*Original Article*

# Intestinal parasitic infection of immunocompromised children with diarrhoea: clinical profile and therapeutic response

Nikmah Salamia Idris[1], Pramita G. Dwipoerwantoro[1], Agnes Kurniawan[2], Mardjanis Said[2]

*Departments of Child Health[1] and Parasitology[2], Faculty of Medicine, University of Indonesia/Cipto Mangunkusumo General Hospital, Jakarta, Indonesia*

## Abstract

Background: Parasitic gastrointestinal infections have been variably reported among immunocompromised adults while data on children have been limited. This prospective cross-sectional study aimed to assess the clinical profile of intestinal parasitic infections among immunocompromised children with diarrhoea and their treatment response.

Methodology: Two freshly voided stool samples taken for two consecutive days were examined by direct and formalin-ether concentrated smears. Modified Ziehl-Neelsen staining was used to detect *Cryptosporidium*, *Isospora belli*, and *Cyclospora cayetanensis*. *Blastocystis hominis* was identified using *in vitro* culture. Subjects positive for stool parasite(s) received standard therapy according to the aetiology and were evaluated afterward.

Results: Forty-two subjects from Jakarta, Indonesia were included in this study, mostly aged one to five years (78%) and HIV infected (52%). Parasites were found in 24/42 (57%) subjects in which *B. hominis* comprised the largest proportion (23/24 = 96%). *Cryptosporidium* was identified in two subjects who were HIV infected with CD4 percentages of < 15%. No helminth infestations were found. Parasites were most frequently found in preschool age children (16/23), in those with recurrent or watery diarrhoea (23/24 and 14/18, respectively), and in HIV subjects not receiving antiretrovirals (16/22). Of 13 subjects evaluated for response to a 10-day metronidazole course for *B. hominis* infection, seven achieved clinical remission and nine had their parasites eradicated.

Conclusions: The prevalence of intestinal parasitic infection in immunocompromised children with persistent and/or recurrent diarrhoea is moderately high and dominated by *B. hominis* infection. Clinical remission and parasite eradication can be achieved in *B. hominis* infection treated with metronidazole.

**Key words:** diarrhoea, immunocompromised, HIV, *B. hominis*, metronidazole

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## Introduction

In Indonesia, as in other parts of the world, immunocompromised children are becoming more commonly encountered in daily clinical practice. This is likely due to the increased prevalence of HIV infection, improved survival rates of children with malignancy, and an increased number of children receiving immunosuppressive agents for differing reasons [1]. Immunocompromised children are prone to various infections, including those affecting the gastrointestinal tract, which can manifest as severe protracted diarrhoea, chronic malabsorption, failure to thrive, and malnutrition [2]. Among different pathogens causing gastrointestinal infection, parasites are likely to have significant roles as the primary cause or co-morbidity of diarrhoea in immunocompromised children. Previous studies on immunocompromised populations (HIV, malignancy, and others), which mainly comprised adults, reported variable prevalence (2-50%) of intestinal parasitic infections with different aetiologic patterns [3,4]. The incidence of parasitic infection in HIV patients with diarrhoea was reported to be 53-83% [5,6]. Similar prevalence rates (42%) were also found in children with malignancy [7].

A recent study in Jakarta on 318 HIV patients (3.1% of subjects were children younger than five years old) reported parasitic intestinal infection in 84.3% of subjects with *B. hominis* as the most frequent parasite found (72.4%) [8]. The prevalence in children might be the same or somewhat lower than in adults but there have been no studies in Indonesia specifically addressing this problem. Moreover, we still do not know the response of this infection to standard therapy, such as metronidazole, which is frequently given either as an empiric or

definite therapy for some intestinal protozoan diseases. This study aimed to assess the profile of intestinal parasitic infections in immunocompromised children with diarrhoea and their treatment response to standard drugs.

## Materials and methods

In a prospective cross-sectional approach, a study was conducted on hospitalized and ambulatory patients in the Paediatric Department, Cipto Mangunkusumo Hospital (RSCM), Jakarta, Indonesia, from April 2008 to February 2009.

Subjects were children aged between six months and 18 years old, suffering from persistent and/or recurrent diarrhea, who also had at least one of the following conditions: HIV infection, malignancy, severe malnutrition, on immunosuppressive therapy for a minimum of four weeks, or primary immunodeficiency. Anyone who had received anti-parasite treatment in the last three months was excluded, except for those who received prophylactic cotrimoxazole given for malignancy and HIV children on alternate-day dosing (4-6 mg/kg/day bid, three times a week). Subjects were also excluded from this study if fresh stool samples could not be obtained or if the parents refused to participate in this study.

Diarrhoea was defined as an increase of stool frequency to three or more times a day and/or the change of stool consistency into more liquid form. Subjects were classified as having either persistent diarrhoea if it lasted for more than two weeks or recurrent diarrhoea if there was a history of two or more diarrhoea episodes in the last six months before participating in this study. HIV infection was diagnosed following World Health Organization (WHO) guidelines [9]. Nutritional states were determined based on the classification proposed by the WHO [10], using weight for height plotted to the CDC-NCHS 2000 growth chart as follows: weight-for-height of less than 70% was classified as severe malnutrition and that of 70-79% was grouped as moderate.

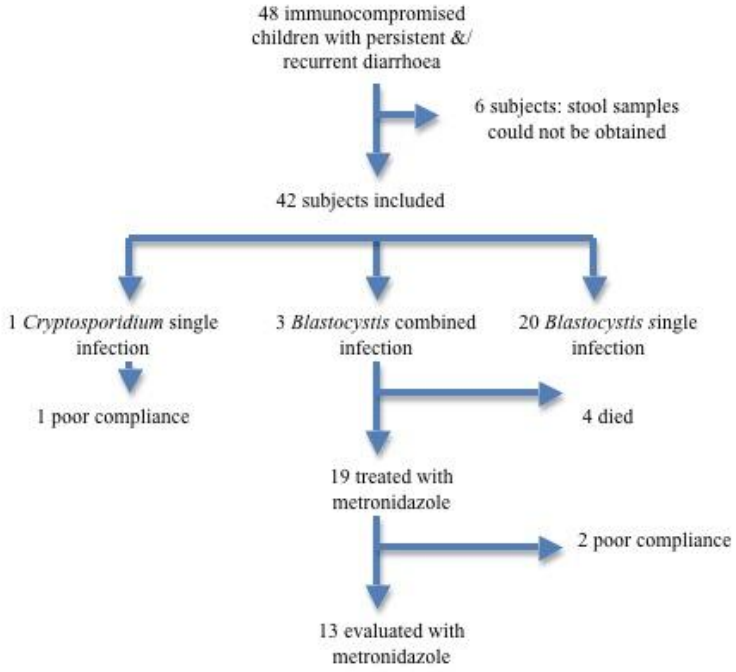
All eligible children were recruited consecutively and underwent clinical as well as parasite stool examinations. Demographic and clinical data were obtained by history taking and physical examination. CD4 cell counts and stool microscopic/chemical characteristics (pH, stool leukocytes, reduction, and fat) were taken from medical records. The CD4 counts were determined by flow cytometry (BD FACSCalibur; BD Biosciences, Franklin Lakes, NJ, USA) in two Jakarta HIV/AIDS centres.

Parasite stool examination was performed on two freshly voided samples taken for two consecutive days to identify helminth eggs/larvae and protozoan oocyst/cyst/trophozoites (*i.e., Giardia lamblia, Entamoeba coli, Entamoeba histolytica/dispaar, Cryptosporidium, Isospora belli, Cyclospora cayetanensis, Balantidium coli, Blastocystis hominis*). Each specimen was examined by direct and formalin-ether concentrated smears. Modified Ziehl-Neelsen staining was used to detect *Cryptosporidium*, *Isospora belli* and *Cyclospora cayetanensis*. Samples were not examined for *Microsporidia* due to the unavailability of the relevant stain. *In vitro* culture was also performed for *Blastocystis hominis* [11]. Further discrimination of *E. histolytica* from *E. dispaar* was not completed because diagnostic kits were not available. When the only parasite found was an *E. histolytica/E. dispaar* cyst and the immunocompromised patient presented with diarrhoea, specific treatment was given.

Subjects with positive parasites in their stool received standard therapy according to our hospital protocols. Those with *B. hominis, E. histolytica*, or *G. lamblia* were treated with metronidazole syrup (Flagyl©, 125 mg/5 ml) at 30 mg/kg/day, divided into 3 doses and rounded to the nearest millilitre. The drug was given for either ten days (*B. hominis* or *E. histolytica* infections) or five days (*G. lamblia*). Patients with *Cryptosporidium* received paromomycin syrup at 10 mg/kg three times a day for ten days. During the course of therapy, drug consumption as well as stool frequency and consistency were recorded to assess patients' compliance and clinical remission, respectively. Two days after therapy was completed, parasite stool examinations were performed to evaluate parasite eradication.

The primary outcome of this study was a profile of intestinal parasitic infection consisting of the prevalence, aetiologic pattern, and the distribution of clinical, demographic, and stool characteristics according to the occurrence of parasitic infection. The secondary outcome was treatment response, which was assessed as the proportion of subjects achieving clinical remission and parasite eradication. Clinical remission was defined as a subject who had decreased in frequency of stool passage to two or less per day with normal consistency (formed stool). Parasite eradication was recorded if no parasite was identified on stool examination after completion of

**Figure 1.** Study subject flow.




treatment. For the study, the required sample size was calculated using the formula for estimation of single population proportion [12]. With an estimated prevalence of 60% and a standard error of 7.5%, a minimum of 42 subjects were required. Data were analysed using SPSS 11.0 for Windows and presented in text, tables, and graphs. A prevalence ratio with a 95% confidence interval was calculated to assess the occurrence of intestinal parasitic infection based on demographic, clinical, and stool characteristics. This study was approved by the Ethics Committee of the Faculty of Medicine, University of Indonesia. Parental informed consent was obtained for every subject included.

## Results

During the study period, there were 48 immunocompromised children who met the inclusion criteria, but stool samples could not be obtained in six subjects. Therefore 42 subjects were included, 20 of whom were hospitalized patients (Figure 1). Twenty-four patients (57%) were found to have intestinal parasitic infection, but four died before completing the therapy course, three had poor compliance, and four were lost at follow up. In total, 13 subjects were analysed to assess the treatment response.

*Subject characteristics*

The subjects consisted of 24/42 (57%) girls and 18/42 (43%) boys, aged between six months and 12 years (Table 1). Subjects were immunocompromised due to HIV infection (52%), followed by malignancy (24%), severe malnutrition (17%) and the remainder due to systemic lupus erythematosus (SLE), nephrotic syndrome and IgA deficiency. Prior to parasite stool examinations, 23/42 (55%) of subjects used cotrimoxazole or cephalosporin as prophylactic antibiotics for infections outside the gastrointestinal tract.

Among the 22 subjects with HIV infection, only four patients received antiretroviral therapy (ARV) for more than six months. Each was given the combination of zidovudine, lamivudine, and nevirapin. Data regarding CD4 cell counts were available in only 14 subjects, of whom 13 were in a severe immune deficiency state. Nine subjects did not have data on CD4 cell counts because of financial constraint.

*The profile of intestinal parasitic infection*

In this study, intestinal parasitic infection was found in 24 of 42 (57.1%) subjects (Table 2). *Blastocystis hominis* was the most frequent parasite found (23/24) among subjects of different causes of immunocompromised status, either as single

infection (20 subjects) or mixed (3 subjects) with other protozoan infection. However, *Cryptosporidium* were found in only two subjects, both of whom were HIV-infected with CD4 count of ≤ 15%, suggesting a severe immune deficiency state.

*Prevalence of intestinal parasitic infection based on demographic and clinical characteristics*

Subjects were further classified into those with and without intestinal parasitic infection and the prevalence ratio(s) of parasitic infection based on subjects' characteristics were sought (Table 3). Among different age groups, toddlers had the greatest proportion of acquiring intestinal parasitic infection (16/24 or 70%), while according to nutritional state, subjects with moderate and severe malnutrition had the greatest proportion (59% and 62%, respectively). Mother's education had no association with the occurrence of intestinal parasitic infection. Based on the drinking water source, subjects using refill or tap water had the biggest proportion of getting intestinal parasitic infection (3/4 and 7/9, respectively) compared to those using commercial sealed water or boiled ground water.

All subjects had diarrhoea with watery consistency or mushy stool, 23/24 (96%) with recurrent diarrhoea. Those with intestinal parasitic infections had stool pH of < 7 with the presence of mucus. Blood in stool was found in only two subjects who were later proven to be infected with *G. lamblia* and *E. histolytica*/*dispaar*. The average duration and frequency of diarrhoea were 14.5 days and 7.2 times, higher than the group without parasitic infection (Table 4). Prophylactic therapy with cotrimoxazole did not clear or prevent intestinal parasitic infection completely; hence 9/14 (64%) were still positive for parasites.

The difference in the occurrence rate of intestinal parasitic infection between the HIV patients who received antiretroviral (2/4) and those who did not (14/18) was observed, with a 0.56 prevalence ratio (95%CI 0.2-0.63). Two HIV subjects who had been on antiretroviral treatment but still acquired intestinal parasitic infection (*B. hominis* and B.hominis/*Cryptosporidium*) were in a severe immunosupressive state with CD4 cell counts of 89 cells/mm3 (4%) and 566 cells /mm3 (11%).

*Response of* B. hominis *infection to metronidazole therapy*

Thirteen children (seven HIV patients, three malignancies, two severe malnutrition without HIV, and one SLE patient) with *B. hominis* infection were evaluated to assess the therapeutic response to a 10-day course of metronidazole; three of them had combined infections, each with *G. lamblia*, *Entamoeba spp*., and *Cryptosporidium*. One subject with combined *B. hominis* and *Cryptosporidium* infection was treated only with metronidazole due to the unavailability of the paramomycin preparation at that time.

Clinical remission was observed in seven subjects, four with single *B. hominis* and three with mixed *B. hominis* infection, while six subjects still experienced diarrhoea after the therapy course was completed. Clinical remission started to occur at the earliest on the third day of therapy (two subjects) and on day nine at the latest. On average subjects achieved clinical remission on day 7.

Nine of 13 subjects achieved parasite eradication, but three of them (HIV patients) did not achieve clinical remission. Of the four subjects who did not have parasite eradication, one who had a combined *B. hominis* and *G. lamblia* infection achieved remission even though *B. hominis* was found at stool examination post therapy.

## Discussion

In this study, the rate of intestinal parasitic infection in immunocompromised children with persistent and/or recurrent diarrhoea was 57%, slightly higher than that found in a similar study in Malaysia (42%) [7] on paediatric cancer patients and one on HIV-positive children in Thailand (33%) [13]. The difference could be due to different epidemiological patterns of parasitic infection in Indonesia.

No helminth infections were found in this study, which is similar to the results of Kurniawan *et al.* [8], where hardly any helminth infestation was observed among HIV patients with chronic diarrhoea. El-diffrawy [4] stated that helminth or luminal parasite infestation is more closely associated with low levels of IgA, while our subjects were mostly HIV infected with reduction in CD4 T-lymphocytes. A study in Iran [14] found a difference in IgA levels between leukemic children having intestinal parasites and those without parasites, and the most frequent parasite found was *Giardia lamblia* (n = 57; 16.7%). Another study in Malaysia involving children with cancer found that helminths were more common than protozoa [7]. This finding suggests that not only immune status but also other factors play a role in acquiring intestinal parasitic infection.

**Table 1.** Subject characteristics

| Characteristics | Number (N = 42) | % |
|---|---|---|
| **Age** (months); median (range) | 33 (6-144) | |
| **Sex** | | |
| Male | 18 | 43 |
| Female | 24 | 57 |
| **Age group** | | |
| Infant (<12 months) | 2 | 5 |
| Toddlers (12-<36 months) | 23 | 55 |
| Preschool (36 -<60 months) | 10 | 23 |
| School-age (5-<144 months) | 5 | 12 |
| Adolescent (144-<228 months) | 2 | 5 |
| **Mother's education** | | |
| Low | 20 | 47 |
| Moderate | 18 | 43 |
| High | 4 | 10 |
| **Water source** | | |
| Commercial sealed mineral water | 16 | 38 |
| Refill water | 4 | 10 |
| Ground water | 13 | 31 |
| Tap water | 9 | 21 |
| **Handwashing with soap** | | |
| Yes | 15 | 36 |
| No | 27 | 64 |
| **Immunocompromised state** | | |
| HIV | 22 | 52 |
| Malignancy | 10 | 24 |
| Severe malnutrition (without HIV) | 7 | 17 |
| SLE | 1 | 2 |
| Nephrotic syndrome | 1 | 2 |
| IgA deficiency | 1 | 2 |
| **Nutritional state** | | |
| Obesity | 1 | 2 |
| Well-nourished | 3 | 7 |
| Moderate malnutrition | 17 | 41 |
| Severe malnutrition | 21 | 50 |
| **Duration of diarrhoea** (days); median (range) | 14 (1-120) | |
| **Concurrent antibiotic usage** | 23 | 55 |
| **Immunosupressive state (HIV subjects) (n=14)** | | |
| Severe (CD4 $\leq$15%) | 13 | |
| Moderate (CD4 15-24%) | 1 | |
| **Antiretroviral therapy for HIV (ARV) (n =22)** | 4 | |

**Table 2.** The frequency of intestinal parasitic infection

| Type of parasites | Number of subjects N = 42 | HIV | Severe malnutrition HIV negative | Malignancy | Imuno-supressive therapy |
|---|---|---|---|---|---|
| *Blastocystis hominis* | 20 | 14 | 3 | 2 | 1 |
| *B. hominis & Cryptosporidium* | 1 | 1 | - | - | - |
| *B. hominis & Entamoeba histolytica* | 1 | - | - | 1 | - |
| *B. hominis & Giardia lamblia* | 1 | - | - | 1 | - |
| *Cryptosporidium* | 1 | 1 | - | - | - |
| Helminths | 0 | - | - | - | - |
| **Total subjects with parasitic infection** | **24 (57%)** | **16** | **3** | **4** | **1** |
| **Total subjects with no parasitic infection** | **18 (43%)** | | | | |

*B. hominis* was the most common parasite found in this study. A previous study in Egypt [15] reported similar results but with lower prevalence. A community-based study on asymptomatic healthy children in Jakarta also reported *B. hominis* as the most frequent parasite found, but the prevalence was much lower (less than 5%) [16]. However, in that study, the stated prevalence of *B. hominis* could have been an underestimate because the investigators did not perform the culture method. Another study in Canada reported that among subjects infected with *B. hominis*, 13% (19 of 143) were asymptomatic [17]. The pathogenicity of *B. hominis* has been a continuing debate [18,19] although recent evidence supports its pathogenic role in causing clinical symptoms in the absence of other intestinal pathogens [20,21]. The high detection of *B. hominis* in this study could reflect the ubiquitous nature of this parasite and the efficiency of detection methods applied.

*Cryptosporidium* was found only in subjects with HIV (2/22 = 9.1%), all with CD4 counts of < 15%. The prevalence was slightly lower than that observed in previous studies in Jakarta and Thailand (11.9% and 12.8% respectively) [8,13]. The prevalence of *Cryptosporidum* among our HIV subjects was higher than that in normal children (2.1%) as reported by a previous community-based study in Jakarta [22]. This result also showed that infection by *Cryptosporidium*, an intracellular protozoan, can be a marker of a severe immune deficiency state in HIV as stated by El-diffrawy [4] and that intracellular protozoan infection is associated with a reduction in CD4 T-lymphocytes. Only HIV infection is specifically associated with CD4 T-lymphocyte deficiency while other conditions, such as malignancy and malnutrition, can adversely affect various elements of the immune system including non-specific and specific mechanisms, and the humoral and cellular response [23,24].

In this study, HIV subjects who received antiretroviral therapy had lower rates of intestinal parasitic infection compared to those did not receive therapy, with a prevalence ratio of 0.57 (95%CI 0.2-0.63). Children receiving antiretrovirals experienced improved immune systems as reflected by undetectable viral RNA after 24 weeks of therapy and an increase in CD4 cell count after 144 weeks [25]. A study in India also reported that the lower the CD4 cell counts, the more frequent intestinal parasitic infection and diarrhoea would be [26].

We found that children with recurrent diarrhoea had a greater proportion of intestinal parasitic infection compared to those without (the prevalence ratio was 1.8), suggesting that parasitic infection should be considered in cases with chronic/recurrent diarrhoea. This observation was consistent with the characteristics of parasites, which were excreted intermittently in stools, causing on-and-off symptoms. In intestinal parasitic infection, diarrhoea episodes could be alternated with normal defecation patterns or even constipation, so careful history taking is essential.

The use of cotrimoxazole could become a confounding factor, as it decreases detection of parasites such as *Isospora* and *Cyclospora*, [27] and *B. hominis* [28]. However, in this study, the recruitment of subjects without cotrimoxazole therapy was almost impossible because all malignancy and HIV patients were prescribed this

**Table 3.** The distribution of demographic characteristics based on the occurence of intestinal parasitic infection

| Demographic characteristics | Parasite (+) N = 24 | Parasite (-) N = 18 | Prevalence ratio | 95%CI* |
|---|---|---|---|---|
| **Age** (months), median (range) | 31.5 (12-144) | 35.5 (6-144) | | |
| **Sex** | | | | |
| Male (N = 18) | 11 | 7 | 1.13 | 0.84-1.96 |
| Female (N = 24) | 13 | 11 | | |
| **Age group** | | | | |
| Infant (<12 months) | 0 | 2 | | |
| Toddlers (12-<36 months) | 16 | 7 | - | |
| Preschool (36 -<60 months) | 4 | 6 | | |
| School-age (5-<144 months) | 2 | 3 | | |
| Adolescent (144-<228 months) | 2 | 0 | | |
| **Mother's education** | | | | |
| Low | 13 | 7 | - | |
| Moderate | 8 | 10 | | |
| High | 3 | 1 | | |
| **Water source** | | | | |
| Commercial sealed mineral water | 9 | 7 | - | - |
| Refill water | 3 | 1 | | |
| Ground water | 5 | 8 | | |
| Tap water | 7 | 2 | | |
| **Handwashing with soap** | | | | |
| Yes | 10 | 5 | 1.28 | 0.77-2.14 |
| No | 14 | 13 | | |

*95%CI = 95% confidence interval

**Table 4.** The distribution of clinical characteristics based on the occurence of intestinal parasitic infection

| Clinical characteristics | Parasite (+) N = 24 | Parasite (-) n= 18 | Prevalence ratio | 95CI%* |
|---|---|---|---|---|
| **Nutritional state** | | | | |
| Well-nourished/obesity | 1 | 3 | - | - |
| Moderate malnutrition | 10 | 7 | | |
| Sever malnutrition | 13 | 8 | | |
| **Immunocompromised state** | | | | |
| HIV | 16 | 6 | - | - |
| Malignancy | 4 | 6 | | |
| Severe malnutrition (no HIV) | 3 | 4 | | |
| Immunosupressive therapy | 1 | 1 | | |
| Primary deficiency | 0 | 1 | | |
| **Persistent diarrhoea** | | | | |
| Yes | 15 | 9 | 1.25 | 0.72-2.18 |
| No | 9 | 9 | | |
| **Recurrent diarrhoea** | | | | |
| Yes | 23 | 16 | 1.8 | 0.36-8.98 |
| No | 1 | 2 | | |
| **Cotrimoxazole usage** | | | | |
| Yes | 9 | 5 | 1.2 | 0.71-2.02 |
| No | 15 | 13 | | |
| **Diarrhoea duration** (days) median (range) | 14.5 (1-120) | 10.5 (2-120) | | |
| **Diarrhoea frequency** [mean, (SD)] | 7.2 (4.8) | 5.3 (2.4) | | |
| **ARV therapy on HIV subjects** (n=22) | | | | |
| Yes | 2 | 2 | 0.56 | 0.2-0.63 |
| No | 14 | 4 | | |

*95%CI = 95% confidence interval

drug as a prophylactic agent against *Pneumocystis jiroveci*. However, we found that the prevalence ratio between subjects who took cotrimoxazole and those who did not was about equal. Nevertheless, there was neither *Isospora* nor *Cyclospora* infection found in this study, which might be related to the use of cotrimoxazole.

A study in an adult non-immunocompromised population found that metronidazole eradicated *B. hominis* in four of 12 subjects receiving therapy for 12 days [28]. Another study using a randomized controlled design reported clinical remission in 87% and parasite eradication in 80% of patients [29]. In this study, nine of 13 (69%) subjects had parasite eradication; thus on average, the treatment response was similar to that of immunocompetent patients. This observation might reflect that *B. hominis* is not only an opportunistic parasite typically attributed to immunocompromised subjects. Three of the HIV patients who had *B. hominis* eradication did not achieve clinical remission, which was probably due to other factors causing diarrhoea, such as co-infection with viruses, bacteria, and fungi which were not evaluated in this study, or enteropathy caused by the HIV virus itself [2].

Our finding that one subject achieved clinical remission even though *B. hominis* was still found in a stool sample after therapy raises questions regarding the pathogenicity of this parasite. Controversies about this issue remain, even though recent studies could prove the cause-and-effect relationship between *B. hominis* and gastrointestinal symptoms that are improved after the eradication of this parasite [20,29]. The pathogenicity of *B. hominis* was suspected to be associated with the number of parasites and certain subtypes [20], which were not evaluated in this study.

In conclusion, the prevalence of intestinal parasitic infection among immunocompromised children with persistent and/or recurrent diarrhoea was moderately high and dominated by *B. hominis* infection. The main groups affected were toddlers and preschoolers as well as those children infected with HIV who were not on antiretroviral therapy. *Cryptosporidium* was found only in HIV children with low CD4 counts. Clinical remission and parasite eradication could be achieved in *B. hominis* infection treated with metronidazole. We recommend additional, larger, well-designed studies to determine the relationship of certain parasitic infections to different causes of immunocompromised status and to evaluate the effectiveness of standard therapy for immunocompromised children with intestinal parasitic infection. Parasite stool examination is recommended for immunocompromised children with persistent and/or recurrent diarrhoea. Until more valid evidence is available, metronidazole could be considered for empiric therapy in immunocompromised children with diarrhoea if the clinical situation warrants.

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**Corresponding author**
Nikmah Salamia Idris
Department of Child Health
Faculty of Medicine
University of Indonesia
nikmahsalamia@gmail.com

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