated jaundice, with a median total serum bilirubin concentration of 159 μmol/L (range: 50–337 μmol/L) at the time of surgery.[26]

The last but not least, the largest group is isolated biliary atresia (accounting for 70–80% of cases), formerly known as perinatal or acquired BA. Harpavat et al. reported that the exact onset of this type of biliary atresia remains unknown.[27] In contrast to CMV-positive BA—where patients are typically older at the time of diagnosis and undergo Kasai surgery later—isolated biliary atresia is believed to be acquired sometime after birth in otherwise healthy infants.[5, 27] However, the elevated direct/conjugated bilirubin (DB/CB) levels detected shortly after birth in their study suggest that biliary obstruction may already be present at birth. Based on these findings, the authors recommend screening all newborns for elevated DB/CB levels regardless of clinical appearance and total bilirubin (TB) levels. Hopefully these recommendations have the potential to transform the management of biliary atresia by enabling earlier identification of affected infants, even before clinically significant liver injury occurs.[27] **Figure 1.** presents the diagnostic algorithm for jaundice during the perinatal period.



* Stool color cards No. 1, 2, and 3 are used as early screening tools.

† Laboratory findings may show elevated levels of complete blood count (CBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase, albumin, prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT), and blood glucose. A GGT level >250 U/L is highly suggestive of biliary atresia.

‡ The procedure should be preceded by a minimum fasting period of four hours to ensure optimal examination conditions.

Clinical suspicion of biliary atresia is based on the following features: normal birth weight, persistent pale or acholic stools, GGT >250 U/L, and characteristic ultrasound (USG) findings, including a non-contractile gallbladder, a small or absent gallbladder, presence of a triangular cord sign, a hepatic artery to portal vein ratio >0.45, hepatic artery diameter >1.5 mm, and detectable arterial flow in the subcapsular region of the liver.

Figure 1. Diagnostic algorithm for biliary atresia in the perinatal period.[28, 29]

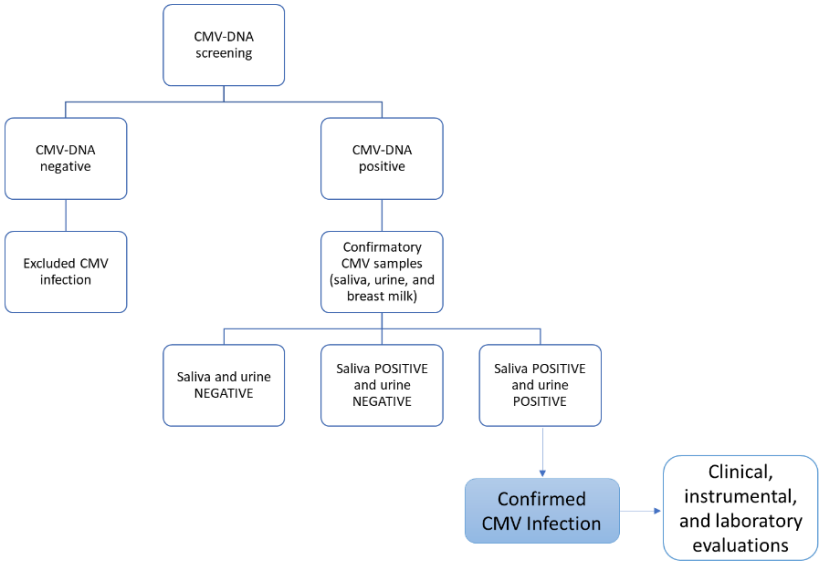


Figure 2. Diagnostic flowchart for Congenital or Perinatal CMV infection.[28, 30]

If CMV-positive biliary atresia is identified, what treatment should be administered?

For acquired CMV-positive BA, antiviral therapy should be administered. There are two treatment options:

1. Valganciclovir with a dose of 7xBody Surface Area (BSA)x Glomerular Filtration Rate (GFR) for 6 weeks and continue for 2 weeks, or
2. Ganciclovir for 2 weeks and continue with Valganciclovir for 4 weeks.

   The therapy can be stopped if the CMV PCR is negative.

While CMV congenital should be treated with Valganciclovir for 16 weeks and continue with 7 days of Valganciclovir. The antiviral therapy (AVT) included:

1. Oral valganciclovir at a dosage of 10–40 (up to 58) mg/kg per day or
2. Intravenous ganciclovir at a dosage of 5.3–11 mg/kg per day.

Antiviral treatment for patients with acquired CMV-positive BA requires regular monitoring.[28]

A prospective study by Parolini et al. investigated the use of adjuvant antiviral therapy in patients with CMV-positive BA following Kasai portoenterostomy (KPE). Treatment involved starting intravenous ganciclovir (5 mg/kg twice daily) within the first week after surgery, and in some cases, switching to oral valganciclovir (520 mg/m^2 twice daily) until CMV DNA levels became undetectable. The results suggest that this antiviral approach, particularly with oral valganciclovir, may counteract the

harmful effects of CMV. Although overall survival rates did not differ significantly between the Antiviral Therapy (AVT) group (100%) and the Control group (82%) (χ^2 = 1.3, P = 0.24), the AVT group showed a statistically significant improvement in native liver survival compared to the Control group (χ^2 = 4.1, P = 0.04).[31]

Retrospective studies examining outcomes in infants with congenital CMV infection, whose mothers received CMV hyperimmunoglobulin (HIG) during pregnancy, have indicated potential benefits. However, inconsistencies in confirming primary maternal CMV infection, variations in CMV HIG preparation and administration, and selection bias complicate the ability to draw definitive conclusions. On the other hand, maternal treatment with valacyclovir during pregnancy has shown a positive impact on fetal CMV infection outcomes. Researchers suggest that a randomized trial comparing valacyclovir treatment to standard care could help confirm these findings.[32]

Current treatment options are limited to a surgical procedure known as Kasai portoenterostomy (KPE). This surgical intervention is required for BA patients to restore bile flow and prevent liver failure. It is most effective when performed early, ideally within the first 60 days of life. However, KPE fails to improve the condition in approximately 50% of patients and does not resolve intrahepatic cholangiopathy. Additionally, BA often leads to complications such as fibrosis, portal hypertension, and liver failure. In many cases, liver transplantation becomes necessary, requiring lifelong immunosuppression, which significantly impacts the quality of life for BA patients. The Kasai procedure fails in approximately 50% of cases, often leading to the need for liver transplantation.[33]

Liver transplantation: When is it necessary?

Early diagnosis of BA is critical as a surgical Kasai portoenterostomy (KPE) may restore bile flow if performed prior to age 3 months and help prevent rapid progression of liver injury and development of cirrhosis. Unfortunately, the vast majority of affected children will eventually develop end-stage liver disease, with BA being the leading indication for pediatric liver transplantation.[34] Biliary atresia (BA) occurs exclusively in childhood and is the most common cause of chronic cholestasis and liver transplantation in children.[35] Kemme et al, summarize several indications and timing of liver transplantation, such as early failed KPE, late diagnosis (defined as age >90, 100 or 120 days), failure to thrive, recurrent bacterial cholangitis, jaundice-associated pruritus, portal hypertension, hepatopulmonary syndrome (HPS), hepatorenal syndrome, and hepatic malignancy.[36]

Other systematic reviews by Utterson et al. shows from 755 patients who will perform liver transplantation, more than 70% were under 1 years old, and 60% were female. Most (82%) were not hospitalized at the time of listing. Most had pediatric end-stage liver disease (PELD) scores between 10 and 20 (mean, 11.7; median, 12.1). More than

40% of patients had growth failure, although only 16% received nasogastric supplements. The mean height z-score at listing was 21.3 ± 1.8, and the mean weight z-score at listing was 21.4 ± 1.8 SD.[37]

Furthermore, what is the prognosis?

CMV-positive BA is associated with a poorer prognosis than CMV-negative BA. We assessed the outcome of CMV-positive BA based on several parameters reported in the literature, including jaundice clearance, incidence of cholangitis, native liver survival, and mortality.

Jaundice Clearance

A meta-analysis conducted by Zhao et al. demonstrated that patients with CMV-positive BA had a significantly lower rate of jaundice resolution. Eight studies with a total of 666 patients (283 CMV-positive BA, 383 CMV-negative BA) described jaundice clearance. The pooled OR was 0.47 (95% CI: 0.32–0.69, $p < 0.001$). Three studies reported jaundice clearance within 6 months. The pooled OR was 0.31 (95% CI: 0.18–0.53, $p < 0.001$).[38]Additionally, Shen et al. demonstrated in their research that CMV infection negatively impacts the prognosis of biliary atresia. In the group with cytomegalovirus infection, the rate of jaundice resolution post-surgery was notably lower ($P<0.05$) than those in the control group, while the occurrence of reflux cholangitis was higher ($P<0.05$). The histopathological analysis further indicated that liver fibrosis and inflammation were more advanced in the CMV infection group rather than the non-CMV infection group ($P<0.05$).[38]

A study conducted by Vig et al. shows a significant difference of mean total bilirubin between CMV-positive BA and CMV-negative BA. Six months post-surgery, the CMV-negative group demonstrated significantly lower mean total bilirubin levels (0.96 mg/dL ± 0.66) compared to the CMV-positive group (5.76 mg/dL ± 4.32). In addition, a marked difference was observed in direct bilirubin levels between the two groups, with the CMV-negative group averaging 0.47 mg/dL, while the CMV-positive group had a considerably higher mean of 3.42 mg/dL. Their study found that, according to the criteria for a successful Kasai portoenterostomy—defined as a serum bilirubin level below 2 mg/dL at six months—all patients the CMV-negative group met this benchmark. In contrast, four infants in the CMV-positive group had total serum bilirubin levels exceeding 2 mg/dL at the six-month follow-up. Additionally, one patient in the CMV-positive group succumbed to liver failure during the postoperative period.[39]

Jaundice clearance following Kasai portoenterostomy (KPE) also showed a significant association with CMV status. a study by Zani et al. showed that only 3 out of 20 (15%) infants with CMV-positive BA achieved jaundice clearance, compared to 57 out of 109 (52.2%) in the CMV-negative (control) group, a difference that was statistically

significant [P = 0.002; OR 5.9, 95% CI: 1.6–21]. Regression analysis further confirmed that CMV positivity was significantly linked to reduced likelihood of jaundice clearance (P = 0.011; 95% CI: 0.188–0.686), with CMV-positive status reducing the log odds of jaundice clearance by 1.671. In contrast, the age at the time of KPE was not significantly associated with jaundice clearance (P = 0.09; 95% CI: 0.98–1.00). During the study period, two infants from the control group required primary liver transplantation.[6]

Interestingly, infants with CMV-positive BA who underwent surgery between 51 and 60 days of age had the highest rate of jaundice clearance (76.2%), compared to those who had surgery before 40 days of age (25%) or between 41 and 50 days of age (50%) (P = 0.036). A similar pattern was observed in syndromic BA with associated malformations, where infants who underwent surgery between 51 and 60 days also had the highest rate of jaundice clearance (77.8%), in contrast to those who had surgery before 40 days of age (25%) or between 41 and 50 days of age (50%) (P = 0.017).[40]

Another study reported notable differences among biliary atresia patients who underwent the Kasai procedure, depending on their CMV status. The 21 CMV-positive patients had significantly higher total bilirubin levels, lower platelet counts, a longer time to jaundice resolution following surgery, and a worse aspartate aminotransferase to platelet ratio index (APRI), suggesting more advanced liver fibrosis. Liver ultrasounds in these patients also revealed larger spleens and more severe inflammation and fibrosis compared to CMV- patients. In contrast, the CMV-negative group showed more pronounced lobular cholestasis, though there was no significant difference between the two groups in terms of ductular cholestasis.[40]

Incidence of Cholangitis

Cholangitis is a common and serious complication of biliary atresia, often linked to poor outcomes following Kasai portoenterostomy (KPE). Repeated cholangitis can promote fibrosis, obstruct bile flow, and exacerbate jaundice and cirrhosis. Patients with active CMV infection (defined as PCR or pp65-positive with or without IgM positivity) had significantly higher rates of cholangitis after the Kasai procedure, along with more extensive bile canaliculi hyperplasia and broader areas of inflammation compared to those who were CMV-negative or had past infection (IgM and/or IgG positive but pp65-negative).[2] A meta-analysis by Zhao et al. also showed that from two studies including 74 patients reported cholangitis data. The pooled OR was 2.76 (95% CI: 0.57–13.45, p = 0.21) and heterogeneity was not significant (I2 = 0.0%, p = 0.534). There was no significant difference in cholangitis incidence between CMV-positive BA and CMV-negative BA patients.[38]

A retrospective study conducted by Shen et al. compared between CMV-positive BA group and CMV-negative BA group based on their prognosis after Kasai procedure

showed that one patient (20%) in the CMV- group was re-hospitalized for treatment of reflux cholangitis 6 months after operation. Two patients (18%) in the CMV-positive group were hospitalized 2 to 3 times for increased levels of serum bilirubin with rectal temperature higher than 38.5ºC with unknown reasons. Four patients (36%) in the CMV-negative group had reflux cholangitis in 6 months post-operation. There was no significant difference between the CMV-negative group and the CMV-positive group, but the incidence of reflux cholangitis in the CMV infection group was obviously higher than those in the other two groups ($P<0.05$).[33] Interestingly, another study conducted by Song et al. showed infants with CMV-positive BA who underwent surgery between 51 and 60 days of age exhibited the lowest incidence of cholangitis (33.3%), as compared with infants who underwent surgery at less than 40 days of age (50% incidence) or between 41 and 50 days of age (40% incidence) ($P=.045$).[40]

Native Liver Survival (NLS)

A single-center study from the UK involving 121 infants with biliary atresia found that those who were CMV IgM-positive at diagnosis were older at presentation, had more severe liver inflammation and fibrosis on biopsy, and experienced significantly worse outcomes after hepatic portoenterostomy (HPE), including lower native liver survival and higher mortality, compared to CMV-negative infants.[6]

Two-year survival rates of autologous liver in CMV-positive BA were significantly lower than in cystic BA, however, there was no significant difference when compared with syndromic BA and associated malformations. Thus, the impact of etiologic heterogeneity on 2-year survival rates of autologous liver may differ between infants who undergo surgery at less than 60 days of age as compared with those who undergo surgery at greater than 60 days of age.[40]

Histopathological findings

In a study by Vig et al., all patients in the CMV-positive group and three in the CMV-negative group had fibrosis greater than Grade 2. Additionally, four CMV-positive patients had progressed to nodular cirrhosis. These findings suggest that CMV-positive BA patients tend to present with more advanced liver fibrosis. However, when the degree of fibrosis was statistically correlated with CMV status, the association was not significant ($P = 0.50$). [39]

Mortality

For patients who ultimately need liver transplantation, CMV-positive BA also comes with a poorer prognosis. Kemme et al. reported that cytomegalovirus infection in biliary atresia is linked to an increased risk of pretransplant mortality. The probability of death prior to transplantation was significantly higher in the CMV-positive group compared to the CMV-negative group ($p = 0.013$). Specifically, 4 out of 29 (14%)

CMV-positive participants died before receiving a liver transplant, compared to 8 out of 220 (4%) CMV− participants. Furthermore, CMV-positive infants with BA had a higher probability of pretransplant death within 40 months after hepatoportoenterostomy (HPE) compared to their CMV-negative counterparts.[36] Zani et al. also reported that there was a significantly higher mortality rate in the CMV BA group (n=5, 25%) in comparison with controls (n=7, 6.3%; P=0.02).[6]

Several studies have indicated that patients with CMV-positive BA tend to develop symptoms later and undergo surgery at a later stage. Furthermore, CMV-positive BA was associated with more severe fibrosis and inflammation during surgery compared to CMV-negative BA. Notably, CMV IgM-positive patients following the Kasai procedure exhibited a worse prognosis, which improved with antiviral treatment (AVT).[38] **Table 1.** summarizes the comparison of prognosis and therapeutic outcomes of antiviral treatment between CMV-positive BA and CMV-negative BA groups.

Table 1. Comparative table of prognosis and therapeutic outcomes of antiviral use between CMV-positive BA and CMV-negative BA groups

	CMV-positive BA	CMV-negative BA
Jaundice Clearance	Earlier	Later (6 months)
Incidence of Cholangitis	Higher	Lower
Fibrosis Grade and Inflammation	Higher	Lower
Native Liver Survival	Lower	Higher
Mortality	Higher	Lower
Antiviral treatment impact	Beneficial	Not Applicable

Prevention

Although the direct role of cytomegalovirus (CMV) infection in the development of biliary atresia remains a subject of ongoing debate, several findings have demonstrated a correlation between neonatal cholestasis and CMV infection. In a study conducted by Setyoboedi et al. among 113 infants with cholestasis, 94.7% (n = 107) were found to be CMV IgG-positive. Based on these findings, the researchers recommended that screening for TORCH infections should be considered in all infants presenting with cholestasis.[41] However, in contrast, a study conducted by Zhao et al. revealed that the incidence of cholestasis was similar between the biliary atresia groups with CMV IgM-positive and CMV IgM-negative status. Thus, the presence of CMV infection did not influence the conventional predictive parameters used to distinguish biliary atresia from intrahepatic cholestasis.[42]

Conclusion

In conclusion, biliary atresia remains a critical condition that requires close attention, characterized by elevated levels of total bilirubin, and is still a leading cause of chronic cholestasis and liver transplantation in children. Given the broad spectrum of potential etiologies, cytomegalovirus (CMV) infection should be prioritized in the diagnostic workup due to its association with poorer outcomes. In addition to abdominal ultrasonography as non-invasive diagnostic tool for biliary atresia, CMV detection via polymerase chain reaction (PCR) serves as a valuable diagnostic tool for the etiology. CMV-positive BA represents a distinct and clinically significant subset of biliary atresia with a demonstrably poorer prognosis compared to CMV-negative cases. CMV-positive BA is associated with delayed diagnosis, more severe liver inflammation and fibrosis at presentation, reduced jaundice clearance after Kasai portoenterostomy (KPE), increased incidence of postoperative cholangitis, and lower native liver survival, often leading to earlier liver transplantation or pretransplant mortality. Therefore, we hope that future studies will explore various strategies for early detection of infection, with the aim of reducing the prevalence of CMV infection in biliary atresia and mitigating its associated poor prognosis.

Acknowledgement

The author would like to express sincere gratitude to all those who contributed to this work.

Conflict of Interest

None declared.

Funding Statement

This study was not supported by any external funding.

References

1. Spada M, Riva S, Maggiore G, Cintorino D, Gridelli B. Pediatric liver transplantation. World J Gastroenterol. 2009;15(6):648-74. https://doi.org/10.3748/wjg.15.648
2. Averbukh LD, Wu GY. Evidence for viral induction of biliary atresia: A review. J Clin Transl Hepatol. 2018;6(4):410-9. https://doi.org/10.14218/jcth.2018.00046
3. Mack CL. The pathogenesis of biliary atresia: Evidence for a virus-induced autoimmune disease. Semin Liver Dis. 2007;27(3):233-42. https://doi.org/10.1055/s-2007-985068
4. Brindley SM, Lanham AM, Karrer FM, Tucker RM, Fontenot AP, Mack CL. Cytomegalovirus-specific t-cell reactivity in biliary atresia at the time of diagnosis is associated with deficits in regulatory t cells. Hepatology. 2012;55(4):1130-8. https://doi.org/10.1002/hep.24807
5. Lakshminarayanan B, Davenport M. Biliary atresia: A comprehensive review. J Autoimmun. 2016;73:1-9. https://doi.org/10.1016/j.jaut.2016.06.005
6. Zani A, Quaglia A, Hadzić N, Zuckerman M, Davenport M. Cytomegalovirus-associated biliary atresia: An aetiological and prognostic subgroup. Journal of Pediatric Surgery. 2015;50(10):1739-45. https://doi.org/10.1016/j.jpedsurg.2015.03.001
7. Rauschenfels S, Krassmann M, Al-Masri AN, Verhagen W, Leonhardt J, Kuebler JF, Petersen C. Incidence of hepatotropic viruses in biliary atresia. European Journal of Pediatrics. 2009;168(4):469-76. https://doi.org/10.1007/s00431-008-0774-2

8. Xu Y, Yu J, Zhang R, Yin Y, Ye J, Tan L, Xia H. The perinatal infection of cytomegalovirus is an important etiology for biliary atresia in china. Clinical Pediatrics. 2012;51(2):109-13. https://doi.org/10.1177/0009922811406264
9. Mohamed SOO, Elhassan ABE, Elkhidir IHE, Ali AHM, Elbathani MEH, Abdallah OOA, et al. Detection of cytomegalovirus infection in infants with biliary atresia: A meta-analysis. Avicenna J Med. 2021;12(01):003-9. https://doi.org/10.1055/s-0041-1739236
10. Ayuputeri M, Oswari H. Evidence-based case report the association between biliary atresia and cytomegalovirus infection. 2017;5(2). https://doi.org/10.23886/ejki.5.7242
11. Davenport M. Biliary atresia: Clinical aspects. Semin Pediatr Surg. 2012;21(3):175-84. https://doi.org/10.1053/j.sempedsurg.2012.05.010
12. Kusumawati NR, Ritonga RS, Kevin C, Sulaiman S, Siahaan SS, Pratiwi J. Demographic characteristics of children with biliary atresia in dr. Kariadi general hospital, semarang. Archives of Pediatric Gastroenterology, Hepatology, and Nutrition. 2022;1(2):1-7. https://doi.org/10.58427/apghn.1.2.2022.1-7
13. Feldman AG, Sokol RJ. Neonatal cholestasis: Updates on diagnostics, therapeutics, and prevention. NeoReviews. 2021;22(12):E819-E36. https://doi.org/10.1542/NEO.22-12-E819
14. Handayani DS, Kadim M. Cholestasis as primary manifestation of cytomegalovirus infection: A case report. Archives of Pediatric Gastroenterology, Hepatology, and Nutrition. 2024;3(4):33-42. https://doi.org/10.58427/apghn.3.4.2024.33-42
15. Hasosah MY, Kutbi SY, Al-Amri AW, Alsahafi AF, Sukkar GA, Alghamdi KJ, Jacobson K. Perinatal cytomegalovirus hepatitis in saudi infants: A case series. Saudi J Gastroenterol. 2012;18(3):208-13. https://doi.org/10.4103/1319-3767.96461
16. Reddy R, Mathur P, Sood T, Agrawal K, Lora SS, Gothwal S. Cholestatic jaundice and cytomegalovirus infection in children – an observational study. CHRISMED Journal of Health and Research. 2024;11(3):134-7. https://doi.org/10.4103/cjhr.cjhr_117_23
17. Anindita A, Setyoboedi B, Arief S, Prihaningtyas R. Accuracy of 2-phase abdominal ultrasound for diagnosing biliary atresia. Bali Medical Journal. 2024;13:514-8. https://doi.org/10.15562/bmj.v13i2.4907
18. Zhou W, Chen D, Jiang H, Shan Q, Zhang X, Xie X, Zhou L. Ultrasound evaluation of biliary atresia based on gallbladder classification: Is 4 hours of fasting necessary? J Ultrasound Med. 2019;38(9):2447-55. https://doi.org/10.1002/jum.14943
19. Lee HJ, Lee SM, Park WH, Choi SO. Objective criteria of triangular cord sign in biliary atresia on us scans. Radiology. 2003;229(2):395-400. https://doi.org/10.1148/radiol.2292020472
20. Lee MS, Kim MJ, Lee MJ, Yoon CS, Han SJ, Oh JT, Park YN. Biliary atresia: Color doppler us findings in neonates and infants. Radiology. 2009;252(1):282-9. https://doi.org/10.1148/radiol.2522080923
21. Lee SM, Cheon JE, Choi YH, Kim WS, Cho HH, Kim IO, You SK. Ultrasonographic diagnosis of biliary atresia based on a decision-making tree model. Korean J Radiol. 2015;16(6):1364-72. https://doi.org/10.3348/kjr.2015.16.6.1364
22. De Tommaso AMA, Andrade PD, Costa SCB, Escanhoela CAF, Hessel G. High frequency of human cytomegalovirus DNA in the liver of infants with extrahepatic neonatal cholestasis. BMC Infectious Diseases. 2005;5(1):108. https://doi.org/10.1186/1471-2334-5-108
23. Boppana SB, Ross SA, Shimamura M, Palmer AL, Ahmed A, Michaels MG, et al. Saliva polymerase-chain-reaction assay for cytomegalovirus screening in newborns. N Engl J Med. 2011;364(22):2111-8. https://doi.org/10.1056/NEJMoa1006561
24. Davenport M. Biliary atresia: From australia to the zebrafish. J Pediatr Surg. 2016;51(2):200-5. https://doi.org/10.1016/j.jpedsurg.2015.10.058
25. Allotey J, Lacaille F, Lees MM, Strautnieks S, Thompson RJ, Davenport M. Congenital bile duct anomalies (biliary atresia) and chromosome 22 aneuploidy. Journal of Pediatric Surgery. 2008;43(9):1736-40. https://doi.org/10.1016/j.jpedsurg.2008.05.012
26. Caponcelli E, Knisely AS, Davenport M. Cystic biliary atresia: An etiologic and prognostic subgroup. Journal of Pediatric Surgery. 2008;43(9):1619-24. https://doi.org/10.1016/j.jpedsurg.2007.12.058
27. Harpavat S, Finegold MJ, Karpen SJ. Patients with biliary atresia have elevated direct/conjugated bilirubin levels shortly after birth. Pediatrics. 2011;128(6):e1428-33. https://doi.org/10.1542/peds.2011-1869
28. Liliemark U, Svensson J, Fischler B. Incidence and antiviral treatment of cytomegalovirus infection in infants with biliary atresia. Pediatric Surgery International. 2023;39. https://doi.org/10.1007/s00383-023-05394-1
29. Oswari H, Mulyani NS, Setyoboedi B, Arief S, Kusumawati NRD, Widowati T, Yudiyanto AR. Pedoman tatalaksana kolestasis bayi Jakarta: Badan Penerbit Ikatan Dokter Anak Indonesia; 2024.
30. Chiereghin A, Pavia C, Turello G, Borgatti EC, Baiesi Pillastrini F, Gabrielli L, et al. Universal newborn screening for congenital cytomegalovirus infection - from infant to maternal infection: A prospective multicenter study. Front Pediatr. 2022;10:909646. https://doi.org/10.3389/fped.2022.909646

31. Parolini F, Hadzic N, Davenport M. Adjuvant therapy of cytomegalovirus igm + ve associated biliary atresia: Prima facie evidence of effect. J Pediatr Surg. 2019;54(9):1941-5. https://doi.org/10.1016/j.jpedsurg.2018.12.014
32. Pass RF, Arav-Boger R. Maternal and fetal cytomegalovirus infection: Diagnosis, management, and prevention. F1000Res. 2018;7:255. https://doi.org/10.12688/f1000research.12517.1
33. Shen C, Zheng S, Wang W, Xiao XM. Relationship between prognosis of biliary atresia and infection of cytomegalovirus. World J Pediatr. 2008;4(2):123-6. https://doi.org/10.1007/s12519-008-0024-8
34. Arnon R, Annunziato RA, D'Amelio G, Chu J, Shneider BL. Liver transplantation for biliary atresia: Is there a difference in outcome for infants? J Pediatr Gastroenterol Nutr. 2016;62(2):220-5. https://doi.org/10.1097/mpg.0000000000000986
35. Pinto RB, Schneider AC, da Silveira TR. Cirrhosis in children and adolescents: An overview. World J Hepatol. 2015;7(3):392-405. https://doi.org/10.4254/wjh.v7.i3.392
36. Kemme S, Canniff JD, Feldman AG, Garth KM, Li S, Pan Z, et al. Cytomegalovirus in biliary atresia is associated with increased pretransplant death, but not decreased native liver survival. Hepatol Commun. 2023;7(8). https://doi.org/10.1097/hc9.0000000000000175
37. Utterson EC, Shepherd RW, Sokol RJ, Bucuvalas J, Magee JC, McDiarmid SV, Anand R. Biliary atresia: Clinical profiles, risk factors, and outcomes of 755 patients listed for liver transplantation. Journal of Pediatrics. 2005;147(2):180-5. https://doi.org/10.1016/j.jpeds.2005.04.073
38. Zhao Y, Xu X, Liu G, Yang F, Zhan J. Prognosis of biliary atresia associated with cytomegalovirus: A meta-analysis. Front Pediatr. 2021;9:710450. https://doi.org/10.3389/fped.2021.710450
39. Vig A, Elhence P, Rathod KJ, Nayak S, Jadhav AS, Pathak M, et al. Effect of cytomegalovirus infection on initial presentation and overall prognosis of biliary atresia patients. J Indian Assoc Pediatr Surg. 2023;28(1):5-8. https://doi.org/10.4103/jiaps.jiaps_92_22
40. Song Z, Dong R, Shen Z, Chen G, Yang Y, Zheng S. Surgical outcome and etiologic heterogeneity of infants with biliary atresia who received kasai operation less than 60 days after birth: A retrospective study. Medicine (Baltimore). 2017;96(26):e7267. https://doi.org/10.1097/md.0000000000007267
41. Setyoboedi B, Prihaningtyas RA, Octariyandra SM, Arief S. Torch serological marker on cholestasis with the occurrence of biliary atresia and its clinical manifestations. Romanian Journal of Pediatrics. 2023;72(4):167-71. https://doi.org/10.37897/RJP.2023.4.7
42. Zhao D, Gong X, Li Y, Sun X, Chen Y, Deng Z, Zhang Y. Effects of cytomegalovirus infection on the differential diagnosis between biliary atresia and intrahepatic cholestasis in a chinese large cohort study. Annals of Hepatology. 2021;23. https://doi.org/10.1016/j.aohep.2020.100286

APGHN

Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

www.apghn.com

Volume 4 / No. 2
May 2025

ISSN 2830-5442

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