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Case Report

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Mebendazole treatment in ascariasis re-infection of two-year-old boy in rural Ambon: a case report and literature review

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Abstract

Ascariasis is currently a health problem in developing countries, especially in rural areas. Successful control of ascariasis is highly dependent on therapeutic interventions, environmental, and individual hygiene practices. Ascariasis is generally asymptomatic but can cause severe problems if treated improperly. Treatment is available, but reinfection may occur. This case aims to emphasize the usage of mebendazole treatment in ascariasis reinfection. A two-year-old boy came to the hospital with mucus diarrhea and worms in the stool. Two months ago, he had the same symptoms and experienced improvement after taking pyrantel pamoate at the previous hospital. The patient was diagnosed with acute diarrhea with mild to moderate dehydration, re-infection ascariasis, and malnutrition. Mebendazole 100 mg was administered twice daily for 3 days. Treatment with mebendazole was repeated twice with an interval of one month after the previous therapy due to the presence of *Ascaris lumbricoides* eggs in fecal examination. Fecal examination in the third month revealed the absence of *Ascaris lumbricoides* egg. Mebendazole can be used as therapy for ascariasis reinfections. However, repeated therapy is required in some cases. By integrating repeated therapy with comprehensive control measures, including health education and improved sanitation infrastructure, sustainable progress in combating ascariasis can be achieved.

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INTRODUCTION

The most prevalent worm infection is ascariasis, which was projected to have 804 million cases worldwide in 2013.[1,2] The most critical parasite in the nematode class and common name for roundworms, *Ascaris lumbricoides*, is the cause of this disease. Ascariasis most often occurs in children living in tropical and developing countries. This occurs due to soil contamination by human waste or the disposal or use of untreated waste, as well as air or food contaminated by ingested eggs.[3] Key factors associated with higher prevalence are poor socio-economic conditions, poor hand hygiene, poor sanitation practices such as not washing hands after defecation, and soil-transmitted helminths (STH) infections in mothers during pregnancy. While infections can occur at any age, they are most common during early childhood, particularly in children under five years old, commonly referred to as toddlers. In Indonesia, the prevalence of worm infections ranges from 2.5% to 62%, indicating a significant variability. This range signifies a relatively high prevalence, and this number is still relatively high, and this is a public health problem in Indonesia.[4,5]

Although this infection can be treated with antiparasitic drugs, sometimes this infection can recur, especially in children who have recovered previously.[2] The phenomenon of ascariasis reinfection is when someone infected with the *Ascaris lumbricoides* worm suffers the infection again after a period of healing. This reinfection can occur several times in a person's life.[6] Ascariasis reinfection remains a public health problem, especially in areas with poor sanitation. Understanding the factors contributing to reinfection and implementing appropriate preventive measures are essential control measures in ascariasis infections. This case describes a two-year-old child who experienced ascariasis reinfection as an illustration of this phenomenon.

CASE REPORT

A two-year-old boy came with his mother to the hospital emergency department with complaints of diarrhea six times a day since three days ago. Worms and mucus accompanied the diarrhea. The patient's mother also complained that the patient was fussier than usual and vomited when he ate and drank. The patient sometimes coughs without mucus. There was no fever. The patient had experienced a similar complaint, which was worm defecation, two months ago and had been hospitalized. The patient was given pyrantel pamoate at the previous hospital during treatment, and his condition improved.

His general condition looked weak on physical examination, and his consciousness was compos mentis. The patient's weight was 9400 grams, height 83 cm, with nutritional status <-2 SD, according to weight for age. Vital signs were within normal limits. The eyes appeared glazed, and other examinations were normal. Laboratory result at admission was shown on Table 1. Abdominal ultrasound examination at Figure 1 showed a hypoechoic tubular structure with parallel echogenic lines in the left paracolic area.

The patient was diagnosed with ascariasis reinfection with acute diarrhea, mild to moderate dehydration, and malnutrition. During treatment, the patient did not defecate but vomited worms approximately 7 times, with a total of around 50 worms. The patient was treated, rehydrated with fluids and Zinc 1 x 20 mg, and an enema was given on the third day of treatment, 30 minutes post enema, the

Table 1. Laboratory result at admission.

	Result	Normal value
Hemoglobin	12.3	11.5-14.5
Leucocyte	12.2	6-17
Platelet	389	150-400
Eosinophils	10.7	1-5
Neutrophils	68.7	25-60
Lymphocytes	14.6%	25-50
NLR	4.79	≦3.13
Feces	Macroscopic: blood (+), worms (+) identified as *Ascaris lumbricoides* and positive 3 (+++) worm eggs	

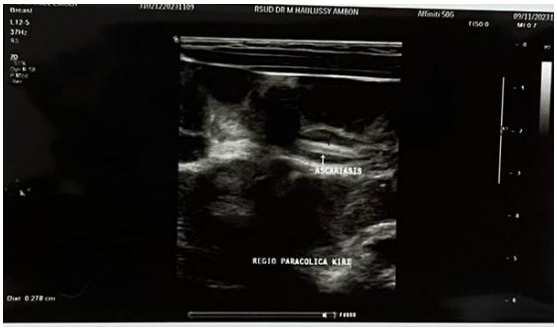

Figure 1. Abdominal ultrasound of a 2-year-old patient with ascariasis.

patient defecated with lumps of worms. After that, Mebendazole was given 2 x 100 mg for 3 days on day 4 of treatment. The patient was discharged on day 6 with an improved condition. The patient was treated with mebendazole again 2 times at 1-month intervals after the previous treatment because worm eggs were still found in the fecal examination. At the end of the third month, the patient's stool examination appears greenish-yellow, soft, and well-formed in consistency. The stool contains fat but does not contain blood, mucus, pus, undigested meat fibers, harmful bacteria, viruses, fungi, or parasites. At the outpatient clinic, a Denver II examination was carried out. There was a failure in 2 components: language and personal social. The patient was given an additional diagnosis, suspecting growth and development delay.

DISCUSSION

Approximately 1.4 billion individuals globally, constituting around 25% of the world's population, are estimated to be infected with *Ascaris lumbricoides*. Ascariasis primarily occurs in tropical and semitropical regions globally. The affected body area typically spans from the stomach to the ileocecal valve, with approximately 99% of cases inhabiting the jejunum and proximal ileum.[7,8] The genus *Ascaris* has 17 species, and *A. lumbricoides* has high host specificity towards humans, although it can sometimes be found in pigs.[9,10] As previously mentioned, ascariasis is the most significant type of worm infection, with the size of male worms around 10 to 30 cm and female worms around 22 to 35 cm.[11]

When the host ingests eggs found in stool-contaminated soil, infection occurs. The larvae are released into the duodenum and pass through the intestinal mucosa to reach the circulation. After that, the larvae penetrate the duodenum wall and migrate into the circulatory system or lymph channels, carrying them to the heart and lungs. In the lungs, the larvae penetrate the blood vessel walls, then the alveolar walls, enter the alveolar cavity, and then move into the trachea through the bronchioles and bronchi. From the trachea, the larvae move to the pharynx and cause stimulation in the pharynx, which ultimately triggers coughing so that the larvae are swallowed back into the esophagus and then into the small intestine. Within the small intestine, the larvae undergo a transformation into adult worms. The time it takes from when the infective eggs are swallowed until the adult worms start laying eggs is around 2-3

months. The female worms can generate up to 200,000 eggs a day when they copulate with the males, which can be expelled in feces and combined with soil trash. In two to eight weeks, the eggs develop into infectious forms in wet, shady, and warm environments, and they can stay viable in the soil for up to 17 months. The infectious cycle can be restarted by consuming them.[2,9].

Re-infection is associated with a higher incidence of a type 1 hypersensitivity reaction, involving considerable pulmonary eosinophilic infiltrates and marked peripheral eosinophilia.[12] Dun et al., done a study at Myanmar, stated that RR for the six-month reinfection period was statistically significant for *A. lumbricoides* infection in school-aged children after given mass drug administration (MDA) (RR = 2.67,95% CI 1.37–5.21).[13]

While the majority cases of ascariasis in pediatric children show long-term signs of malnutrition and developmental retardation, some patients may not exhibit any symptoms at all. When symptoms do occur, the most typical ones are bloating, nausea, vomiting, anorexia, and intermittent diarrhea. Clinical symptoms of ascariasis generally occur during the larval migration phase. During migration, larvae can cause responses in the tissues they pass through. For example, when the larvae reach the lungs, the antigens produced by the larvae can induce an inflammatory response that appears as infiltrates on chest radiographs and generally disappears within three weeks. Symptoms of pneumonia include wheezing, dyspnea, dry cough, fever, and phlegm may be mixed with blood in cases of more severe infections. When pneumonia is accompanied by an increased number of eosinophils and high levels of IgE in the blood, the condition is known as Loeffler's syndrome.[10,14] When the larvae die in the liver, this can cause the formation of eosinophil-rich granulomas. The patient's condition indicates the migration phase of larvae to the lungs, characterized by a dry cough that lasts for quite a long time but comes and goes and is accompanied by an increase in eosinophils in laboratory results of 10.7%. However, the diagnosis of Loeffler syndrome cannot be confirmed because a chest x-ray was not taken.

In the intestinal phase, digestive symptoms are usually subtle and caused by adult worms inhabiting the digestive tract. When symptoms appear, they tend to be general and non-specific, such as nausea, low intake, digestive problems such as diarrhea or constipation, lethargy, and difficulty concentrating, which can significantly affect a child's development.[14,15] *Ascaris* infection can also trigger lactose intolerance and interfere with vitamin A and essential micronutrient absorption. Chronic infections can result in growth failure in children due to decreased appetite, digestive disorders, and malabsorption problems.[16,17] In our case, at the intestinal phase, complaints were found, including diarrhea, vomiting, constipation, and even suspicion of developmental delay and poor nutritional status, which may be related to the underlying worm infection.

More severe impacts occur when adult worms clump together in the intestines, causing intestinal obstruction (ileus). In addition, adult worms can migrate into the lumen of the appendix and cause acute appendicitis or gangrene. Suppose adult worms enter and block the bile ducts. In that case, it can trigger problems such as colic, cholecystitis, cholangitis, pancreatitis, and liver abscess.[7,16,18] Apart from migrating to these organs, adult worms can also exit through the anus, mouth or nose. This worm migration is often triggered by factors such as high fever or the use of certain

medications.

In diagnosing cases of ascariasis, the gold standard diagnostic test is still a direct wet stool examination to look for eggs and parasites. In *Ascaris* infection, the infertile eggs have characteristics of brownish color with an elongated oval shape (both ends are slightly flat), have layered walls (2 or 3) with a thick, winding outer layer that is very rough/irregular (albumin layer), and an inner layer relatively smooth (hyaline layer). It's crucial to highlight that the stool may test negative as the worms migrate and reach maturity, typically occurring within approximately 20 to 30 days.[14] Egg laying begins only after the worms reach maturity. Occasionally, adult worms may be visible in stool or expelled from the rectum, but they can also be discharged through coughing or in urine. Both *Ascaris lumbricoides* parasites and eggs were found in the patient's stool examination. In addition, a history of bowel movements with worms had also been previously reported by the parents. During follow-up at the hospital, the patient vomited worms and expelled lumps of worms after 30 minutes post-enema, as shown in Figure 2.

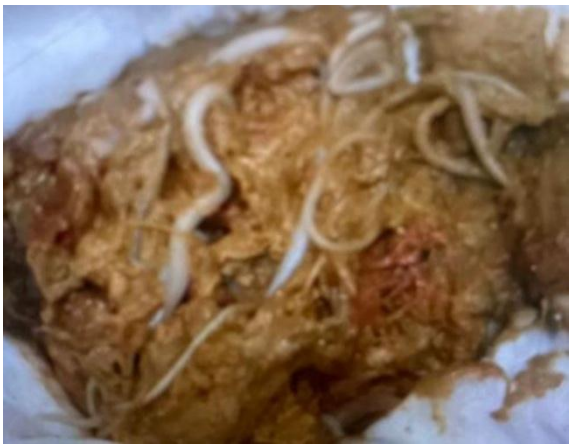

Figure 2. Stool of a 2-year-old patient with *Ascaris*.

Peripheral eosinophilia is one of the hallmarks of helminth infection.[19] Eosinophilia is usually present in the early stage, increasing several days after symptom onset and remaining high for a few weeks. Sputum analysis may demonstrate eosinophilia and Charcot-Leyden crystals. Eosinophil counts are usually 5 to 12 percent but can be as high as 30 to 50 percennt.[12] Neutrophil, lymphocyte ratio (NLR) has recently been shown to be superior due to its better stability compared with the other parameters that can be altered by various physiological, pathological, and physical factors. However, no previous work has been done on the predictive ability of NLR in helminthic infection. NLR represents a combination of two markers where neutrophils constitute the active nonspecific inflammatory mediator that initiates the first line of defense, while lymphocytes reflect the regulatory or protective component of inflammation.[20]

During the phase of active migration from the intestines to the lungs, larvae can be observed in sputum, and eosinophilia can be evident in a comprehensive blood count examination. Abdominal X-rays may show sensitivity in detecting signs like whirlpools indicative of volvulus or intussusception, although they may lack specificity.[2,8] Gallbladder worms and bile ducts can be detected using Computed Tomography (CT) scans and Ultrasonography (USG). ERCP (Endoscopic Retrograde Cholangiopancreatography) serves as both a diagnostic and treatment option. On the other hand, ERCP reports with ascariasis abnormalities are more common in affluent nations and sometimes result from misdiagnosis of other conditions.[21,22] In our patient, an increase in eosinophils was found in the complete blood count, and the ultrasound showed the presence of adult worms in the left paracolic area.

Serological diagnosis has been proposed as well. Infection with *A. lumbricoides* prompts the production of antibodies, whose levels can vary depending on the extent of exposure and the severity of the infection, especially in areas with high endemicity. The humoral response to *Ascaris* may be influenced by co-infections, age, atopy, genetic predisposition, and dietary status. In those who live in endemic locations, total immunoglobulin (Ig) titer is correlated with worm burden. Prior research has demonstrated that specific and sensitive markers for chronic *A. lumbricoides* infection, such as IgG4, may be identified and that these markers positively correlate with the infection's severity. These results align with other parasitic infections, albeit investigations on *Ascaris* show more inconsistent outcomes. Antibodies against *Ascaris* frequently cross-react with epitopes from other helminths. It's crucial to standardize *Ascaris* antigens, encompassing recombinant antigens, allergens linked with *Ascaris*, and antigens from different *Ascaris* species, to facilitate research and diagnostic accuracy.[14,23,24]

Previous research has not assessed the community's application of serological diagnostics for ascariasis. Antibody levels against *Ascaris* are mostly linked to infections during the larval stage of the parasite. They may endure for several months post-treatment, especially in areas prone to frequent reinfection. Consequently, the presence of anti-*Ascaris* antibodies might exaggerate the count of individuals requiring treatment in mass control programs, and they are generally not deemed suitable for identifying active *Ascaris* infections. Numerous commercial diagnostic assays are available to identify IgG and IgM antibodies against *Ascaris lumbricoides*. Nonetheless, they most frequently cross-react with other helminths and are based on the helminth antigens of somatic *A. lumbricoides*. Antigen detection indicates the current infection, whereas antibody detection can indicate the current infection and any previous infections or exposures.[2]

As control programs aim to eliminate soil-transmitted helminths (STH) in children, antibodies can serve as a valuable indicator of childhood infections, particularly in regions where children are regularly exposed to enteric pathogens.[2,14] Meanwhile, biomedical target markers for *A. lumbricoides* infections have also been reported. Products of fatty acids resulting from *A. lumbricoides* infection can be identified in urine using gas-liquid chromatography, and their concentrations correspond with the severity of the worm infestation. Nevertheless, there are currently no commercially available tests for this purpose.[25]

Even mild symptoms of ascariasis necessitate treatment to avert complications arising from parasite migration. However, owing to the heightened risk of pneumonitis, medical intervention is not recommended during the phase of active migration through the lungs. In our patient at the beginning of treatment, we did not immediately treat the patient with anthelmintic drugs. Therapy with anthelmintic drugs is given post-enema, and the patient defecates worm lumps. This follows studies to prevent parasite migration, which can worsen symptoms such as intestinal obstruction. In cases of partial intestinal obstruction, insertion of a nasogastric tube is recommended, and oral intake should be withheld; instead, intravenous fluids and piperazine should be administered. In situations of complete intestinal obstruction, surgical intervention such as laparotomy may be necessary to extract the worms. If necrosis, resection and re-anastomosis may

be necessary. After surgery, medical antiparasitic treatment should be initiated to eradicate any remaining eggs.[9,14] The patient's condition did not lead to intestinal obstruction, so surgery was unnecessary.

The recommended medication for medical therapy is 400 mg of albendazole in a single dose. The second therapeutic option includes Mebendazole at 100 mg twice a day for three days, a single dose of 500 mg, or Ivermectin at 100 to 200 micrograms per kilogram once. Treatment options for pregnancy include piperazine at a dose of 50 mg/kg per day for five days or 75 mg/kg in one dose or the recommended medication and pyrantel pamoate at a dose of 11 mg/kg up to a maximum of 1 g. Since medical therapy targets adult worms, repeating the treatment after one to three months is best. It gives any larvae that may be present time to mature and become therapeutically responsive. Levomisole and nitazoxanide are examples of substitute agents.[9,26] Research carried out in Asia and Africa demonstrated that a single dose of albendazole treatment achieved a cure rate of over 95%, with a gradual decline in egg count observed in the subsequent weeks across 995 cases. Nonetheless, patient relocation is vital to prevent recurrence.[9,12] Besides albendazole, mebendazole is an equivalent alternative to albendazole in treating *Ascaris* infection.[27] The patient was treated with pyrantel pamoate once, followed by mebendazole 3 times over 5 months. Although it is not the first line, pyrantel pamoate is known to be a neuromuscular blocking agent that causes paralysis in worms. After it was proven to be an ascariasis reinfection, Mebendazole 100 mg twice daily was given for three days. This is in line with the literature, which states that Mebendazole works by inhibiting the energy formation of worms, resulting in their death. This repeated treatment aligns with the literature because both drugs are active against adult worms but insufficient against larvae.

Anthelmintic resistance may occur in the treatment of ascariasis. In a study about worm infection in Rwanda, the efficacy of deworming school children with albendazole against *Ascaris* infection was highly variable and, overall, inadequate. In Rwanda, with very high rates of helminth treatment coverage, these findings are considered a warning sign of the emergence of the spread of resistance. The β-tubulin genotype does not explain the inappropriate efficacy of albendazole.[28] This particularly emphasizes the need for continuous monitoring of the results of routine deworming.[29,30]

Before confirming a diagnosis of anthelmintic resistance, several factors need to be assessed. Initially, it's crucial to recognize that various illnesses can manifest clinical symptoms like parasitic infections. Additionally, failure of anthelmintic treatment to manage nematodes may occur due to factors unrelated to resistance. Failure in this situation is often caused by problems such as underdosing due to incorrect weight estimation. Both in vivo and in vitro approaches are utilized to detect and monitor resistance. In vivo, the Fecal Egg Count Reduction Test (FECRT) compares the number of worm eggs in animals before and after treatment to assess efficacy. Resistance is identified when two criteria are fulfilled: the percentage reduction in egg count is less than 95%, and the lower limit of the 95% confidence interval is 90% or lower. Different approaches can be utilized to evaluate resistance, encompassing in vitro methods like Egg Hatch Assays (EHA), larval development assessments, larval motility evaluations, and polymerase chain reaction (PCR) tests. Nevertheless, EHA isn't adequate for assessing tetrahydropyrimidines, imidazothiazoles,

and macrocyclic lactones due to their lack of ovicidal properties. The examination involved depositing fresh eggs into the compartments of a multiwell plate, and then determining the LD_{50}. In the larval development test, the ability of the larvae to survive and develop in different concentrations of anthelmintic drugs is examined. Variations in LD_{50} are reported depending on the time of infection, mainly when macrocyclic lactones are used. In the locomotion test, larvae are incubated in various drug concentrations, and larval movements are counted after light stimulation. In the PCR test, the genotype of adult worms or larvae that are resistant (rr) or susceptible (rS and SS) can be detected using PCR.[31]

Nitazoxanide, a recently developed antiprotozoal agent, has demonstrated effectiveness against various parasites, including *A. lumbricoides*. It has been suggested as a promising candidate for treating soil-transmitted helminthiasis in humans, prompting the need for additional research.[27] The process of developing new anthelmintic drugs to counter resistance is both slow and costly. Hence, it is crucial to utilize current anthelmintics judiciously to mitigate the effects of resistance. Various management strategies exist to prevent parasite infections or maintain low infection pressure, including pasture and refugia management. This will reduce the need for the use of anthelmintic drugs, which can delay the development of resistance. Necessary actions needed to slow the development of resistance include using appropriate doses of anthelmintic drugs, reducing dependence on anthelmintics, maintaining worm populations susceptible to anthelmintics, and regular anthelmintic resistance testing. Combinations of anthelmintics with related spectrums of activity and different modes of action have been recommended to slow the development of anthelmintic resistance. Developing an efficient vaccine against intestinal parasites would allow the use of antiparasitic drugs less frequently. However, currently, there is only one commercially available vaccine for Dictyocaulus viviparus.[30,31] The recurrence of ascariasis is a significant public health problem, especially in the pediatric population. Reinfections can reduce a child's overall quality of life and decrease cognitive and developmental outcomes due to malnutrition and anemia. This is caused by decreased food intake and malabsorption of nutrients, which is proven in patients when fecal examination finds food residues (+) and fat (+). Patients with poor nutritional status but not yet anemic can be seen from the blood test results of Hb 12.3g/dL. It is also possible that anemia has not occurred in the patient because the worms have not yet attached themselves to the intestinal mucosa, which will cause gastrointestinal bleeding.

Stool testing may be performed two months following treatment of patients in non-endemic areas to ensure successful clearance.[12] Conterno et al. stated that the egg reduction rate (ERR) measured up to 60 days after the treatment was high in all treated groups, regardless of the anthelmintic used (range 96% to 100%).[27]

Several causes and predisposing factors play an essential role in the incidence of reinfection infections. Children who live in areas with poor sanitation or have limited access to clean water are at higher risk of reinfection. Additionally, conditions such as a weakened immune system or nutritional deficiencies can make a person more susceptible to reinfection after recovering from previous ascariasis. Inadequacy or imperfection in treatment when treating the initial infection, as well as increased drug resistance due to genotype or widespread

use of certain drugs, can also increase the risk of ascariasis reinfection. Over time, surviving worms can grow into adult worms and release eggs that cause new infections.[4,5] Enhancing basic sanitation and ensuring access to clean drinking water are essential in regions with poor sanitation and low socioeconomic status. Essential measures for preventing ascariasis include avoiding contact with soil, wearing appropriate footwear, and education. In our patient, ascariasis reinfection was likely caused by inadequate previous treatment with pyrantel pamoate, economic factors where the patient's family came from a family with a lower middle socioeconomic background. The patient's father's job is a pedicab driver. According to his mother, he has poor nutritional intake because he rarely consumes protein. Besides that, poor environmental sanitation is due to living in rural areas with non- permanent house buildings as shown in Figure 3 and a lack of family knowledge about preventing ascariasis, for example, using footwear and poor hand hygiene.

Figure 3. Home environment of a 2-year-old patient with ascariasis.

STRENGTH AND LIMITATION

The strength of this study is the review of the existing literature regarding mebendazole treatment for ascariasis, most of which focused on albendazole as the first-line treatment. The limitation of this study is the challenge in determining the effectiveness of mebendazole treatment for ascariasis reinfection compared with alternative treatments or no treatment. Additionally, this study did not involve other family members of the patients.

CONCLUSIONS

Ascariasis reinfection may occur in children. Inadequate treatment when treating the initial infection can increase the risk of ascariasis reinfection, impacting the child's quality of life, growth, and development. Adequate treatment, improved sanitation, proper personal hygiene, and maintaining balanced nutrition in children are needed to prevent reinfection worm infections.

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CONFLICT OF INTEREST

The authors confirm that they are not associated with any organization or entity that has a financial interest in the subject matter or materials discussed in this manuscript.

AUTHOR CONTRIBUTION

MTT as the main author and contribute to preparing the manuscript. MRP and DH reviewed the paper and suggested changes. All authors read and approved the final manuscript.

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