

Case Report

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Hemolytic Anemia Due to Glucose-6-Phosphate Dehydrogenase Deficiency in Neonate

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ABSTRACT

Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme in erythrocytes that functions to maintain glycolysis, form an erythrocyte membrane, and protect hemoglobin from oxidative denaturation. Clinical manifestations of anemia and severe jaundice are risk factors for acute hyperbilirubinemia encephalopathy, which can progress to kernicterus. G6PD deficiency is X-linked. The incidence is most common in males with an incidence in Indonesia of 1-14%.

A 3-day-old male baby appeared yellowish and had a history of being pale since 1 day of age. There was a history of phototherapy and packed red blood cell transfusion from a previous hospital. The baby was born via caesarean section, term baby, with a birth weight of 2700 grams. The Physical examination revealed Kramer V, tachypnea, but no hepatosplenomegaly. A previous laboratory examination at AM Hospital showed total bilirubin of 23.3 mg/dL, indirect bilirubin 23 mg/dL, and pre-transfusion hemoglobin 9.8 g/dL. Chest X-rays revealed grade I-II hyaline membrane disease. Meanwhile, the laboratory test results at the Dr Wahidin Sudirohusodo Hospital showed a total bilirubin of 38.5 mg/dL, indirect bilirubin 37.17 mg/dL, reticulocytes 9.95%, hemoglobin 11.8 g/dL, CRP 5.2 mg/L, Procalcitonin 0.5 ng/mL, and a negative Coombs test. The peripheral blood smear showed fragmented cells of erythrocytes. The G6PD level was 17.2 U/dL (reference value >20.5 U/dL). The patient received low-flow oxygenation, antibiotics, and 72 hours of intensive phototherapy. On the 7th day of treatment, the condition improved, and the baby was discharged. Therefore, Rapid diagnosis and treatment of G6PD deficiency are important to prevent other potential complication such as acute hyperbilirubinemia encephalopathy.

Keywords: Hemolytic anemia; glucose-6-Phosphate dehydrogenase; neonates



GREEN MEDICAL
JOURNAL
E-ISSN 2686-6668

Article history:

Received: 22 February 2023
Accepted: 10 December 2023
Published: 1 April 2024

Published by:

Faculty of Medicine
Universitas Muslim Indonesia

Mobile number:

+62821 9721 0007

Address:

Jl. Urip Sumoharjo Km. 5, Makassar
South Sulawesi, Indonesia

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greenmedicaljournal@umi.ac.id

Introduction

Glucose-6-phosphate dehydrogenase (G6PD) is one of enzymes in erythrocytes that maintains glycolysis, shape and flexibility of erythrocyte membrane, and protects hemoglobin from oxidative denaturation. The most common clinical manifestations are hemolysis and indirect hyperbilirubinemia. Bilirubin is a primary breakdown product of red blood cells by the reticuloendothelial system. Bilirubin concentrations > 5 mg/dL bilirubin will appear clinically in the form of yellow staining of the skin and mucous membranes called jaundice.^{1,2}

It is estimated that around ± 400 million people worldwide suffer from G6PD enzyme disorder/deficiency. This is spread across Africa (7.5%), the Middle East (6%), Asia (4.7%), Europe (3.9%), and the America (3.4%). The highest frequency is found in the tropical area, such as Southeast Asia, with the most common causes were jaundice and acute hemolytic anemia. In Indonesia, the incidence was estimated at 1-14%.^{1,3}

In many countries, G6PD screening is conducted as part of the national newborn screening program, but Indonesia has not yet implemented it. G6PD deficiency has been identified as a major risk factor in severe neonatal hyperbilirubinemia which can lead to the complication of acute encephalopathy hyperbilirubinemia which could lead to kernicterus and causes permanent neurological damage if left untreated.^{1,2,4}

Case

A 3-day-old male baby appeared yellowish and had been pale since the first day of life. He received phototherapy and packed red blood cell transfusion from a previous hospital. He had shortness of breath since birth. The baby was born via caesarean section due to previous section history during first pregnancy (this was the 2nd pregnancy), 37 weeks gestation, and weight 2700 grams. There was no history of antepartum hemorrhage or birth trauma in delivery. The mother has blood type O Rhesus +, and the father has blood type B Rhesus +, while the baby's blood type is B Rhesus +. During the time of treatment at Dr. Wahidin Sudirohusodo Hospital, a negative Coombs test was obtained, and we ruled out the possibility of ABO incompatibility.

The physical examination revealed Kramer V (figure 1), tachypnea, but no hepatosplenomegaly. A previous laboratory examination at AM Hospital (when the baby was aged 1 day) showed a total bilirubin of 23.3 mg/dL, indirect bilirubin 23 mg/dL, and hemoglobin 9.8 g/dL pre-transfusion (> 13 g/dL), leucocyte 6.350/uL (3.100/uL - 21.600/uL), platelet 338.000/uL (150.000/uL – 450.000/uL). Chest X-ray revealed grade I-II hyaline membrane disease. After packed red cell transfusion (when the baby was 2 days old) hemoglobin 14.5 g/dL (> 13 g/dL), leucocyte 17.500/uL (3.100/uL - 21.600/uL), platelet

306.000/uL (150.000/uL – 450.000/uL).



Figure 1. Baby when admitted to Dr. Wahidin Sudirohusodo Hospital.

The laboratory test results at the Dr Wahidin Sudirohusodo Hospital, complete blood count, peripheral blood smear, septic workup, bilirubin, albumin, SGOT, SGPT, Coombs test, and G6PD enzyme examination were performed. Septic workup was done because of respiratory distress. Laboratory results showed high reticulocytes (9.95%), HB 11.6, MCV 107 fl, MCH 36 pg, total bilirubin 38.5 mg/dl, direct bilirubin 1.33 mg/dl, albumin 3.5 mg/dL, procalcitonin 0.5 ng/mL, CRP 5.2 mg/L, SGOT and SGPT within normal limits, a negative Coombs test, and G6PD enzyme 17.2 U/dL (reference value >20 U/dL). Blood culture showed no bacterial growth. Peripheral blood examination showed normochromic normocytic erythrocytes, anisopoikilocytosis, positive ovalocytes, positive spherocytes, positive fragmented cells, positive normoblasts and no toxic granulation or vacuolization in leukocytes. These results indicate non-autoimmune hemolytic anemia due to G6PD deficiency, which is accompanied by indirect hyperbilirubinemia.

The patient was diagnosed with respiratory distress of the newborn, hemolytic anemia, indirect hyperbilirubinemia, and G6PD deficiency. The patient received low-flow oxygenation (0.5 liter/minute), antibiotics (ampicillin 125 mg/12 hours/intravenously and gentamicin 13 mg/24 hours/intravenously) for five days, and 72 hours of intensive phototherapy (after 48 hours after phototherapy, bilirubin total 16.87 mg/dL, bilirubin direct 0.8 mg/dL, and phototherapy continued). On the 7th day of treatment, the condition improved (figure 2), the baby was discharged, and the family was educated on how to prevent things that can trigger G6PD deficiency.



Figure 2. Baby after intensive phototherapy

Discussion

Anemia in the neonatal period (0-28 days) at gestational age > 34 weeks is defined as hemoglobin (HB) in central venous < 13 g/dL or capillary blood < 14.5 g/dL. The incidence of anemia in neonates is the most frequent blood abnormality. Normal reticulocytes in neonates are 3-5%. The average MCV value in neonates is 107 fL. In preterm infants, HB is slightly lower, MCV and reticulocytes have higher values. HB levels do not change until the 3rd week of life and then decrease to 11 g/dL.^{2,5}

The etiology of anemia in neonates comes from 3 processes:² 1) Erythrocyte loss or bleeding such as placenta previa, placental abruption, caesarean section, birth trauma, cephalhematoma, caput succedaneum, intracranial hemorrhagic, 2) Increased erythrocyte destruction or hemolytic (most common) such as autoimmune (Rh and ABO incompatibility, autoimmune hemolytic anemia), nonimmune (sepsis, TORCH), Congenital erythrocyte defects (G6PD deficiency, Thalassemia, hereditary spherocytosis), 3) Low erythrocyte production or hypoplastic anemia such as sideroblastic anemia, congenital leukemia.

In this case, the patient was pale and jaundiced at 1 day of age. The causes of anemia followed by jaundice on the first day of life are ABO and Rhesus incompatibility, as well as G6PD deficiency. Other risk factors that could cause anemia in this case included cesarean section surgery and respiratory distress (sepsis risk).

ABO and rhesus incompatibility is an isoimmune hemolytic anemia caused by blood group differences between the mother and infant. Infants with blood type A or B are typically incompatible with mother with blood type O. This is because in the mother's blood type O, the dominant isoantibody is 7S-IgG and can cross the placenta, whereas in blood types A or B, the dominant isoantibody is 19S-IgM so that it cannot cross the placenta. The clinical manifestations are hemolytic anemia and early onset unconjugated hyperbilirubinemia.²

G6PD deficiency is the most prevalent human enzyme deficiency, with an estimated global frequency of 4.9% and approximately 400 million people affected worldwide. In Indonesia, the incidence is estimated at 1-14%. A study by Soemantri stated that the G6PD deficiency prevalence in Central Java was 15%. Suhartati et al study in small isolated islands in Eastern Indonesia (Babar, Tanimbar, Kur and Romang Islands in Maluku Province) reported that the incidence of G6PD deficiency was 1.6-6.7%.^{1,3,6,7}

G6PD deficiency affects one-third of male infants with neonatal jaundice, while the frequency in female infants is lower. Jaundice usually appears at 1-4 days of age, similar to physiological jaundice. If kernicterus occurs, it can cause permanent nerve damage if not treated immediately. Premature infants with G6PD deficiency have more severe neonatal jaundice. If G6PD deficiency is not routinely screened, more comprehensive screening should be done in newborns who have hyperbilirubinemia >150 mmol/L

(> 9 mg/dL) in the first 24 hours or have relatives with a history of neonatal jaundice, and in Asian males.^{4,6,8} In this case, the bilirubin on the first day of life was 23.3 mg/dL.

G6PD deficiency is an x-linked defect. The basic biochemical abnormalities of G6PD deficiency are due to mutations in the G6PD gene. Women have two X-chromosomes, therefore they can be homozygous normal, homozygous G6PD deficient, and heterozygous G6PD deficient. Males have only one X-chromosome, therefore males are at greater risk than females. In this case, G6PD occurred in a male baby. The WHO categorizes G6PD deficiency into several classes (Table 1)^{1,6,8}

Table 1. Classification of G6PD deficiency^{7,8}

Class	Variant	Enzyme Activity	Symptoms	Prevalence
I	Mediterranean type	<1%	Chronic spherocytic anemia	Uncommon across non-population
II	A ⁻ /Med	1 – 10%	Intermittent hemolysis	More common in Asian and Mediterranean populations
III	A ⁻ /Med	10 – 60%	Intermittent hemolysis	US black males
IV	A ⁺ /Med	60 – 150%	No clinical symptoms	Rare
V	A ⁺ /Med	>150%	No clinical symptoms	Rare

Acute hemolysis can also occur in G6PD-deficient infants and cause hemolysis crises in children and adults when consuming drugs or fava beans, or exposure from the environment. Mothballs is an example of a widespread and inexpensive household item used as an insecticide in the clothes closet of Asian, Latin American, and African populations. Mothballs contain naphthalene, a polycyclic aromatic hydrocarbon that causes oxidative stress in G6PD-deficient RBCs.⁹ A more toxic naphthalene-derived metabolite, alpha-naphthol, could cause hemolysis, severe anemia, and the production of Heinz bodies after accidental intake. In addition, severe jaundice and kernicterus was experienced by a 4-day-old Panamanian baby boy with G6PD deficiency after direct contact or inhaling vapors from naphthalene-containing clothing.¹⁰ Some medications that should be avoided can be seen in table 2.⁶

Table 2. Drugs to avoid in patients with G6PD deficiency¹¹

Unsafe for Class I, II, and III	Safe for Class II and III
Acetanilid	Acetaminophen
Dapsone	Aminopyrine
Furazolidone	Ascorbic acid
Methylene blue	Aspirin
Nalidixic acid	Chloramphenicol
Naphthalene	Chloroquine

Niridazole	Colchicine
Nitrofurantoin	Diphenhydramine
Phenazopyridine	Isoniazid
Phenylhydrazine	L-DOPA
Primaquine	Menadione
Sulfacetamide	Paraaminobenzoic acid
Sulfamethoxazole	Phenacetin
Sulfanilamide	Phenytoin
Sulphapyridine	Probenecid
Thiazosulfone	Procainamide
Toluidine blue	Pyrimethamine
Trinitrotoluene	Quinidine
Vitamin K	Quinine
Anesthetic Agents	Sulphamethoxypyridazine
Diazepam	Streptomycin
Isoflurane	Sulfisoxazole
Sevoflurane	Tripelethamine
	Trimethoprim
	Anesthetic Agents
	Halothane
	Prilocaine
	Ketamine
	Fentanyl
	Propofol
	Benzodiazepines (except Diazepam)

In this report, the physical and laboratory examination results support non-autoimmune hemolytic anemia due to G6PD deficiency followed by induced hyperbilirubinemia. The principal treatment for G6PD deficiency is to avoid oxidative stress-causing agents such as medications, certain foods, and infections. However, the anemia may be severe enough to require blood transfusions. Neonates with G6PD deficiency may also develop chronic hemolysis leading to hyperbilirubinemia with a more gradual increase in total bilirubin. Phototherapy is required if bilirubin levels meet the criteria for phototherapy. Phototherapy is still the first choice therapy and exchange transfusion is done for patients who are not responsive to phototherapy.^{2,8,12,13}

In our case, the patient received packed red cell transfusion from the previous hospital, and received intensive phototherapy. In Dr. Wahidin Sudirohusodo Hospital, the patient underwent intensive phototherapy again for approximately 72 hours because the baby still appeared yellow throughout the body (Kramer V jaundice), with a total bilirubin level of 38.5 mg/dL, direct bilirubin 1.33 mg/dL. The patient also received antibiotics for the management of respiratory distress for five days. On the 7th treatment, the patient's condition improved and the patient was discharged.

The American Academy of Pediatric guidelines recommend an exchange transfusion when the patient's total serum bilirubin (TSB) level continues to rise and is still higher than the exchange transfusion

threshold after 4-6 hours of intensive phototherapy. Furthermore, exchange transfusion is recommended when there are clinical signs of acute bilirubin encephalopathy.¹⁴ In his study, Zhang M et al reported that intensive phototherapy is an effective and secure treatment for severe hyperbilirubinemia. Indications for exchange transfusion for patients with hyperbilirubinemia can be more stringent. However, emergency exchange transfusion should be planned as soon as intensive phototherapy begins, especially for newborns with risk factors. If intensive phototherapy can be guaranteed and proven effective, exchange transfusion should be avoided wherever possible.¹⁵ In this case the bilirubin level was improved with intensive phototherapy.

Conclusion

A 3-day-old male baby with hyperbilirubinemia and anemia due to hemolytic anemia due to G6PD deficiency had been reported. Physicians should focus on early recognition to decrease the morbidity of the patient. Rapid diagnosis and treatment are important to prevent other potential complications such as acute hyperbilirubinemia encephalopathy.

Conflicts of Interest

There is no conflict of interest

Funding sources

There is no funding source

Acknowledgments

There is no acknowledgment

References

1. Timan IS, Pattiasina F, Pasaribu MM, et al. G6PD Deficiency in Indonesian Newborn. *Adv Sci Lett*. 2018;24(9):6602-6604. doi:10.1166/asl.2018.12792
2. Gomella TL. Gomella, T.C., Cunningham, M.D., Eyal, F.G. Neonatologi Management, Procedures, On-Call Problems, Disease, and Drugs. 7th Edition. New York: Mc Graw-Hill. In: ; 2013:558-567.
3. Rahardjani KB. Kadar Bilirubin Neonatus dengan dan Tanpa Defisiensi Glucose-6-Phosphate Dehydrogenase yang Mengalami atau Tidak Mengalami Infeksi. *Sari Peditr*. 2008;10(2):122. doi:10.14238/sp10.2.2008.122-8
4. Kurniawan L. Coninuing Medical Education: Skrining , Diagnosis dan Aspek Klinis Defisiensi. *CDK*. 2014;41(11):807-811.

5. Sari T, Muhaimin R, Fazlurrahman U. Hemolytic disease of newborn: fokus pada inkompatibilitas ABO. *J Kedokt Syiah Kuala*. 2021;21(2):197-203.
6. Lee HY, Ithnin A, Azma RZ, Othman A, Salvador A, Cheah FC. Glucose-6-Phosphate Dehydrogenase Deficiency and Neonatal Hyperbilirubinemia: Insights on Pathophysiology, Diagnosis, and Gene Variants in Disease Heterogeneity. *Front Pediatr*. 2022;10(May):1-13. doi:10.3389/fped.2022.875877
7. Sumathipala S. Glucose-6-Phosphate Dehydrogenase Deficiency : A Review. *World Fam Med Journal/Middle East J Fam Med*. 2020;18(9):92-97. doi:10.5742/mewfm.2020.93862
8. Frank JE. Diagnosis and management of G6PD deficiency. *Am Fam Physician*. 2005;72(7):1277-1282.
9. Volney G, Tatusov M, Yen AC, Karamyan N. Naphthalene toxicity: methemoglobinemia and acute intravascular hemolysis. *Cureus*. (2018) 10:e3147. doi: 10.7759/cureus.3147.
10. de Gurrola GC, Araúz JJ, Durán E, Aguilar-Medina M, Ramos-Payán R, García-Magallanes N, et al. Kernicterus by glucose-6-phosphate dehydrogenase deficiency: a case report and review of the literature. *J Med Case Rep*. (2008) 2:146. doi: 10.1186/1752-1947- 2.
11. Dogra N, Puri GD, Rana SS. Glucose-6-phosphate dehydrogenase deficiency and cardiac surgery. *Perfusion*. 2010;25(6):417-421. doi:10.1177/0267659110380770
12. Luzzatto L, Nannelli C, Notaro R. Glucose-6-Phosphate Dehydrogenase Deficiency. *Hematol Oncol Clin North Am*. 2016;30(2):373-393. doi:10.1016/j.hoc.2015.11.006
13. Olusanya BO, Kaplan M, Hansen TWR. Neonatal hyperbilirubi- naemia: a global perspective. *Lancet Child Adolesc Health* 2018; 2:610–620. doi: 10.1016/S2352-4642(18)30139-1.
14. American Academy of Pediatrics Subcommittee on Hyperbilirubi- nemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2004;114:297–316. doi: 10.1542/peds.114.1.297.
15. Zhang M, He Y, Tang J, et al. Intensive phototherapy vs . exchange transfusion for the treatment of neonatal hyperbilirubinemia : a multicenter retrospective cohort study. 2022;135(5). doi:10.1097/CM9.0000000000001962

Case Report

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The Use of Azithromycin in Pediatric Typhoid Fever without Complication: A Case Report

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ABSTRACT

Typhoid fever is an infection caused by the bacterium *Salmonella typhi*. The prevalence is still high among emerging countries, such as Indonesia. There are limited options for the treatment of typhoid fever in children and more so is complicated by the emergence of antimicrobial resistance. The use of azithromycin has evolved as an important drug in the treatment of typhoid.

A male, aged 7 years and 2 months, was admitted to our hospital with remittent fever 4 days prior. The patient also presented with a period of cough since 2 days, and constipation, with full consciousness. The child had basic immunization completed for his age. He had a history of frequent consumption of street food. The diagnosis of typhoid fever was confirmed by serologic testing of positive 8 IgM Salmonella. Initially, the patient was treated with intravenous antibiotics of ceftriaxone for 8 days but showed no clinical improvement, then the treatment was changed to intravenous azithromycin for 4 days and his condition improved greatly. The patient showed a better response with the use of azithromycin.

The management of typhoid fever remains challenging up to this day with variations in treatment response. From this case, we can conclude that azithromycin in some patients may show better improvement in the management of typhoid fever in pediatric patients. Although, ceftriaxone and other third-generation cephalosporins are still highly effective against *Salmonella typhi*.

Keywords: Typhoid fever; salmonella typhi; enteric fever; azithromycin



GREEN MEDICAL
JOURNAL
E-ISSN 2686-6668

Article history:

Received: 20 November 2023

Accepted: 1 April 2024

Published: 29 April 2024

Published by:

Faculty of Medicine
Universitas Muslim Indonesia

Mobile number:

+62821 9721 0007

Address:

Jl. Urip Sumoharjo Km. 5, Makassar
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Introduction

Salmonella enterica serovar typhi is the agent causing typhoid fever predominantly in the developing world and is still associated with mortality and morbidity rates in the pediatric population. It is transmitted by water contamination and through unhygienic food ingestion. In Indonesia, it is estimated 800-100.000 people are with typhoid fever all year round. The prevalence is 91% among 3-19 group of age.^{1,2,3} Treatment of choice is with antibiotics. Chloramphenicol was first used in around 1948 by Woodward, but in the 1970s, *Salmonella* became resistant. In 1980 and 1990, *Salmonella* became resistant to ampicillin and cotrimoxazole. This trend of multiple-drug resistance for the strain *Salmonella typhi* in recent years has made treatment for typhoid more complicated. Azithromycin has been proven in vitro to have a role in enteric pathogen elimination including *Salmonella spp*, excellent penetration into most tissues, and achievement of concentration in macrophages and neutrophils that are > 100-fold higher than concentration in serum.^{4,5,6}

Here, we report a case of a boy of 7 years and 6 months with typhoid fever without complication that was treated with azithromycin.

Case

A boy aged 7 years and months was admitted to W hospital emergency room with an infrequent fever 4 days before admission, the fever was relieved with antipyretic, the fever mostly felt at night. The patient also presented with infrequent cough 2 days, nausea, and has not defecated for the past 4 days. The appetite was rather good.



Figure 1. Picture of the patient

In physical examination, the patient showed full consciousness, a fever of 38.7C and tachypnea of 42 times per minute, other vital signs were normal. Hyperemic pharynx and audible rales on both lungs with no wheezing. Laboratory work revealed a normal Hemoglobin level of 13.7 g/dl, leukocyte of 5,100/mm³, and platelet of 170,000/mm³. The liver, and kidney functions were normal. The chest x-ray revealed pneumonia dextra.

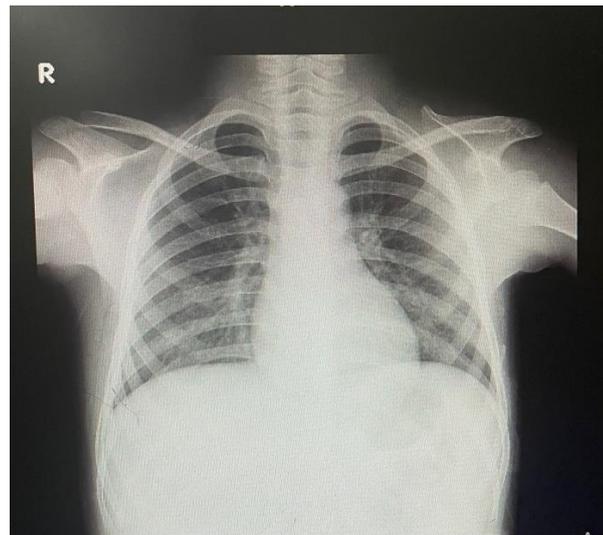


Figure 2. The chest x-ray of the patient with an impression of pneumonia dextra

The patient was initially treated for pneumonia and was given intravenous antibiotics of ceftriaxone and gentamicin, however, after 7 days of treatment, the clinical symptoms of pneumonia were relieved but the fever was still persistent accompanied by nausea and constipation. We further tracked the cause of the fever and found that the Tubex test was positive 8. The patient then was treated as typhoid fever and was given azithromycin intravenous for 4 days continued with oral azithromycin. The fever, and nausea were relieved, the patient had defecated, so the patient was then discharged.

Discussion

Our patient initially presented with a fever for 4 days, accompanied with cough, nausea, and constipation as the marked symptoms. Due to Covid situation in our hospital, the patient was suggested to have a chest x-ray examination and the result was pneumonia dextra. We initially treated this patient as having pneumonia for the reasons, this patient had fever, cough, and shortness of breath. The treatment was started with intravenous antibiotics of ampicillin and gentamicin. The cough, shortness of breath were relieved but the fever was still ongoing, so we tracked for possible typhoid fever causing the persistent fever.

Typhoid fever caused by an invasive pathogen of *Salmonella typhi* from contaminated feces, food,

and water. *S.typhi* is a negative gram bacteria, has flagella, no capsule, and not forming anaerob facultative spores. It has antigen somatic O, flagel antigen H, and envelope antigen K. *S.typhi* invade the body from the mouth and into the gastric mucosa in terminal ileum, in the peyeric patch, *S.typhi* crosses the epithelial barrier and enter the mesenteric lymphnodes and into the bloodstream via lymphatic channel. This is called primary bacteremia. The bacteria that is already in the bloodstream then replicated at the macrophages, and can be released again into the bloodstream causing secondary bacteremia. This condition marked the end of incubation period and will end up in clinical signs and symptoms of typhoid. The clinical signs of typhoid fever in most cases is called step-ladder temperature. Initiated with insidious symptoms, then got higher and peak at the first week. Many parents reported that the fever is higher at night, and it can be accompanied with decrease of consciousness. Prodromal signs are malaise and anorexia. Other signs and symptoms are dominantly gastrointestinal tract which include stomachache, constipation, diarrhea. Several parents also reported cough and pain when swallowing in their children^{7,8,9,10}

The test for serologic testing tubex was positive 8 which was deemed as strong positive. The IgM for *Salmonella* can be detected in the blood for 3 months after infection. The gold standard for *Salmonella* diagnosis, is still through isolation from culture. However, this is quite challenging as it requires a longer time for the result and the condition of the patient may deteriorate before the result is out.

Based on the latest recommendation from Ikatan Dokter Anak Indonesia (IDAI), the antibiotic used for the first line is chloramphenicol, amoxicillin, and cotrimoxazole. The second line is ceftriaxone and cefixime, indicated for multi-drug resistant strains of *S.typhi*. However, WHO South East Asian Region (SEARO) recommends the use of azithromycin or third-generation cephalosporin for enteric fever case caused by *S.typhi* in the Southeast Asia region. Azithromycin is from the macrolide group of antibiotics, and has a broad spectrum, that works to inhibit protein synthesise and lower the formation of biofilm. This antibiotic is of bacteriostatic. Azithromycin is an antimicrobial agent from the macrolide group given orally that is stable in acidic environment. Due to its wide antibacterial spectrum for *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and atypical pathogen, Azithromycin has widely been used for infectious disease therapy in children and is considered one of the most prescribed antibiotic in children. It also has better accumulation in the phagocytes, hence, better distribution to the source of infection. Up to this day, there is no report of resistance *S.typhi* to azithromycin.^{11,12,13,14} The typhoid vaccine is considered an efficient tool to prevent typhoid fever. In March 2018, WHO recommended the use of typhoid conjugate vaccines in endemic countries, in 2019, Pakistan has become the first country in the world to introduce the WHO-recommended typhoid vaccine to its routine immunization program.¹⁵ In Indonesia however, typhoid vaccine has now been introduced and is considered safe to be delivered to

children from the age of 2 years.

The limitation of this case is the limited number of patients treated with Azithromycin, therefore, this study can't yet be used as the guideline therapy for typhoid fever in pediatric cases.

Conclusion

A case of typhoid fever without complication that was treated with azithromycin from a boy aged 7 years and 6 months is reported. The patient was initially treated with ceftriaxone for 7 days but showed no clinical improvement in the duration of a fever. The diagnosis of typhoid was based on history taking, physical examination, and laboratory support. After treatment with azithromycin for 6 days, the patient's condition improved greatly. This report may help in providing additional information regarding the treatment of typhoid.

Conflicts of Interest

There is no conflict of interest

Funding sources

There is no funding source

Acknowledgments

There is no acknowledgment

References

1. Kadir S, et al. Salmonella Hepatitis in Children: A Update. Dhaka, Pakistan: Northern International Medical College Journal. 2019.
2. Ahmad S. Assessment of Liver Function Tests in Children with Typhoid Fever: A Hospital Based Study. Nepal: Journal of Nepal Medical College. 2019
3. Parry MC, Hien TT, Dougan G et al. Typhoid Fever. The new England journal of medicine. 2002; 347(22): 1770-82.
4. Rao KN, Pratusha R, Acharya A. Azithromycin and ceftriaxone in uncomplicated typhoid fever in paediatric patients: a prospective comparative and randomized open labelled trail. Int J Contemp Pediatr 2020;7:2316-20
5. Effa EE and Bukirwa H. Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever). The Cochrane library. 2008. 1-38
6. Abramowics M, Zuccoti G, editors: Handbook of antimicrobial drugs: drugs for bacterial infections. The Medical Letter, ed 20, New Rochelle, NY 2015.
7. Hadinegoro, Sri Rezeki, et al. Demam Tifoid dalam Buku Ajar Infeksi dan Penyakit Tropis edisi Keempat. Jakarta: Badan Penerbit Ikatan Dokter Anak Indonesia. 2016.
8. Kliegman, Robert, et al. Typhoid Fever in Children. Philadelphia. 2016: Nelson Textbook of Pediatrics 20th Edition.
9. Suwatro S, et al. Laboratory Parameters for Predicting Salmonella Bacteremia: a Prospective Cohort Study. Jakarta, Indonesia: SAGE pub journal. 2016
10. Karoli R, Fatima J, Chandara A, Singh G. Salmonella hepatitis: An uncommon complication of a common

- disease. *J Fam Med Primary Care* 2012;1:160-2.
11. Zmora N, Shrestha S, Neuberger A, Paran Y, Tamrakar R, Shrestha A, et al. (2018) Open label comparative trial of mono versus dual antibiotic therapy for Typhoid Fever in adults. *PLoS Negl Trop Dis* 12(4): e0006380. <https://doi.org/10.1371/journal.pntd.0006380>
 12. Sumit Raim Umesh Shukla, Arti Kapil, Suhsila Dahiya, Priyanka Sharma, Ceftriaxone treatment failure in two cases of Enteric Fever caused by CTX-M15 positive Salmonella Typhi and its gastrointestinal carriage, *Indian Journal of Medical Microbiology*, 2022, <https://doi.org/10.1016/j.ijmmb.2022.04.001>
 13. Craig WA, Andes DR. In vivo activities of ceftazalone, a new cephalosporin, with and without tazobactam against *Pseudomonas aeruginosa* and Enterbacteriaceae, including strains with extended spectrum B-lactamses, in the thighs of neutropenic mice. *Antimicrob Agents Chemother.* 2013;57:1577-1582.
 14. Antolis Y, Rampengan T, Wilar R, Homenta Rampengan N. Azithromycin vs. chloramphenicol for uncomplicated typhoid fever in children. Vol. 53, Original Article *Paediatr Indones.*
 15. Ullah I, Khan K, Mehmood Q, Malik M, Ahmed A, Munir U. Irrational use of azithromycin in typhoid endemic areas: A challenge on multidrug-resistant typhoid treatment. Vol. 1, Review Article, *Trends in Infection and Global Health* 2021

Case Report

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Biliary Atresia with Cytomegalovirus Infection, Congenital Heart Disease and Pneumonia: A Case Report

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ABSTRACT

Biliary atresia (BA) is a condition of biliary obstruction. Kasai portoenterostomy (KPE) is a treatment option. The aim to determine the success rate of kasai procedure and prognosis in BA patients with other underlying diseases. This is a descriptive case study research. We report a boy, 2 months and 11 days with jaundice all over his body since one week old; putty stool, and dark urine. Old man's face, icteric, rib xylophone, subcostal retraction, rales, continuous heart murmur, and wasting. Total and direct bilirubin, SGOT, SGPT, and gamma GT are increased. A Kasai surgical procedure was carried out, but did not significantly improve his condition because the operation was performed at the age of 4 months and 8 days with liver cirrhosis, sepsis, pneumonia, and malnutrition. Cytomegalovirus (CMV) infection and acyanotic congenital heart disease also worsened his preoperative condition. Kasai portoenterostomy is a method of managing biliary atresia, but our patient was diagnosed with biliary atresia accompanied by CMV infection, congenital heart disease, or pneumonia, so the procedures not enough for this condition, and mortality rate is higher than biliary atresia alone. Age at surgery time also influences the prognosis.

Keywords: Biliary atresia; jaundice; congenital heart disease



GREEN MEDICAL
JOURNAL
E-ISSN 2686-6668

Article history:

Received: 11 January 2023

Accepted: 20 March 2024

Published: 29 April 2024

Published by:

Faculty of Medicine
Universitas Muslim Indonesia

Mobile number:

+62821 9721 0007

Address:

Jl. Urip Sumoharjo Km. 5, Makassar
South Sulawesi, Indonesia

Email:

greenmedicaljournal@umi.ac.id

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Introduction

The intrahepatic and extrahepatic bile ducts are involved in the obstructive cholangiopathy known as biliary atresia.¹ About 25 to 30 percent of patients and long-term survivors have biliary atresia. The incidence of BA worldwide varies from 1 in 8,000 to 18,000 live births.² The reported incidence of BA varies by geography, with larger occurrences found in the Asia and Pacific region. About 1 in 5000 live births in Taiwan, 1 in 10,000 in Japan, 1 in 17,000–19,000 in the UK and France, 1 in 19,000 in the Netherlands, and 1 in 15,000 in the United States have the condition.³ There are no clear reports regarding the incidence of biliary atresia in Indonesia.

Putty stools, hepatomegaly, and prolonged jaundice are the newborn signs of biliary atresia.¹ At the time of diagnosis, biliary atresia in newborns and babies is linked to cytomegalovirus (CMV) infection. It is hypothesized that CMV infection triggers an immunological response that damages the liver and biliary tree, leading to biliary atresia.⁷ Infants with biliary atresia frequently have congenital structural abnormalities. The incidence rate varies between 13.4% and 20.3%. One of the most prevalent congenital malformations is congenital heart disease (CHD) that coexist with biliary atresia, occurring in 6.3% to 15% of infants. Therefore, it is believed that newborns with CHD are at a significant risk of developing biliary atresia.⁴ 69% of all CHD fatalities in 2017 were in newborns under the age of one year. Meanwhile, respiratory infections (i.e., pneumonia) are the leading cause of death in children globally. Infants with hemodynamically severe CHD are at high risk of developing acute respiratory failure (ARF), the majority of which is caused by pneumonia (70% of cases).⁵

The biliary atresia must be recognized early in these patients. It is lethal if untreated, with a reported 3-year survival rate of fewer than 10%.¹ In cases of cholestasis due to biliary atresia, the success rate of Kasai procedure is highest when performed before the baby is 30-45 days old.⁶ Meanwhile, if accompanied by CMV infection, congenital heart disease, or pneumonia, it will further worsen the prognosis. This report aims to determine the success rate of Kasai procedure performed on BA patients with CMV, congenital heart disease and pneumonia aged > 45 days and the prognosis. Therefore we report on a male infant who was diagnosed with biliary atresia, accompanied by CMV infection, congenital heart disease and pneumonia.

Methods

This research design is a descriptive case study, which is a research method used to create a picture of the problem that occurred, which aims to describe what happened when the research was carried out. The subject in this case report is a boy aged 2 months 11 days who was diagnosed with biliary atresia with CMV, congenital heart disease and pneumonia and was treated at Wahidin Sudirohusodo General

Hospital, Makassar. This research uses secondary data. We selected data on patients with biliary atresia with CMV, congenital heart disease and pneumonia who were treated at Wahidin Sudirohusodo General Hospital, Makassar based on medical records. This study did not use informed consent because data was taken secondary (medical records). This case report keeps the patient's personal data confidential.

Case

A boy, 2 months 11-days of age came to the hospital with the chief complaint 2 months of jaundice all over his body. There was putty stool and dark urine from the age of 1 week. The patient had shortness of breath since birth. The patient was also diagnosed with acyanotic congenital heart disease. The patient had undergone phototherapy for 2 days.

On physical examination, there was an old man's face, scleral icteric, jaundice, xylophone ribs, and wasting. There was subcostal retraction, rales, and continuous heart murmur. Based on physical examination of the abdomen, hepatomegaly was found.

Laboratory values revealed altered liver function test direct bilirubin (17.14 mg/dL) and total bilirubin (20.35 mg/dL). There was elevated, increased SGOT (420 U/L) and SGPT (388 U/L), increased Gamma GT (430 U/L), hyponatremia (124 mmol/L) and hypoalbuminemia (3.3 gr/dL), On investigation there was anemia (8.4 gr/dL), ferritin >1200 ng/ml, leukocytosis (16,500/ μ L), reactive thrombocytosis (513,000/L), Anti-Toxoplasma IgG reactive (titer 10), and anti-CMV IgG reactive (titer 11).

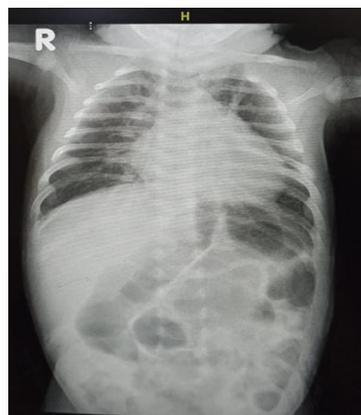


Figure 1. Thorax Imaging

The peripheral blood smear is examined, and the result is normocytic normochromic anemia, a presumed chronic disease source, together with leukocytes displaying indications of infection. Procalcitonin was 0.81 ng/dL. Routine urine examination results showed bilirubin 2+.

The chest X-ray showed an L to R shunt (Figure 1). Echocardiography showed a small atrial septal defect + ventricular septal defect PMO + small hemodynamic significant patent ductus arteriosus. The results of a 2-phase ultrasound examination showed an uncontracted gallbladder (CI: 13.95 % (Normal

CI: 86% +/- 18%) (Figure 2)

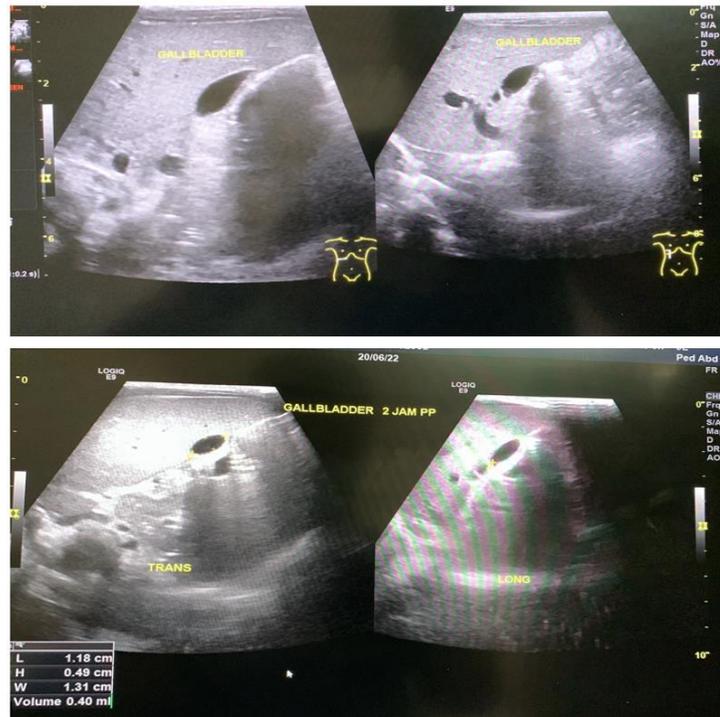


Figure 2. 2-phase ultrasonography. a) during fasting, b) post-prandial)

The results of MR cholangiopancreatography (MRCP) showed the structure of the cystic duct, common bile duct, and no connection between the right and left intrahepatic hepatic ducts according to type IIa biliary atresia (Figure 3).

On the 25th day of treatment, the cascading procedure was performed (Figure 4). A black liver was found and there was a gallbladder, not dilated, no left and right hepatic ducts, and no common bile duct. The common hepatic and left and right hepatic ducts and the common bile duct were fibrotic tissue, a remnant appearance.



Figure 3. MR Cholangiopancreatography

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Figure 4. Kasai procedure

This patient was diagnosed with septic shock, extrahepatic cholestasis et causa biliary atresia type III, intrahepatic cholestasis et causa cytomegalovirus infection, acyanotic congenital heart disease et causa ASD+VSD+PDS, community-acquired pneumonia, hypoalbuminemia, elevated transaminase enzymes, malnutrition-marasmus type, and electrolyte imbalance.

On Treatment, the patient received ampicillin 85 mg/6 hour/intravenously, gentamicin 8,5 mg/12 hours/intravenously, then changed into ceftriaxone 340 mg/24 hours/intravenously to meropenem 115 mg/8hours/intravenously to ceftazidime 170 mg/12 jam/intravenously, amikacin 85 mg/24 hours/intravenously, valganciclovir 60 mg/12 hours/oral, ursodeoxycholic acid 35 mg/8 hours/sonde, cholestyramine 0.85 gram/24 hours/sonde, spironolactone 3.5 mg/12 hours/sonde, furosemide 2 mg/24 hours/sonde. However, on the 56th day of treatment, the patient was passed away.

Discussion

Biliary atresia (BA) is an idiopathic cholangiopathy, which is a disease that progressively damages the extrahepatic bile ducts due to obliterative fibroscleral lesions. This is the most common cause of liver cirrhosis and liver failure and death if not treated.⁷ Biliary atresia's underlying etiology is unknown. According to many views, the aberrant embryogenesis or ductal inflammation, damage, and necrosis that results in progressive fibrosis of the intrahepatic and/or extrahepatic bile ducts are caused by a complex etiology. Between 3% and 20% of kids with BA have a congenital disorder or related condition.⁸

Our patient had a positive anti-CMV IgG result. Perhaps the presence of CMV can trigger biliary atresia. Several viruses such as cytomegalovirus (CMV), reovirus, human herpes virus, human papillomavirus, adenovirus, Epstein-Barr virus, hepatitis B virus, parvovirus B19 and rotavirus (RV) may play a role as etiology. Poisoning as well as genetic and immunological factors are also suspected as the cause of biliary atresia.^{3,8} Intrahepatic cholestasis initially had a higher prevalence of cytomegalovirus infection (without BA). However, several investigations have demonstrated that extrahepatic cholestasis can be a site of CMV infection (BA). According to the study, viruses like CMV might function as catalysts for immune system dysregulation due to genetic effects, which can ultimately result in BA. Hepatocytes and cholangiocytes can both become infected with cytomegalovirus and grow the virus. The virus can directly harm the liver and bile duct system as well as the immune system of infected cells, which causes inclusion bodies to develop in hepatocytes and epithelial vascular cells, particularly when they are combined with bile duct epithelial cells.^{3,9,10} As Zhao's study (2021) showed that biliary atresia patients who were also infected with CMV had a poorer prognosis, concerning jaundice clearance.¹¹

Antiviral medications have been a feasible therapy option during the past three decades. Several preliminary investigations in kids with symptomatic CMV treated for 6 weeks with intravenous ganciclovir show encouraging clinical improvement. Ganciclovir has been superseded by the antiviral medication valganciclovir, which is taken orally. It is used to treat CMV symptoms. 16 mg/kg/dose is administered twice day for six months. Valganciclovir was administered orally every 12 hours to our patient.¹²

Clinically, Biliary atresia comes in two different kinds: perinatal and embryonic. In the early postpartum weeks, there is jaundice in the perinatal kind, which is (acquired, or non-syndromic), asymptomatic, and. The embryonic form, on the other hand, lacks a jaundice-free interval and has one or more congenital anomalies, including intestinal malrotation, site anomaly, bronchial anomaly, polysplenia or asplenia, discontinuity of the inferior vena cava's suprarenal section with azygote continuation, and preduodenal portal vein. Thus, the biliary tree's aberrant growth appears to be the cause of embryo formation, which includes children with biliary atresia splenic malformation syndrome

(BASM).¹³

Jaundice, which occurs when the liver does not eliminate bilirubin, is the initial sign of biliary atresia. Jaundice is brought on by bilirubin accumulation in the blood due to bile duct obstruction.¹⁴ It can be challenging to spot jaundice. Due to an underdeveloped liver, many healthy newborns experience moderate jaundice during their first one to two weeks of life. Unlike biliary atresia jaundice, which worsens over time, this kind of jaundice goes away 2 to 3 weeks after birth.³ Gray or white stools indicate a lack of bilirubin reaching the intestines, as do poor weight gain and growth. Dark urine indicates excessive levels of bilirubin in the blood leaking into the urine.¹⁴ Our patient complained of hepatomegaly, white stools, black urine, and persistent icterus more than two weeks after birth. It is crucial to know what color this chalky/putty stool is. Three separate (8-hour) stools are referred to as stool three servings. The three servings of feces collected in biliary atresia will typically be pale white (putty).

The infant appears healthy and shows no symptoms of failure to thrive in the early stages. At a more advanced stage, however, there will be obvious clinical symptoms, such as gastrointestinal and cerebral bleeding caused by portal hypertension or reduced vitamin K absorption, ascites and splenomegaly, which are signs of portal hypertension.^{4,12} Patients may also experience malnutrition and malabsorption brought on by chronic liver disease, gallbladder removal, and cholestasis. Our patient has been malnourished. In BA patients, the patient's daily caloric needs will increase, and it must be ensured that the patient maintains an intake of 125-150 percent of the recommended caloric intake. Due to its capacity to be absorbed directly through the portal vein, medium chain triglycerides (MCTs) should be included in enteral nutrition when it is necessary. A feeding tube should be available if required. To avoid developing a deficit in fat-soluble vitamins, vitamins A, D, E, and K should also be administered. The suggested doses of vitamin A are 5000–25000 IU/day, vitamin E is 25 IU/kg/day, vitamin D is 1200–4000 IU/day, and vitamin K is 2.5 mg three times per week. Prothrombin time and vitamin levels should be frequently checked. Our patient received 0.5 ml/24 hours/sonde vitamin drop and 12x50ml infant milk via sonde.¹⁵

Diagnosing biliary atresia is a challenge. The particular cause of intrahepatic cholestasis can be determined using diagnostic investigations that are guided by the history and physical examination.¹⁶ One study in Taiwan reported that clay excreta had high sensitivity (76.5%) but low specificity (99.9%) in predicting biliary atresia.¹⁷ Since time is an important factor in the prognosis of biliary atresia, a broad investigative approach is recommended. Ruling out other possible etiologies serology of congenital infection (TORCH; Toxoplasmosis, Rubella, CMV, Herpes simplex virus) is indicated.¹⁸ High serum Gamma GT (GGT) levels are usually found. Alkaline phosphatase is produced by bile duct epithelial cells and serum levels are elevated in cases of extrahepatic obstruction, cholangitis, and intrahepatic

cholestasis. Because alkaline phosphatase is also produced in bone, associated bone conditions may cause difficulties in interpreting the results. In cases of high alkaline phosphatase levels and GGT above 600 U/L, biliary atresia, or other obstructive ductal lesions, or even alpha-1 antitrypsin deficiency would be prime diagnostic candidates. GGT has been reported as a BA discriminatory tool and at a cutoff value of 250.5 U/L it has a sensitivity of 86.7% and a specificity of 65%.¹⁹

We performed an MRCP examination on our patients. An accurate non-invasive imaging method for the diagnosis of biliary atresia is functional MRCP. To prevent needless surgery in newborns with cholestatic jaundice, preoperative MRCP is highly advised. A tiny gall bladder on an MRCP has been said to be strongly indicative of biliary atresia.²⁰ Because MRCP does not directly demonstrate bile flow like hepatobiliary scintigraphy or ERCP does, this is one of its weaknesses.¹³ We diagnosed our patient with biliary atresia because it was clinically consistent with biliary atresia. The patient had icterus, puffy stools, and dark urine, as well as hepatomegaly. An investigation also lead to biliary atresia, which indicates an underdeveloped gallbladder.

To identify the existence and location of obstruction, every patient with suspected biliary atresia should have an exploratory laparotomy and direct cholangiography. Patients with lesions that can be repaired can receive direct drainage. In the absence of a correctable lesion, biliary epithelium can be identified and the size and patency of the remnant bile duct can be assessed using a frozen section taken from the transected porta hepatis.²⁰ Even though 80% of people with biliary atresia will eventually need a liver transplant, the Kasai procedure is still the preferred initial treatment. The Roux-en-Y branch, which is anastomosed to the porta hepatis following biliary resection, is used in the Kasai procedure to reestablish biliary flow between the liver and the gut. At the start of surgery, the liver and biliary tract are examined to make the diagnosis of biliary atresia. If the Kasai procedure is carried out before the baby is eight weeks old, the success rate for restoring normal bile flow is substantially higher (90%) than otherwise. Therefore, it's crucial to report infants with suspected biliary atresia early and evaluate them right away.²¹ Likewise, research by Verkade, et al (2016) concluded that kasai surgery must be carried out immediately before the age of 35 days to get a better prognosis.²²

In general, the diagnosis can be made if there is a fibrotic gallbladder and a cholestatic or even fibrotic liver. Cholangiography should be done if the gallbladder is patent or if there is a cyst near the liver's hilum. The color of the cyst or gallbladder's contents (yellow-green vs. translucent) should be noted since it can be used to determine the kind of biliary atresia and alter the surgical strategy. By using conventional techniques, jaundice can be lost in 50 - 60% of cases.⁷ In this patient, Kasai surgery was performed with the identification of the liver when opening the peritoneum, the impression was black and the gallbladder was present, not dilated. There were no left and right hepatic ducts, and no common bile ducts were found.

Common hepatic and left and right hepatic duct and common bile duct are only fibrotic tissue, remnant impression. Based on the anatomy of biliary atresia it is classified according to the degree of obstruction according to Japanese and Anglo-Saxon classification which consists of 3 main types, namely: Atresia of type 1 affects just the common bile duct, gallbladder, and patent hepatic duct (distal biliary atresia). The hepatic duct is affected by type II atresia, although the proximal intrahepatic duct is patent (proximal biliary atresia). Type IIa, gallbladder and patent common bile duct (sometimes with hilum cysts) (cystic atresia). Obliteration of the gallbladder, cystic duct, and common bile duct in type IIb. Type III: bilateral intrahepatic hepatic duct discontinuity as well as the entire tract extrahepatic biliary obstruction (complete biliary atresia).⁷ Based on the findings during the Kasai procedure, our patient was diagnosed with type III biliary atresia.

Effective postoperative management includes prevention and treatment of complications such as cholangitis and effective nutrition and family support. Although solid data supporting their utility is lacking, prophylactic antibiotics (to avoid cholangitis) and choleric drugs are sometimes administered.¹³ In addition, in severe cholestasis, ursodeoxycholic acid (UDCA) 20 mg/kg/day, rifampicin 5-10 mg/kg/day and phenobarbitone (5-10 mg/kg/day) can be given. Our patient received ursodeoxycholic acid 35 mg/8 hours/sonde and cholestyramine 0.85 gram/24 hours/sonde. In addition, our patient also received meropenem 115mg/8hours/iv and amikacin 85mg/24hours/intravenously.²³ This is in accordance with the results of the stool culture examination of this patient that the bacteria are sensitive to meropenem and amikacin.

In a study conducted by Mahmud et al, it was found that more than 2,000 extrahepatic cases died and only 6% of cases improved. But among intrahepatic cases 72.9% improved, 12.5% worsened and 14.6% died.²⁴ Complications of cholestasis can be avoided if intervention is done early. The success rate in making bile flow depends on the age of the baby at the time of surgery as well as the experience of the surgeon. The success rate can reach 80% if the operation is performed at the age of less than 30 to 45 days.¹³ The patient's prognosis is not good because the patient underwent Kasai surgery at the age of 4 months 8 days.

Our patient also has acyanotic congenital heart disease which may worsen the prognosis. The combination of BA and congenital heart abnormalities is linked with an especially high mortality risk and is one of the leading causes of death in BA. Mortality in the first year of life was found to be 20% in a recent analysis of the UK National Cohort of Children with Serious Congenital Heart Defects.²⁵ Shunt lesions were more prevalent than other types of lesions, such as pulmonary stenosis (7.7%), including patent ductus arteriosus (PDA), atrial septal defect (ASD), and ventricular septal defect (VSD) (23%). The most frequent congenital cardiac abnormality among patients with biliary atresia is patent ductus arteriosus.²⁶ ASD, VSD, and PDA all affect our patient. Some researchers assumed that BA was caused

by an inflammatory process involving the extrahepatic bile ducts in the late intrauterine or early neonatal period, despite the fact that the exact cause of BA is still unclear. Therefore, faulty organogenesis during the early embryonic phase may be a contributing factor in the pathogenesis of BA with structural malformations. Beginning as early as day 10 of pregnancy, the cardiovascular system develops, and by the end of the seventh week, the heart is virtually fully formed.²⁶ Digitalis and diuretics have long been the cornerstones of pharmacological therapy for heart failure in kids with big left-to-right shunts. Furosemide and spironolactone are two of the diuretics that are commonly used to treat CHF in newborns and young children due to their efficacy and lack of adverse effects. Optimizing diet, maintaining proper hemoglobin levels, and managing the accompanying respiratory symptoms are all part of the overall therapy.²⁷ According to our patients who underwent spironolactone medication at a dosage of 3.5 mg every 12 hours and furosemide at a dosage of 2 mg every 24 hours. However, our patient's electrolyte balance deteriorated after taking diuretics. As in the case of our patient, furosemide may cause clinically severe disturbances in fluid and electrolyte balance, including hypovolemia, hyponatremia, hypochloremia, hypokalemia, and alkalosis.²⁷

Our patient also had complaints of shortness of breath, and on physical examination, there are crackles. Our patient was diagnosed with community-acquired pneumonia. Acute lower respiratory tract infections are made worse by congenital heart disease, which is a significant risk factor. Pneumonia is the most typical acute lower respiratory tract illness. Pneumonia can be caused by a number of circumstances, including severe starvation.²⁸ There is pulmonary overcirculation and pulmonary oedema in CHD, such as acyanotic CHD, due to a left to right shunting of blood via a septal defect or the artery duct. The lower respiratory tract infection spreads to the pulmonary oedema, which results in congestive heart failure. Children who have cyanotic CHDs such as VSD, PDA, or atrioventricular septal defect (AVSD) are more likely to develop bronchopneumonia.⁵ In hospitalized cases, neonates with respiratory compromise should always be assumed to have bacterial pneumonia until proven otherwise. Administration of the antibiotic's ampicillin and gentamicin with or without cefotaxime should be started as soon as possible. Ampicillin is also the first-line antibiotic given to children aged > 3 months who have been immunized with uncomplicated pneumonia. For children with severe infections (those in the ICU), those who are not immunized, or in areas with high levels of penicillin-resistant pneumococci, a third-generation cephalosporin antibiotic (ceftriaxone or cefotaxime) should be given. If there is suspicion of an atypical pathogen or if the patient does not improve with this regimen, then a macrolide class can be added.²⁹

On the 56th day of treatment, the patient experienced decreased consciousness, shortness of breath and fever. The patient was diagnosed with septic shock. That same day, the patient was passed away. The poor prognosis of these patients is worsening by congenital heart disease, pneumonia, electrolyte

disturbances, malnutrition, and septic shock. The incidence of cardiac anomalies in biliary atresia was reported to be 8%-16% in a North American multicenter review. Congenital heart disease is associated with a very high risk of death and is one of the leading causes of death in biliary atresia overall.²⁵

Conclusion

Biliary atresia is a rare disease, and has a poor prognosis. Appropriate management should be given immediately to promote a more favorable prognosis. Pneumonia, sepsis, and congenital heart disease may further worsen the prognosis in patients with biliary atresia. The earlier treatment is given, the better the prognosis.

Conflict of Interest

There is no conflict of interest

Funding Sources

There is no funding sources

Acknowledgments

There is no acknowledgments

References

1. Siddiqui A, Ahmad T. Biliary atresia. StatPearls. 2022. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK537262/>
2. Sundaram SS, Mack CL, Feldman AG, Sokol RJ. Biliary atresia: Indications and timing of liver transplantation and optimization of pretransplant care. *Liver Transplant.* 2017;23(1):96–109.
3. Vij M, Rela M. Biliary atresia: Pathology, etiology and pathogenesis. *Futur Sci OA.* 2020;6(5):1-3
4. Fujishiro J, Sugiyama M, Ishimaru T, Watanabe M, Sato K, Hoshino N, et al. Direct hyperbilirubinemia in infants with congenital heart disease. *Pediatr Int.* 2018;60(2):179–82.
5. Jat NK, Bhagwani DK, Bhutani N, Sharma U, Sharma R, Gupta R. Assessment of the prevalence of congenital heart disease in children with pneumonia in tertiary care hospital: A cross-sectional study. *Ann Med Surg.* 2022;73(11):103111.
6. Setyoboedi B, Tri Utomo M, Aji Prihaningtyas R, Kusuma Winahyu A, Arief S. Tingkat pengetahuan atresia bilier pada bidan di Puskesmas Kabupaten Sidoarjo. *J Abdi Insa.* 2022;9(4):1839–46.
7. Manoppo J. *Atresia Bilier. Buku ajar gastrohepatologi anak.* Ikatan Dokter Anak Indonesia; 2022.
8. Davenport M. *Biliary atresia.* Springer. 2020
9. Kumaheri MA, Oswari H. The association between biliary atresia and cytomegalovirus infection. *eJournal Kedokt Indones.* 2017;5(2):1-7
10. Situmorang L, Setyoboedi B, Arief S, Mastutik G. Infection of cytomegalovirus (cmv) in cholestasis infant with biliary atresia. *Indones J Clin Pathol Med Lab.* 2019;26(2):175–81.
11. Zhao Y, Xu X, Liu G, Yang F, Zhan J. Prognosis of biliary atresia associated with cytomegalovirus: A meta-analysis. *Front Pediatr.* 2021;9(8):1–9.
12. Jenks C, Mithal L, Hoff S. Early identification and amnagement of congenital cytomegalovirus. *Otolaryngol Clin N Am.* 2021.
13. Sira. *Biliary atresia: A challenging diagnosis.* *Glob J Gastroenterol Hepatol.* 2013.
14. Schreiber RA, Harpavat S, Hulscher JBF, Wildhaber BE. Biliary atresia in 2021: epidemiology, screening and public policy. *J Clin Med.* 2022;11(4).

15. Islek A, Tunggor G. Biliary atresia and congenital disorders of the extrahepatic bile ducts. *World J Gastrointest Pharmacol Ther.* 2022;13(4):33–46.
16. Shah R, John S. Cholestatic Jaundice. *StatPearls.* 2021. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK482279/>
17. Ghazy RM, Adawy NM, Khedr MA, Tahoun MM. Biliary atresia recent insight. *Egypt Pediatr Assoc Gaz.* 2018;66(1):1–8
18. Pollock G, Minuk GY. Diagnostic considerations for cholestatic liver disease. *J Gastroenterol Hepatol.* 2017;32(7):1303–9.
19. Liu JQ, Chen WJ, Zhou MJ, Li WF, Tang J, Zhou QC. A nomogram predicting the prognosis of children with biliary atresia after hepatoportoenterostomy. *Front Pediatr.* 2021;9(2):1–10.
20. Alkan M, Tutus K, Fakioglu E, Ozden O, Hatipoglu Z, Iskit SH, et al. Laparoscopy-assisted percutaneous cholangiography in biliary atresia diagnosis: comparison with open technique. *Gastroenterol Res Pract.* 2016.
21. Kliegman R, Geme J, Blum N, Shah J, Tasker R. *Nelson textbook of pediatrics.* 21th ed. Canada: Elsevier; 2020.
22. Verkade HJ, Bezerra JA, Davenport M, Schreiber RA, Mieli-Vergani G, Hulscher JB, et al. Biliary atresia and other cholestatic childhood diseases: Advances and future challenges. *J Hepatol.* 2016;65(3):631–42
23. Bhatia V, Bavdekar A, Matthai J, Waikar Y, Sibal A. Management of neonatal cholestasis: Consensus statement of the pediatric gastroenterology chapter of Indian academy of pediatrics. *Indian Pediatr.* 2014;51(3):203–10.
24. Mahmud S, Gulshan J, Parvez M, Tasneem F, Ahmed SS. Etiology and outcome of neonatal cholestasis: an experience in a tertiary center of Bangladesh. *Egypt Liver J.* 2022;12(1):1–11.
25. Aldeiri B, Giamouris V, Pushparajah K, Miller O, Baker A, Davenport M. Cardiac-associated biliary atresia (CABA): A prognostic subgroup. *Arch Dis Child.* 2021;106(1):68–72.
26. Fattouh AM, Mogahed EA, Hamid NA, Sobhy R, Saber N, El-Karakasy H. The prevalence of congenital heart defects in infants with cholestatic disorders of infancy: A single-centre study. *Arch Dis Child.* 2016;101(9):803–7.
27. Ogawa K, Kawachi F, Mori T, Hishitani T, Hoshino K. Electrolyte Imbalance Caused by Diuretic Therapy in Infants with Congenital Heart Diseases. *Pediatr Ther.* 2017;07(1):7–10.
28. Harelina T, Setyoningrum RA, Sembiring YE. Faktor risiko pneumonia pada anak dengan penyakit jantung bawaan. *Sari Pediatr.* 2020;21(5):276.
29. Suci LN. Pendekatan diagnosis dan tatalaksana pneumonia pada anak. *J Kedokt Nanggroe Med.* 2020;3(1):30–8.

Original Article

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Effect of Dangke on Changes in Neutrophil to Lymphocyte Ratio in Obese White Rats

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ABSTRACT

Introduction: Obesity is associated with inflammation. Previous research has found that obesity determined by Body Mass Index (BMI) and Waist Circumference (LP) is associated with inflammation. Dangke contains *Indigenos Lactic Acid Bacteria*. The presence of lactic acid bacteria in fermented products has very positive benefits for health. The function of papaya sap which is used in making dangke, can act as an antibacterial and anti-inflammatory ingredient.

Methods: Pure experimental research with a design, namely Pre-Post Randomized Clinical Trial Design. Data analysis used the independent T-test/Mann-Whitney test with a value <0.05 .

Results: The difference in the mean levels of Neutrophil to Lymphocyte (NLR) in the Intervention and control groups obtained a p-value of 0.94 which means that there is no relationship between control and intervention on NLR levels. The average change in NLR levels in the control group p-value of 0.61 which means there is no significant change in NLR levels in test 1 and test 2. The average change in NLR levels in the intervention group before and after the intervention was given a p-value of 0.07, which means there was no significant change in NLR levels in the intervention group.

Conclusion: This study showed that intervention with Dangke did not yield a significant alteration in the NLR levels within the animal model of obesity.

Keywords: Dangke; neutrophil lymphocyte ratio; obesity; inflammation



GREEN MEDICAL
JOURNAL
E-ISSN 2686-6668

Article history:

Received: 3 December 2023

Accepted: 23 April 2024

Published: 30 April 2024

Published by:

Faculty of Medicine
Universitas Muslim Indonesia

Mobile number:

+62821 9721 0007

Address:

Jl. Urip Sumoharjo Km. 5, Makassar
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Introduction

Obesity is associated with inflammation. Waist circumference (LP) and body mass index (BMI) show that obesity is associated with inflammation. An imbalance between incoming and outgoing energy intake is the main cause of obesity. Too much food intake causes high energy intake, but low metabolism and physical activity in the body cause low energy output. Body fat, skinfold thickness, and other measurements of abdominal fat were also positively correlated with inflammation. Many diseases are caused by obesity. The morbidity and mortality rate in obese sufferers is very high. Obesity involves systemic inflammation due to the accumulation of excess adipose tissue and is generally associated with negative health impacts. The adverse health impacts associated with obesity occur primarily in people with fat distribution in the upper body.⁽¹⁾⁽²⁾

The obesity epidemic in the world with more than 1 billion adults who are overweight, 300 million adults are obese. The prevalence of obesity in the world increased by 8.7% - 13.1%, increasing to 10.5% -15.1% in women, and by 6.6% - 11.1% in men. In addition, prevalence in Asian countries that are members of the World Health Organization increased by 1.9–4.7% from 2000 to 2016, 2.7–6.1% in women, and 1.1–3.3 % in men.^{(3),(4)}

The prevalence of overweight o obesity in the Indonesian adult population increased from 2007 to 2018. The prevalence of obesity was around 8.6% to 11.5% from 2007 to 2013 and around 13.6% in 2018. However, from 2007 to 2018, namely 10.5%, 14.8%, and 21.8% respectively. Based on gender, the prevalence of obesity in adult women (>18 years) was 32.9% in 2013, an increase of 18.1%. The prevalence of obese adult male population in 2013 was 19.7%, higher than in 2007 (13.9%) and 2010 (7.8%)⁽⁴⁾.

There are keys to the human defense system when inflammation occurs, namely neutrophils and lymphocytes. Several studies suggest that increases in neutrophils, lymphocytes, and total leukocytes are associated with metabolic disorders caused by obesity. NLR is the ratio of neutrophils to lymphocytes and has been shown in several studies to be a marker of inflammation associated with metabolic syndrome, insulin resistance, and obesity^{(4),(5)}.

Neutrophil To Lymphocyte (NLR) is measured as the ratio of the absolute number of neutrophils to the number of lymphocytes, which is a new inflammatory biomarker that is used as a prognostic factor for various diseases and NLR as a marker for assessing the severity of inflammation in obesity. The higher the NLR level, the higher the value of neutrophil cells in the body and the more severe the inflammation^{(6),(7)}.

Dangke is a buffalo or cow's milk product that is traditionally produced in South Sulawesi. Its distinctive characteristics are its oval shape, chewy texture, and strong milky aroma and taste. Danke contains indigenous lactic acid bacteria (BAL indigenos). The presence of lactic acid bacteria in fermented products has a very positive impact on health. Danke is made by coagulating milk with papaya sap. The benefits of papaya sap used in danke production have been reported to have anti-inflammatory and antibacterial properties^{(8),(9),(10)}.

Methods

The research method used was pure experimental with a design, namely Pre-Post Randomized Clinical Trial Design. This experiment aims to see the treatment before and after giving dangke to the NLR levels of obese white mice. The rats used were 16 wistar strain rats. How to fatten the rats by feeding fat feed. How to measure NLR by using routine blood tests.

Results

Table 1 Results of Analysis of Differences in Average NLR

Treatment Category	N	Mean±SD	P value
Control	8	0.28±0.14	0.94
Intervention	8	0.27±0.12	

Table 1 shows that in the intervention and control groups after being given the intervention, there is a difference in the average NLR in the intervention and control groups after being given the intervention, where the NLR level obtained a p-value of 0.94, which means there is no relationship between the intervention and the NLR level.

Table 2 Results of Analysis of Changes in Average NLR in the Control Group

Treatment Category	N	Mean±SD	P value
Test 1	8	0.23±0.16	0.61
Test 2	8	0.28±0.14	

Table 2 shows the average change in NLR in the control group. NLR levels obtained a p-value of 0.61, which means there was no significant change in NLR levels in test 1 and test 2.

Table 3 Results of analysis of changes in average NLR in the intervention group before and after being given the intervention

Treatment Category	N	Mean±SD	P value
Before	8	0.18±0.08	
After	8	0.12±0.12	0.07

Table 3 shows the average change in NLR in the intervention group before and after being given the intervention, where the NLR level obtained a p-value of 0.07, which means there was no significant change in NLR levels before and after the intervention in the intervention group.

Discussion

NLR has been included as a marker of inflammation, believed to reflect the balance between innate (neutrophils) and adaptive (lymphocytes) immune responses. Previous research shows that an increase in NLR is associated with an increase in the concentration of various pro-inflammatory cytokines which can cause cellular DNA damage. However, despite research studying the relationship between these parameters and various chronic diseases with inflammation there are only a few papers discussing their relationship with obesity and diet quality ⁽¹⁾.

From the research results, it was found that the average NLR level in the intervention group before administration was 0.18 ± 0.08 and after administration was 0.12 ± 0.12 . Meanwhile, in the control group, the average NLR level before administration was 0.23 ± 0.16 and after administration was 0.28 ± 0.14 . In this study, giving dangke did not have a significant impact on NLR levels because the results of the study for the intervention group consisting of 8 mice showed an increase in NLR levels in 6 mice, a decrease in NLR levels in 1 mouse, and NLR levels remained the same in 1 mouse. mice, while in the Control group consisting of 8 mice there was an increase in NLR levels in 5 mice, and a decrease in NLR levels in 3 mice. The intervention group's NLR levels increased by 5 mice and the control group's NLR levels increased by 6 mice, which is only a difference of 1 point, so giving dangke to mice did not affect NLR levels.

This research is in line with Igor N which can be used as a synbiotic supplement combined with foods containing low carbohydrates and high protein. The results of the research from the 2 groups, namely intervention and placebo, showed that there was no significant difference in BMI and weight loss for 3 months. The study shows that there are limitations in the use of supplements used to adjust the gut microbiota by inhibiting microbial fermentation associated with foods high in protein and low in carbohydrates related to metabolism that requires further research ⁽¹¹⁾.

This research is not in line with Payam Syarifan's research findings published in the Journal of Health,

Population, and Nutrition regarding "Efficacy of Low Fat Milk and Yogurt Fortified with Vitamin D3 on Systemic Inflammation in Adults with Abdominal Obesity." Here, the results showed that serum levels of neutrophils, lymphocytes, platelets, and red blood cell distribution (RDW) before and after treatment were significantly lower in the fortified dairy group. The results showed that serum neutrophil, lymphocyte, platelet and RDW levels before and after intervention were significantly lower in the fortified milk product group ($p < 0.05$). The values of neutrophils to lymphocytes (NLR), platelets to lymphocytes, and RDW to platelets (RPR) decreased significantly in the enriched group ($p < 0.05$). There were significant differences between groups. It has been shown that administration of probiotics has been shown to have an effect on the immune response, increase lactose tolerance, prevent diarrhea, have anti-inflammatory effects, and even reverse intestinal dysbiosis associated with obesity ⁽¹²⁾.

In the *danke* there is (BAL indigenos). BAL is milk which also has the potential to be a probiotic for the development of functional foods. BAL is generally marketed as bacteria that contain probiotics, especially from the genera *Bifidobacterium* and *Lactobacillus*. Probiotics are proven to have benefits for health, reducing (BMI) and body weight because probiotics can prevent toxic substances, proteins, lipopolysaccharides from passing through the epithelium, and can reduce intestinal permeability, causing reduced energy absorption, and can provide an anti-inflammatory mechanism that can reduce fat in the body. adipocyte cells as an anti-obesity effect. NLR was included as an inflammatory marker thought to reflect similarities between adaptive immune (lymphocyte) and innate immune (neutrophil) responses. Previous research shows that an increase in NLR is associated with an increase in various pro-inflammatory cytokines because they can damage DNA in cells. However, although there are studies investigating the relationship between these parameters and various chronic diseases involving inflammation, few publications address the relationship with obesity and diet quality ^{(1),(11),(13)}.

NLR is a more sensitive parameter for bacterial infection than an increase in the number of red blood cells. The prospective longitudinal observational study reports the association between clinical severity and lymphocytopenia in patients with severe sepsis and septic shock in an oncology intensive care unit ^{(14),(15)}.

NLR is a parameter used to determine the inflammatory response and immune system in the body, especially those related to certain diseases or conditions. The NLR value is calculated by dividing the number of neutrophils (a type of white blood cell) by the number of lymphocytes (another type of white blood cell). An increase in NLR indicates inflammation or stress and a decrease in NLR indicates a less effective immune response. The value of NLR levels in mice is not significant or does not show the expected results, including: errors in blood collection methods or blood analysis methods, diseases suffered by mice, administration of drugs, inadequate nutrition, genetic factors, and environmental factors such as stress, temperature, light, and the social environment of mice can also influence the immune

system response and NLR levels of mice.

Conclusion

This study is the first study with the results of research on the effect of dangke on changes in NLR levels in obese white rats concluded as follows. There is no significant relationship in NLR levels in both the control group and the intervention group to the administration of dangke. Therefore, further research is needed to produce more accurate findings. For researchers, it is hoped that the dose of dangke administration needs to be increased so that the results of NLR levels in the research sample can be more significant changes, the treatment of rats during the study is more concerned both from high-fat feeding both the environment in white rats.

Conflicts of Interest

There is no conflict of interest

Funding sources

There is no funding source

Acknowledgments

There is no acknowledgment

References

1. Parveen KZ, AvabrathaRodríguez-Rodríguez E, López-Sobaler AM, Ortega RM, Delgado-Losada ML, López-Parra AM, Aparicio A. Association between neutrophil-to-lymphocyte ratio with abdominal obesity and healthy eating index in a representative older Spanish population. *Nutrients*. 2020;12(3). doi:10.3390/nu1203085
2. Novri, SD Risk Factors for Obese Women in Lower Middle Socioeconomic Status, Thesis, Health Nutrition Study, Muhammadiyah University of Gresik. 2021;2(2):163-168.
3. Suryaalamsah Ii, Akbar Z, Harisatunnasyitoh Z, Et Al. Increasing Knowledge About Overweight and Obesity among Caregivers at the IGBS Darul Marhamah Islamic Boarding School, Jatisari Village, Cileungsi District, Bogor Regency, West Java. *Proceedings of the National Seminar on Community Service LPPM Umj*; 2019.
4. Wijayanti E, Retnoningrum D, Hendrianintyas M. The relationship between inflammatory markers and hemoglobin in obesity at the Faculty of Medicine, Diponegoro University for the period May-September 2018. *DiscoverSys Digest of Medical Sciences*. 2019;10(1):242-246. doi:10.1556/ism.v10i1.347
5. Sofia Yusnur Rafida, Hairuddin, Muhammad Hasan. Relationship Between Neutrophil-to-Lymphocyte Ratio (NLR) Values and Procalcitonin (PCT) Levels in COVID-19 Patients in Jember Regency. *Andalas Medical Faculty Journal*; 2022.
6. Aydın M, Ahsen Yilmaz, Feti Tulubas. Neutrophil lymphocyte ratio in obese adolescents. *Northern Clinics of Istanbul*. Published online 2019. doi:10.14744/nci.2015.25238.
7. Harun, A. 2022. Systematic Review: The Role of Neutrophil Cells in the Metabolic Disease Diabetes Mellitus Type 2. *Faculty of Health Sciences*. Aisyiyah University Yogyakarta; 2022.
8. Nugraha KA. Bacteriostatic and Bactericidal Agents in Dangke, Thesis, Fkg Hasanuddin University Makassar; 2021.

9. Rifah HA, Budiartman S, Harsi DK. Antibacterial Activation of Dried Papaya Sap Against *Staphylococcus Aureus* in Dangke. *Journal of Technology and Food*. Bogor Agricultural Institute. 2019;25(1).
10. Sulmiyati S, Said NS. Characteristics of Buffalo Milk Dangke with the Addition of Dry Papain Crude. *agriTECH*. 2019;38(3):345.
11. Bila Yunisa Tri Utami S, Ary Lantika U, Rachmi A. Scoping Review: Effectiveness of Consuming Probiotics on Body Weight in Overweight and Obese Adults. *Bandung Conf Ser Med Sci*. 2022;2(1):402–9.
12. PayamSharifan. Effectiveness of Low Fat Milk and Yogurt Enriched with Vitamin D3 on Systemic Inflammation in Adults with Abdominal Obesity. *Journal of Health, Population and Nutrition*. 2022;41(8).
13. Nurwilda Kaswi. The Effect of Milk Type on Lactic Acid Bacteria Species in Dangke from Enrekang Regency. Faculty of Science and Technology, Uin Alauddin Makassar; 2020.
14. YuliatiWidiastuti. The Effect of Probiotic and Selenium Supplementation on the Immune Response of NLR (Neutrophil Lymphocyte Count Ratio), Hemoglobin and Albumin in Wistar Rats Induced by *Mycobacterium Tuberculosis*. Diponegoro University Faculty of Medicine; 2019.
15. Nishimura Mie. Effects of Yogurt Containing *Lactobacillus Plantarum* HOKKAIDO on Immune Function and Stress Markers. Hokkaido Information University, Ebetsu, Hokkaido, Japan. 2019;6(3):275-277.

Personal Hygiene and Environmental Sanitation Factors that Influence the Incidence of Scabies in Al-Bayan

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ABSTRACT

Introduction: The scabies is a skin disease caused by an infestation of *Sarcoptes scabies mites*. The scabies prevalence in Makassar city health profile in 2012 was 8 of 10 major diseases with a huge 6.63 %.

Methods: Analytical description with cross-sectional design. Data was collected through interviews using personal hygiene questionnaires and environmental sanitation observation sheets. The sample for this study was total sampling, a total of 67 junior high school Al Bayan Hidayatullah students were selected.

Results: Chi-square test results that showed that there was a relationship between skin hygiene and the incidence of scabies (p-value = 0.000), there was a relationship between hand hygiene and the incidence of scabies (p-value = 0.014), there was a relationship between nail hygiene and the incidence of scabies (p-value = 0.023), there is a relationship between clothing hygiene and the incidence of scabies (p-value = 0.000), there is a relationship between towel hygiene and the incidence of scabies (p-value = 0.006), there is no relationship between bed and bed linen hygiene and the incidence of scabies (p-value = 0.095), There is no relationship between environmental sanitation and the incidence of scabies (p-value = 0.538), There is no relationship between residential density and the incidence of scabies (p-value = 0.538).

Conclusion: Improve personal hygiene and improve environmental sanitation so that they can avoid scabies as early as possible.

Keywords: Scabies; personal hygiene; environmental sanitation



GREEN MEDICAL
JOURNAL
E-ISSN 2686-6668

Article history:

Received: 24 November 2023

Accepted: 25 April 2024

Published: 30 April 2024

Published by:

Faculty of Medicine
Universitas Muslim Indonesia

Mobile number:

+62821 9721 0007

Address:

Jl. Urip Sumoharjo Km. 5, Makassar
South Sulawesi, Indonesia

Email:

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Introduction

Dermatosis is a disease of the outer layer of the body characterized by itching, redness and swelling. Which occurs due to exposure to chemical substances, exposure to hot sun, bacteria, low immunity, microorganisms, fungi, and personal hygiene factors ⁽¹⁾.

Teenagers who live in Islamic boarding schools often suffer from various kinds of skin disorders, both contagious and non-contagious. Many things that pose risks, for example, hormonal changes, clean living habits and, overcrowding in residential areas which can increase the risk of skin disorders for teenagers in Islamic boarding schools. Skin disorders, for example, scabies in teenagers, are often overlooked ⁽²⁾.

Scabies is an infectious skin disorder that occurs due to exposure to parasites or mites. Scabies mites enter the layers under the skin, causing discomfort in the form of itching. This discomfort occurs continuously, and peaks at night. Touch between two skins can transmit this microorganism, so people closest to someone with scabies are at the highest risk. It is estimated that hundreds of millions of people across continents are exposed to scabies every year, especially in developing countries. High prevalence is associated with poor hygiene, low economy and also homelessness ⁽³⁾.

The spread of scabies in Indonesia itself is quite high. From the number of cases found, this skin disease is ranked third out of 12 skin disorders. In 2016 the number of patients exposed was 3.6% of the population, which was an increase from the previous year of 0.7% ⁽⁴⁾.

There are many things that influence the spread of these mites, including limited access to suitable water, inadequate hygiene practices, and overcrowded housing. Disturbances by these mites are often found in places that have inappropriate density levels and often have close interactions, thus encouraging the spread of scabies ⁽⁵⁾.

Methods

In this study, the analytical description method was used and a cross-sectional design was used. Where the design for this is used to describe personal hygiene factors and environmental sanitation which can influence scabies cases in Al Bayan Hidayatullah Islamic Boarding School Middle School students, Makassar. The population and sample in this research were junior high school students who were selected as a whole 67 people, where the sampling technique is total sampling. Data collection was obtained by interviews as well as observations using observation sheets and questionnaires. The instruments or tools used in this research are data obtained from filling out questionnaires and direct observation. In this research, a Likert scale questionnaire was used. The Likert scale is used to measure the attitudes, opinions and perceptions of a person or group of people. The measuring scale used is ordinal. The measurement

results obtained were often, rarely and never. Each question has a value or score. Then the data is entered into a table adjusted for the variable to be measured. For statistical tests, use univariate and bivariate tests and use the SPSS 23 application services. Univariate analysis to determine the distribution of data for both independent and dependent variables. This is followed by bivariate analysis, namely carrying out statistical analysis using the chi-square test to see what factors are related to scabies cases.

Results

This research was carried out at the Al Bayan Hidayatullah Islamic Boarding School in Makassar, carried out in August 2023, with a total of 67 respondents. The data was then processed using Microsoft Excel 2013 and SPSS 23 applications.

Univariate Results

Table 1. Distribution of Scabies Incidence

Scabies Occurrence	Amount	Presentation (%)
Positive	21	31.3
Negative	46	68.7
Total	67	100

From Table 1, it was found that the number of respondents who were negative for scabies was 46 with a percentage of (68.7%), and the number of respondents who were positive for scabies was 21 respondents with a percentage of (31.3%).

Table 2. Distribution of Characteristics Based on Respondent Age

Respondent Characteristics	Scabies Occurrence		%
	Yes	No	
Age	10-14	20	89.55
	15-19	1	10.44
Total		21	100
Class	7	7	40.29
	8	7	22.38
	9	7	23.88
Total		21	100

From Table 2, it is found that respondents for the highest age at an average age of 10-14 years amounted to 20 respondents with a percentage of (89.55%), and respondents for the highest class level were in the entire class with 7 respondents each in each class with a percentage of (33.33%).

Table 3. Distribution of Personal Hygiene Categories

Personal Hygiene	category	n	Presentation (%)
Hygiene skin	Good	37	(55.2)
	Not enough	28	(41.8)
	Bad	2	(3)
Hygiene Hand	Good	26	(38.8)
	Not enough	37	(55.2)
	Bad	4	(6)
Hygiene Nail	Good	42	(62.7)
	Not enough	25	(37.3)
	Bad	0	(0)
Hygiene Clothes	Good	45	(67.2)
	Not enough	18	(26.9)
	Bad	4	(6)
Hygiene Towel	Good	14	(20.9)
	Not enough	47	(70.1)
	Bad	6	(9)
Hygiene Bed and bed linen	Good	7	(10.4)
	Not enough	34	(50.7)
	Bad	26	(38.8)

From table 3. above, it was found that there were 37 respondents with good skin hygiene (55.2%), 37 respondents with poor hand hygiene (55.2%), 42 respondents with good nail hygiene (62.7%), respondents with good clothing hygiene 45 people (67.2%), respondents with poor towel hygiene 47 people (70.1%) and respondents with poor bed hygiene and bed linen 34 respondents (50.7%).

Table 4. Residential Density Distribution

Room	Residential density		Room
	Good	Bad	
1	0	8	8
2	0	8	8
3	0	8	8
4	0	8	8
5	0	7	7
6	0	7	7
7	0	8	8
8	6	0	6
9	7	0	7
Total	13	54	67

From table 4. above, the results show that the rooms occupied by the Santri are categorized as bad for the density level of 7 rooms and occupied by 54 people with a percentage of (80.6%) and the rooms occupied by the Santri are categorized as good for the density level as many as 2 rooms and occupied by 13 people with a percentage (19.4%).

Table 5. Distribution of Environmental Sanitation

Assessment Components	Criteria	Frequency (%)
Clean water facilities	Good	54 (80.6%)
	Bad	13 (19.4%)
Latrine (means of waste disposal)	Good	13 (19.4%)
	Bad	54 (80.6%)
Waste water disposal facilities (SPAL)	Good	13 (19.4%)
	Bad	54 (80.6%)
Waste disposal facilities	Good	13 (19.4%)
	Bad	54 (80.6%)

From Table 5. above, the results show that the rooms occupied by the students are categorized as bad for the density level of 7 rooms and occupied by 54 people with a percentage of (80.6%) and the rooms occupied by the students are categorized as good for the density level as many as 2 rooms and occupied by 13 people with a percentage (19.4%).

Bivariate Analysis Results

Table 6. Relationship between personal hygiene and the incidence of scabies at the Al Bayan Hidayatullah Islamic boarding school in Makassar

Personal Hygiene	Category	Scabies incidence		Total	<i>p</i>
		Yes	No		
Hygiene skin	Good	4 (6%)	33 (49.3%)	37 (55.2%)	0,000
	Not enough	15 (22.4%)	13 (19.4%)	28 (41.8%)	
	Bad	2 (3%)	0 (0%)	2 (3%)	
Hygiene hand	Good	3 (4.5%)	23 (34.3%)	26 (38.8%)	0.014
	Not enough	17 (25.4%)	20 (29.9%)	37 (55.2%)	
	Bad	1 (1.5%)	3 (4.5%)	4 (6%)	
Hygiene nail	Good	9 (13.4%)	33 (49.3%)	42 (62.7%)	0.023
	Not enough	12 (17.9%)	13 (19.4%)	25 (37.3%)	
	Bad	0 (0%)	0 (0%)	0 (0%)	
Hygiene clothes	Good	5 (7.5%)	40 (59.7%)	45 (67.2%)	0,000
	Not enough	12 (17.9%)	6 (9%)	18 (26.9%)	
	Bad	4 (6%)	0 (0%)	4 (6%)	
	Good	0 (0%)	14 (20.9%)	14 (20.9%)	

Hygiene towel	Not enough	17 (25.4%)	30 (44.8%)	47 (70.1%)	0.006
	Bad	4 (6%)	2 (3%)	6 (9%)	
Hygiene bed and bed linen	Good	0 (0%)	7 (10.4%)	7 (10.4%)	0.095
	Not enough	10 (14.9%)	24 (35.8%)	34 (50.7%)	
	Bad	11 (16.4%)	15 (22.4%)	26 (38.8%)	

From Table 6, based on the chi-square test, the p value is 0.000 for skin hygiene (p-value < 0.05). The p value is 0.014 for hand hygiene (p-value < 0.05). The p value is 0.023 for nail hygiene (p-value < 0.05). The p-value is 0.000 for clothing hygiene (p-value < 0.05). The p value is 0.006 for hygiene towels, (p-value < 0.05), with these results it was found that there was a relationship with the incidence of scabies at the Al Bayan Hidayatullah Islamic Boarding School, Makassar. Meanwhile, for the Chi-square test for bed and bed sheet hygiene, the p value is 0.095 (p-value > 0.05), this explains that there is no relationship between the incidence of scabies and bed and bed sheet hygiene at the Al-Bayan Hidayatullah Islamic Boarding School in Makassar.

Table 7. Relationship between environmental sanitation and the incidence of scabies at the Al Bayan Hidayatullah Islamic boarding school in Makassar

Environment sanitation	Category	Scabies incidence		Total	p
		Yes	No		
Clean water	Good	16 (23.9%)	38 (56.7%)	54 (80.6%)	0.538
	Bad	5 (7.5%)	8 (11.9%)	13 (19.4%)	
Waste disposal facilities	Good	5 (7.5%)	8 (11.9%)	13 (19.4%)	0.538
	Bad	16 (23.9%)	38 (56.7%)	54 (80.6%)	
Waste water disposal facilities	Good	5 (7.5%)	8 (11.9%)	13 (19.4%)	0.538
	Bad	16 (23.9%)	38 (56.7%)	54 (80.6%)	
Waste disposal facilities	Good	5 (7.5%)	8 (11.9%)	13 (19.4%)	0.538
	Bad	16 (23.9%)	38 (56.7%)	54 (80.6%)	

From Table 7, based on the chi-square test, the p value is 0.538 (p-value > 0.05), this result explains that there is no relationship between environmental sanitation and the incidence of scabies at the Al Bayan Hidayatullah Islamic Boarding School in Makassar.

Table 8. The relationship between residential density and the incidence of scabies at the Al Bayan Hidayatullah Islamic Boarding School, Makassar

Residential Density	Scabies incidence		Total	p
	Yes	No		
Good	5 (7.5%)	8 (11.9%)	13 (19.4%)	0.538
Bad	16 (23.9%)	38 (56.7%)	54 (80.6%)	
Total	21 (31.3%)	46 (68.7%)	67 (100%)	

From

Table 8, based on the chi-square test, the p value is 0.538 ($p\text{-value} > 0.05$), this result explains that there is no relationship between residential density and the incidence of scabies.

Discussion

From the results of data testing, the p-value is 0.000, where the value is lower than $\alpha = 0.05$, meaning that there is a significant relationship between skin hygiene and the incidence of scabies. This research is in line with Aulia's 2022 research regarding the relationship between skin hygiene and the incidence of scabies, showing a value of $p = 0.021$ ($p < \alpha$)⁽⁶⁾.

In questionnaires and interviews with Islamic boarding school students, it was found that students bathed less than twice a day, did not use soap, rubbed their bodies and did not clean their genitals when cleaning themselves so that parasites could grow and reproduce. However, this is in contrast to what was stated by Rahmawati in 2021, who stated that there was no relationship. The skin's function is to protect the body, and regulate body temperature, excretion and others, therefore ideally it must maintain hygiene. Unclean skin conditions are one of the reasons for unclean bathing habits, improper bathing frequency will cause scabies to infect more easily, especially on the fingers, thigh creases and others. Therefore, it is important to maintain skin hygiene to avoid skin diseases caused by fungi, germs, and parasites.

From the results of data testing, the p value is 0.014, where the value is lower than $\alpha = 0.05$, meaning that there is a significant relationship between hand hygiene and the incidence of scabies. This research is in line with Asyari's 2023 research regarding the relationship between hand hygiene and the incidence of scabies showing a value of $p = 0.000$ ($p < \alpha$)⁽⁷⁾.

Based on questionnaires and interviews with Islamic boarding school students, it was found that there is still very low awareness of rinsing hands after cleaning the bed, rinsing hands using soap before and after eating, which due to this lack of awareness causes mites to persist because they are rarely cleaned. However, this is in contrast to what was stated by Zuheri in 2021, who stated that there was no relationship.

From the results of data testing, the p-value is 0.023, where the value is lower than $\alpha = 0.05$, meaning that there is a significant relationship between nail hygiene and the incidence of scabies. This research is in line with Sarma's 2023 research regarding the relationship between nail hygiene and the incidence of scabies, showing a value of $p = 0.01$ ($p < \alpha$)⁽⁸⁾.

From the questionnaires and interviews with Islamic boarding school students, was found that there are still many students who do not cut their nails regularly once a week and do not pay attention to the condition of their nails being clean. However, this research is in contrast to Marzuki's research in 2019 which stated that the factors that influence scabies are not only nail cleanliness, in this case compliance and nail care habits as well.

From the results of data testing, the p-value is 0.000, where the value is lower than $\alpha = 0.05$, meaning that there is a significant relationship between clothing hygiene and the incidence of scabies. This research is in line with Novitasari's 2021 research regarding the relationship between clothing hygiene and the incidence of scabies, showing a value of $p = 0.003 (p < \alpha)$ ⁽⁹⁾.

In questionnaires and interviews with students at the Al Bayan Hidayatullah Islamic boarding school, the results showed that there are still many students who rarely change their clothes twice a day plus other factors such as there are still students who rarely change clothes when they sweat, sometimes do not wash their clothes with detergent and still There are students who don't dry their clothes under the sun. However, this is in contrast to Aulia's 2022 research which stated there was no relationship.

From the results of data testing, the p-value is 0.006, where the value is lower than $\alpha = 0.05$, meaning that there is a significant relationship between towel hygiene and the incidence of scabies. This research is in line with Tajudin's 2023 research regarding the relationship between towel hygiene and the incidence of scabies, showing a value of $p = 0.004 (p < \alpha)$ ⁽¹⁰⁾.

Based on questionnaires and interviews with Islamic boarding school students, it was found that there are still many students who do not dry their towels in the sun after use, many still use towels in damp conditions and rarely change towels within 2-3 days. This damp condition causes microorganisms to settle. However, this is in contrast to what was stated by Imartha in 2018, which stated that there was no relationship.

From the results of data testing, the p-value is 0.095, where the value is more than $\alpha = 0.05$, meaning that there is no significant relationship between bed and bed linen hygiene and the incidence of scabies. This research is in line with Rahmawati's 2021 research regarding bed and sheet hygiene and the incidence of scabies showing a p value = 0.966 ($p > \alpha$) ⁽¹¹⁾.

Based on questionnaires and interviews with Islamic boarding school students, the results show that there are still some students who often sleep with friends, rarely change bed sheets every 2 weeks, and rarely dry the mattress once every 2 weeks, where this action allows the mattress to become a place for the growth and development of scabies mites, but not to be one of the main causes. This is in contrast to Zuheri's research in 2021 which stated that there was a relationship.

From the results of data testing, the p value is 0.538, where the value is more than $\alpha = 0.05$, meaning that there is no significant relationship between clean water sanitation and the incidence of scabies. This research is in line with Indriani's 2021 research regarding the relationship between clean water sanitation and the incidence of scabies, showing a p value = 0.571 ($p > \alpha$) ⁽¹²⁾.

Based on observations made at the Islamic boarding school, the results showed that in general the physical nature of the water was colorless, tasteless and odorless and the use of the bathtub in each bathroom was different. Therefore, when the supply of clean water is sufficient, the cause of scabies will

die and disappear. However, this is in contrast to what Farihah stated in 2019, which stated that there was a relationship.

From the results of data testing, the p-value is 0.538, where the value is more than $\alpha = 0.05$, meaning that there is no significant relationship between waste disposal facilities and the incidence of scabies. This research is in line with Ritonga's 2023 research regarding the relationship between waste disposal facilities and the incidence of scabies, showing a p value = 0.317 ($p > \alpha$)⁽¹³⁾.

Based on observations made at the Islamic boarding school, the general results showed that the waste disposal facilities were categorized as poor. Garbage disposal facilities are said to be good if they meet the criteria in the form of a septic tank, covered and gooseneck, whereas in the cottage the septic tank does not have a gooseneck. However, this is not one of the factors that causes scabies. However, this is in contrast to what was stated by Intan in 2018 which stated that there was a relationship.

From the results of data testing, the p-value is 0.538, which is more than $\alpha = 0.05$, meaning that there is no significant relationship between waste water disposal facilities and the incidence of scabies. This research is in line with Fitria's 2020 research regarding the relationship between wastewater disposal facilities and the incidence of scabies, showing a p value = 0.725 ($p > \alpha$)⁽¹⁴⁾.

Based on observations made at Islamic boarding schools, the results showed that in general wastewater disposal facilities were categorized as poor. This facility is said to be good if it fulfills the criteria in the form of a place where the waste water flows through a closed ditch. Meanwhile, in Islamic boarding schools, sewers are found that are still open and not kept clean, which has a negative impact on the students. However, this is not one of the causes of scabies. However, this is in contrast to Saragih's 2021 research which stated that there was a relationship.

From the results of data testing, the p-value is 0.538, which is more than $\alpha = 0.05$, meaning that there is no significant relationship between waste disposal facilities and the incidence of scabies. This research is in line with Fitria's 2020 research regarding the relationship between waste disposal facilities and the incidence of scabies, showing a p value = 0.481 ($p > \alpha$)⁽¹⁴⁾.

Based on observations made at the cottage, the general results showed that waste disposal facilities were categorized as poor. Waste disposal facilities are said to be good if they meet the criteria in the form of a watertight and closed trash can, whereas in cottages there are trash cans that are still uncovered. But in some trash bins, some fall into the sufficient category. However, this is in contrast to what was stated by Ubaidillah in 2021, which stated that there was a relationship.

From the results of data testing, the p-value is 0.538, which is more than $\alpha = 0.05$, meaning that there is no significant relationship between residential density and the incidence of scabies. This research is in line with Selvianty's 2023 research regarding residential density and the incidence of scabies showing a

p-value = 0.710 ($p > \alpha$)⁽¹⁵⁾.

Based on observations made at Islamic boarding schools, the results showed that on average students occupy rooms with an area that does not match the existing capacity. However, there are still students who have rooms according to capacity. However, this is in contrast to what was stated by Indriani in 2021, which stated that there was a relationship.

Conclusion

The incidence of scabies was 21 people, there was a significant relationship between skin hygiene and the incidence of scabies, there was a significant relationship between hand hygiene and the incidence of scabies, there was a significant relationship between nail hygiene and the incidence of scabies, there was a significant relationship between clothing hygiene and the incidence of scabies, there is a significant relationship between towel hygiene and the incidence of scabies, Further research is needed to produce maximum findings. The researchers after this are expected to understand more deeply the specific factors in personal hygiene that have a significant impact on the incidence of scabies. Then carrying out comparative studies with other populations, such as students or the general public, can help in comparing the factors that influence scabies and see whether there are significant differences.

Conflicts of Interest

There is no conflict of interest

Funding sources

There is no funding source

Acknowledgments

There is no acknowledgment

References

1. Srisantyorini T, Cahyaningsih NF. Analysis of the incidence of skin diseases among scavengers at the Integrated Waste Processing Site (TPST) Sumur Batu Village, Bantar Gebang District, Bekasi City. *J Medicine and Health*. 2019;15(2):135.
2. Rayinda T, Susetiati DA, Febriana SA. Profile of skin diseases in boarding school students in Magelang Regency, Central Java. *J Community Empower Heal*. 2019;1(2):79.
3. Anderson KL, Strowd LC. Epidemiology, diagnosis, and treatment of scabies in dermatologyoffice. *J Am Board Fam Med*. 2019;30(1):78–84.
4. Winandar A, Muhammad R. Factors that influence the recovery of scabies sufferers in the working area of the Sibigo Health Center, West Simeulu District. *J Science And Apps*. 2021;IX(2):140–9.
5. Wulandari A. The Relationship between Personal Hygiene and Environmental Sanitation and the Incident of Scabies in Students at the Ulum Islamic Boarding Schoolul Qur'an, Bebesen District, Central Aceh Regency. *Glob Heal Sci [Internet]*. 2019;3(4):322–8. Available from:

- <https://jurnal.csdforum.com/index.php/GHS/article/download/299/141>
6. Aulia N, Tono W, Din A. Personal Hygiene with the Incidence of Scabies at the Thawalib Islamic Boarding School, Padang City. *J Environmental Sanitation*. 2022;2(2):72–8.
 7. Rahmawati, Lili. LD's daughter. *Indonesian Community Health Journal Vol 18 no 2 September 2022*. *J Indonesian Community Health [Internet]*. 2023;19(1):52–60. Available from: <http://103.123.236.7/index.php/jkki/article/view/6862/2649>
 8. Mayestika P, Hasmira MH. The relationship between the level of knowledge and personal hygiene on the incidence of scabies among students at the Dar El Iman Islamic boarding school, Padang City. *J Perspect*. 2021;4(4):519.
 9. Novitasari D, . S, Ferizqo FA. The Relationship between Santri's Personal Hygiene and Scabies Incidents at the As – Syafi'iyah Sidoarjo Islamic Boarding School in 2020. *Health Environment Echoes*. 2021;19(2):129–37.
 10. Tajudin IM, Wardani HE, Hapsari A, Katmawanti S. The Relationship between Personal Hygiene and Environmental Sanitation and the Incident of Scabies (Gender-Based Comparative Study at the Asy-Syadzili Islamic Boarding School 4 Gondanglegi Malang). *Sports Sci Heal*. 2023;5(2):200–17.
 11. Noviana Rahmawati A, Hestingsih R, Arie Wuryanto M. The Relationship between Personal Hygiene and the Incident of Scabies in Students of Islamic Boarding School X Semarang. *J Ilm Mhs [Internet]*. 2021;11(1):21–4. Available from: <https://ejournal.undip.ac.id/index.php/jim/index>
 12. Indriani F, Guspianto G, Putri FE. Relationship between Environmental Sanitation Conditions and Personal Hygiene Factors with Scabies Symptoms at the Darul Hikam Islamic Boarding School, Rimbo Ulu District, Tebo Regency, 2021. *Electron J Sci Environ Heal Dis*. 2021;2(1):63–75.
 13. Ritonga S, Putra MS, Bustanul S, Langsa U. Relationship between Water Quality and Environmental Sanitation with Complaints of Skin Diseases among Santri in Dayah Amal, East Aceh Regency Relationship between Water Quality and Environmental Sanitation with Complaints of Skin Disease in Santri at Dayah Amal, East Aceh D. *J Promot Prev [Internet]*. 2023;6(1):110–6. Available from: <http://journal.unpacti.ac.id/index.php/JPP>
 14. Fitria N, Tosepu R, Nurmaladewi. The Relationship between Environmental Sanitation and Personal Hygiene with Complaints of Scabies in Children at the Amaliyah Orphanage, Kendari City, 2019. *J Health Masy Celeb [Internet]*. 2020;1(3):13–20. Available from: <http://ojs.uho.ac.id/index.php/JIMKESMAS/article/view/2914%0Ahttps://ejournal.undip.ac.id/index.php/jim/index%0Ahttps://sardjito.co.id/2019/10/30/mengenal-scabies%0Ahttps://proceedings.unisba.ac.id/index.php/BCSMS/article/view/1302%0Ahttps://www.jurnal.un>
 15. Pada S, Di S, Pesantren P, Mempawah AK, Selvianty W, Alamsyah D, et al. Open Access Environmental Sanitation and Personal Hygiene with the Incident of Scabies in Female Students at the Al-Mukhlisin Islamic Boarding School, Mempawah Regency INTRODUCTION Public health problems are increasingly complex, especially environmental-based diseases, namely sa. 2023;10(1):95–105.