Original Article

Anemia, leukocytosis and eosinophilia in a resource-poor population with helmintho-ectoparasitic coinfection

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Abstract

Introduction: Eosinophilia and anemia are very common hematological alterations in the tropics but population-based studies scrutinizing their value for diagnosing parasitic infections are rare.

Methodology: A cross-sectional study was conducted in a rural district in northeast Brazil where parasitic infections are common. Stool and blood samples were collected and individuals were clinically examined for the presence of ectoparasites.

Results: In total, 874 individuals were examined. Infection with intestinal helminths occurred in 70% (95% CI 67 – 75), infestation with ectoparasites in 45% (95% CI 42 - 49) and co-infection with both helminths and ectoparasites was found in 33% (95% CI 29% - 36%) of all inhabitants. Eosinophil counts ranged from 40/µl to 13.800/µl (median: 900/µl). Haemoglobin levels ranged from 4.8 g/dl to 16.8 g/dl (median: 12.5 g/dl), and anemia was present in 24% of the participants. Leukocytosis was found in 13%, eosinophilia in 74%, and hypereosinophilia in 44% of the participants. Eosinophilia was more pronounced in individuals co-infected with intestinal helminths and ectoparasites ($p < 0.001$) and correctly predicted parasitic infection in 87% (95% CI 84%-90.7%) of all cases.

Conclusions: Eosinophilia is strongly associated with the presence of intestinal helminthiases and accentuated by co-infestation with ectoparasites. Our study confirms in a population with high prevalence of intestinal helminthiases and ectoparasites that eosinophilia can be used to accurately diagnose current parasitic infection and initiate treatment.

Key words: anemia; leukocytosis; eosinophilia; intestinal helminths; ectoparasites; epidemiology; resource-poor community

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Introduction

Leukocytosis, eosinophilia and anemia are haematological alterations associated with a wide variety of disorders. Skin diseases, malignancies, allergic disorders and cytotoxic treatments can cause eosinophilia, and leukocytosis is an unspecific indicator for an inflammatory response of infectious or non-infectious origin [1-4]. Worldwide, anemia is most commonly caused by iron deficiency. In developing countries anemia, leukocytosis and eosinophilia are usually considered as indicators of a helminthic infection resulting in anthelminthic treatment without precise diagnosis [1,4,5].

The predictive values of the three haematological parameters in a tropical environment depend on occurrence and distribution in a population and the degree of correlation with the presence of defined intestinal helminthiases. Furthermore, ectoparasitic infestations may also cause hematological alterations such as leukocytosis or eosinophilia [6-12]. In addition, in severe cases, persistent pediculosis may contribute to anemia [12].

In Brazil, intestinal helminth infections and ectoparasitic infestations are common in impoverished urban and rural communities [13,14]. However, community-derived data on the prevalence of eosinophilia, leukocytosis and anemia and their association with intestinal and skin parasitism are scanty [14-16]. To investigate to which extent ectoparasites contribute to eosinophilia in the context of intestinal helminthiases, we conducted a

Table 1. Diagnostic criteria for parasitic skin diseases

Disease	Diagnostic criteria
Hookworm-related cutaneous larva migrans	Presence of a characteristic linear or serpiginous lesion associated with itching [38, 39]
Pediculosis capitis	Visual inspection of the entire head after parting the hair. Active pediculosis was defined as the presence of vital nymphas or adult parasites and or embryonated eggs [38, 40]
Scabies	Presence of erythematous papular, vesicular, pustular or bullous lesions associated with itching at defined prediliction sites [38, 41]
Tungiasis	Presence of embedded sand fleas in stages I to IV [42, 43]

community-based study in a rural community in Alagoas State, Northeast Brazil.

Methodology

Study area and population

The study was performed in Feliz Deserto, a rural district (called "municipality") about 60 km from the state capital Maceio of Alagoas State, Northeast Brazil (lat/long 9° 40' 0" S / 35° 43' 0" W). Feliz Deserto consists of several typical resource-poor communities (town centre and hamlets). Socioeconomic characteristics have been described elsewhere [17]. The communities are served by the Brazilian Unified Health Care System (SUS) and the so-called Family Health Programme. To achieve a self-weighted sample, the different hamlets were listed and two hamlets were selected using a random number list. A census was performed, all houses and inhabitants registered, and demographic data collected. The inclusion criterion was presence in the study area at least four nights per week during the last six months.

Study design

A cross-sectional survey was performed. During November and December 2003, all households of the selected hamlets were visited twice. During the first visit, household members were examined for the presence of ectoparasites. Containers for fecal samples were distributed. The containers contained 20 ml merthiolat iodine formaldehyde solution (MIF) and were collected three, five and seven days after distribution. Twenty ml of peripheral blood was drawn using BD Vacutainers (BD Diagnostics, Franklin Lakes, NJ, USA) and transported twice daily to Maceio. Diagnosis of parasitic skin diseases was made clinically. Table 1summarizes diagnostic criteria used.

Stool samples were examined using Hoffman's sedimentation method [18]. Briefly, in this method, helminth eggs are concentrated by passing the feces-MIF suspension through gauze followed by centrifugation for two minutes at 1000 rpm. The upper liquid phase was discarded using a pipette. To facilitate the microscopic examination, two drops of Lugol solution were added to the sediment. Three slides per fecal sample were prepared and read by two investigators (A.D., B.S.). Ten percent of the slides were randomly selected for cross-reading by an expert microscopist, who was blinded to the results of the first reading.

EDTA blood was analyzed at the day of collection in the laboratory of Santa Casa Hospital in the state capital Maceio, by an ABX Pentra 120 cell counter (Diamond Diagnostics, Holliston, USA). The following cut-off values were used: Leukocytosis: Leukocytes > 15.000/µl (0-7 years), > 13.000/µl (8-12 years) and > 10.000 cells/µl (> 12 years); eosinophilia: eosinophilic granulocytes > 500/µl; hypereosinophilia: eosinophilic granulocytes > 1.000/µl; anemia: hemoglobin < 13 g/dl (adult males), < 12g/dl (adult females), for both sexes: < 11g/dl (< 6 years), < 12 g/dl (6-12 years) [19]. Iron concentration was not measured.

Statistical analysis

Data were entered using Epi Info (Version 6.04d, CDC, Atlanta, USA) and checked for entry-related errors. For statistical analysis Stata (Version 7, Stata Corporation, College Station, USA) and SPSS (Version 13.0, Command Syntax Reference, Chicago, USA) were used.

Before applying any statistical test the data was tested for normality. To test for significances of proportions, the chi-squared test and Fisher's exact test were used. Not normally distributed data was compared using the Mann-Whitney and the Kruskal-Wallis tests as appropriate. Logistic regression analysis was performed to identify independent risk factors for eosinophilia and hypereosinophilia.

Table 2. Prevalence of intestinal helminths, protozoa and ectoparasites

	n	Prevalence % (95% CI)
Ascaris lumbricoides	370	55 (50 – 60)
Ancylostoma duodenale	277	36 (30 – 41)
Trichuris trichiura	260	34 (30 – 37)
Schistosoma mansoni	64	8 (6 – 10)
Strongyloides stercoralis	41	5 (3 – 7)
Enterobius vermicularis	3	0.4 (0.1 – 1)
Hymenolepis nana	3	0.4 (0.1 – 1)
Any intestinal helmtinth	538	70 (66-73)
Tunga penetrans	239	32 (29 – 36)
Pediculus humanus var. capitis	103	14 (11 – 16)
Sarcoptes scabiei	66	9 (7 – 11)
Hookworm-related cutaneous larva migrans	14	2 (1 – 3)
Any ectoparasitic infestation	333	33 (29-36)
Any parasite (intestinal and/or ectoparasite)	553	81 (78-83)

CI = Confidence Interval

Significance of correlations was tested by Cramer's V correlation coefficient (comparing nominal with nominal data) and Eta correlation coefficient (comparing nominal with interval data).

Two-by-two tables were used to calculate positive predictive values (PPV). The laboratory diagnosis of eosinophilia and hypereosinophilia was used as a gold standard to which different infection statuses were correlated.

Ethics

The study was approved by the Ethical Committee of the School of Medical Sciences of Alagoas State (UNCISAL, Maceió, Brazil) and conducted in accordance with the Helsinki Declaration (1964), as revised in 2008. Prior to the census, contacts were established with local community leaders and the objectives of the study explained. Informed written consent was obtained from all study participants. In the case of minors, informed written consent was obtained from the carer and the participant. Individuals' scabies or cutaneous larva migrans were treated topically (scabies: 10% benzyl benzoate for 3 days; cutaneous larva migrans: 5% thiabendazol 3x/d for 5 days). At the end of the study, all individuals living in the study area were treated with ivermectin (200µg/kg; Revectina, Solvay Farma, São Paulo, Brazil), provided there were no contraindications, irrespective of whether they had participated in the study or not. Ivermectin treatment was repeated after 10 days. Contraindications for ivermectin were as follows: age < 5 years; weight < 15 kg; pregnancy or breastfeeding; or presence of renal or hepatic disease. In case of contraindications, mebendazole or albendazole were administered (mebendazole for children < 2 years: 100 mg twice daily for three days; albendazole for children aged 2 - 4 years: 400 mg albendazole in a single oral dose). Pregnant women were excluded from treatment and referred to the primary health care center for appropriate treatment after delivery.

Results

During the census, 1,130 inhabitants were registered. Of these, 907 fulfilled the inclusion criteria, 472 of whom were females and 402 males. The median age was 17 years (range 1-90 years).

Hematological examinations were performed for 874 study participants, stool examinations for 767 participants, and 735 individuals were clinically examined for the presence of ectoparasites.

The overall prevalence of intestinal helminthiases and ectoparasitoses was 70% (95% CI 67 – 75) and 45% (95% CI 42 - 49), respectively. Coinfection with both helminths and ectoparasites was found in 33% (95% CI 29% - 36%) of all cases. Table 2 summarizes the findings classified by infectious agents. Prevalence of intestinal helminthiases followed an age-specific pattern with a peak in children aged 5-9 years for females and in adolescents aged 15 to 19 years for males. Thereafter, prevalence almost constantly decreased (Figure 1A). The prevalence was significantly higher in younger individuals (aged 0-19 years) than in adults aged older than 20 years (77% versus 61%; $\chi 2$ test $p = 0.02$).

The prevalence of ectoparasitoses followed the typical age-dependent s-curve as describe by Heukelbach *et al*. (Figure 1B) [16].

Table 3. Multivariate analysis by logistic regression of factors predisposing to eosinophilia and hypereosinophilia

Variable	Adjusted odds ratio	95% CI	P-value
	Presence of eosinophilia		
Sex			
Female	Ref		
Male	1.4	0.1-1.9	0.23
Age (years)			
0-4	16.6	2.8-19.5	<0.001
5-9	22.7	3.6-22.8	<0.001
10-14	15.9	2.4-14.4	<0.001
15-19	6.7	1.3-9.9	<0.001
20-39	2	0.8-3.8	0.15
40-59	0.9	0.6-3.4	0.33
> 59	Ref		
Presence of			
Ectoparasitosis	1.4	0.7-2.9	0.27
Intestinal helminthiasis	3.	1.5-5.8	0.001
Coinfection with helminths and ectoparasites	2.6	1.5-4.3	<0.001
Number of helminth species (1-5)	1.1	0.9-1.4	0.17
	Presence of hypereosinophilia		
Sex			
Female	Ref		
Male	1.5	1.05-2.2	0.025
Age (years)			
0-4	25.2	6.8-93.7	<0.001
5-9	20.5	5.8-72.4	<0.001
10-14	15.1	4.2-53.8	<0.001
15-19	11.8	3.1-45.3	<0.001
20-39	3.1	0.8-11.1	0.07
40-59	2.9	0.7-11	0.1
> 59	Ref		
Presence of			
Ectoparasitosis	1.2	0.5-3	0.57
Intestinal helminthiasis	2.8	1.3-5.7	0.005
Coinfection with helminths and ectoparasites	1.7	1.1-2.6	0.008
Number of helminth species (1-5)	1.2	1.04-1.4	0.01

Ref = reference; CI = Confidence Interval

Table 4. Median number of eosinophils stratified by infection status and number of helminth species

Number of different helminth species	Individuals without ectoparasitic infestation		with		P Value
	n	Median number of eosinophils per µl (IQR)	n	Median number of eosinophils per µl (IQR)	
0	102	480 (240-830)	62	575 (390-970)	0.05
1	92	655 (420-1165)	66	1025 (610-1780)	<0.001
2	96	910 (425-1445)	88	1380 (740-2020)	0.001
3	58	1040 (530-1630)	53	1530 (990-2640)	0.001
4	19	840 (535-1415)	30	1225 (760-2340)	0.07
5	11	1035 (790-1080)	6	1200 (875-1795)	0.2

IQR= Interquartile

Figure 1. Prevalences stratified by age group of (A) intestinal helminthiases (B) ectoparasitoses (C) leukocytosis, eosinophilia and hypereosinophilia (D) anemia.

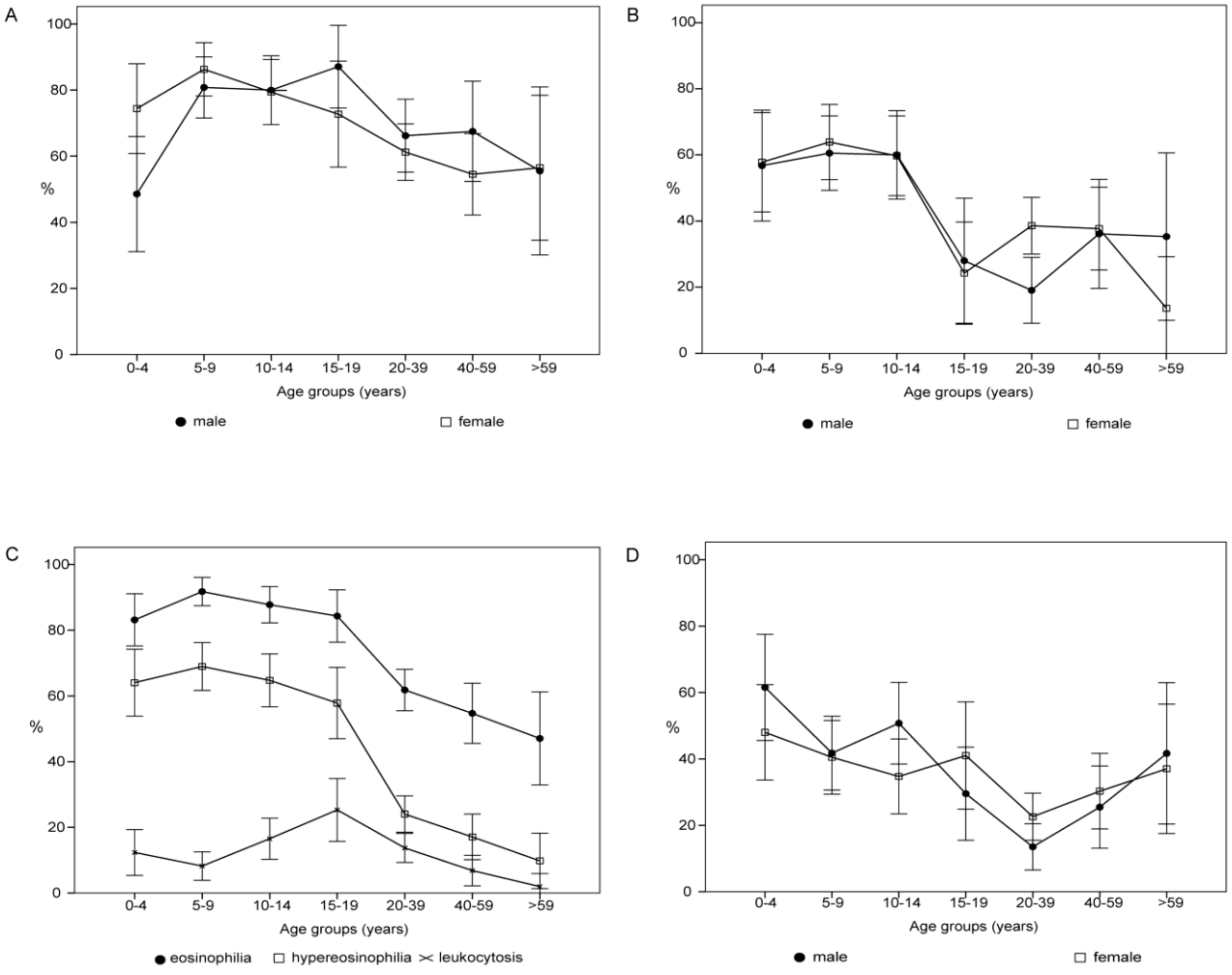
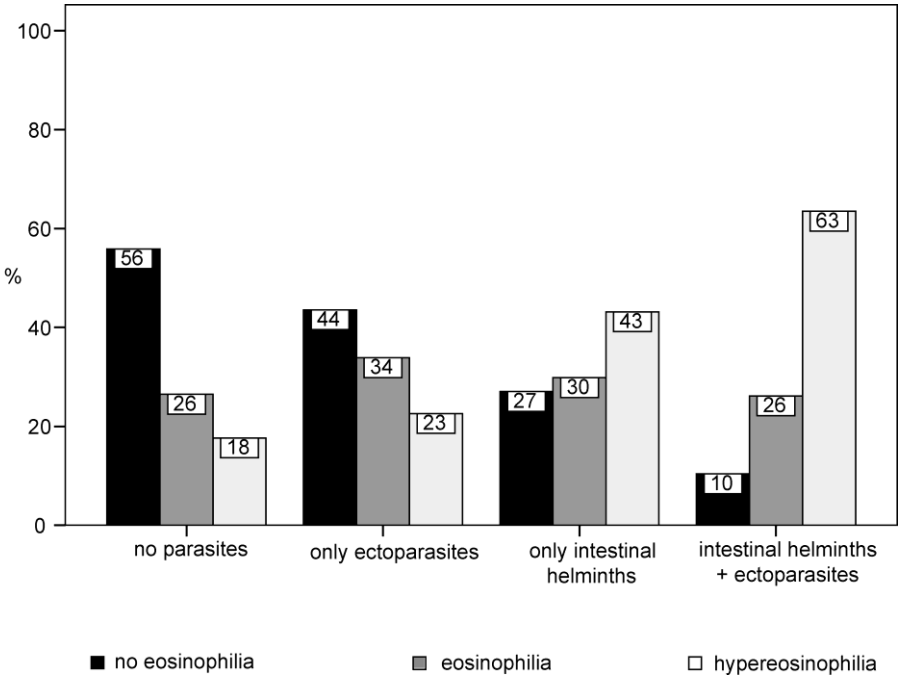


Figure 2. Distribution of eosinophilia and hypereosinophilia according to infection status



Hematological alterations

The median number of leukocytes was 8100/µl (interquartile range [IQR] 6475/µl –10300/µl). In both genders a significantly higher number of leukocytes was found in the youngest age group of 0 to 4 years (median 11000/µl, IQR 8400/µl – 13200/µl), as compared to the oldest age group of older than 60 years (median 6000/µl, IQR 4900/µl – 7200/µl; Mann Whitney U test $p < 0.001$)

Age-specific leukocytosis was found in 13% of participants with no significant difference between genders. With increasing age, prevalence of age-specific leukocytosis increased ($\chi 2$-test for trends $p < 0.05$) to reach a maximum between 15 to 19 years (Figure 1C). Thereafter, prevalence declined (Figure 1C; $p = 0.03$) and no case of leukocytosis was detected in the age group older than 60 years.

The median number of eosinophils was 900/µl (IQR 500/µl – 1500/µl) with no significant differences between genders. The highest number of eosinophils was found in children aged 5-14 years (median 1400/µl, IQR 800/µl – 2000/µl). In individuals aged younger than 20 years, the number of eosinophils was significantly higher than in individuals older than 20 years of age (median 1260/µl eosinophils versus 580/µl; Mann Whitney U test $p < 0.001$).

Prevalence of eosinophilia was 74% with no significant difference between males and females (71% vs. 77%, $\chi 2$-test $p = 0.06$). The highest prevalence (92%) was found in the 5- to 9-year-olds (Figure 1C); thereafter, the prevalence of eosinophilia decreased significantly ($\chi 2$-test for trends $p < 0.001$). Hypereosinophilia was found in 44% of the individuals with a distribution pattern identical to eosinophilia, but significantly more frequent in men than in women ($\chi 2$-test $p = 0.02$). As for eosinophilia, the age group younger than 20 years showed a significantly higher prevalence than older individuals ($\chi 2$-test $p < 0.001$; Figure 1C).

The overall prevalence of anemia was 34% ranging from 13% (40-59 years) to 58% (0-4 years) in men and 22.6% (20-39 years) to 46% (0-4 years) in women (Figure 1D). For both sexes the prevalence of anemia was significantly higher in individuals older than 40 years ($\chi 2$-test $p < 0.001$). In the age group 0-14 years, anemia was significantly more frequent in males (49%) than in females (40%) ($\chi 2$-test $p < 0.05$). In the majority of cases (86%), anemia existed in children younger than 2 years irrespective of sex. Fifty-six percent of anemic individuals had a low mean corpuscular volume (MCV) < 85 fl) and 62% a low mean corpuscular hemoglobin (MCH) < 28 pg).

Parasites and eosinophilia

The number of eosinophils varied according to infection status. In individuals without any parasitic disease, normal eosinophil counts were observed significantly more frequently than in individuals with eosinophilia or hypereosinophilia (χ2-test $p < 0.001$, Figure 2). A similar pattern was noted in the group of individuals with at least one ectoparasite species but without intestinal helminths, although the differences were not significant. In the group with both intestinal helminthiasis and ectoparasitosis, hypereosinophilia and eosinophilia were observed significantly more frequently than in individuals with normal eosinophil counts (χ2-test $p < 0.001$, Figure 2).

Multivariate analysis suggested that age younger than 20 years, presence of intestinal helminthiases, and a coinfection with helminths and ectoparasites were independent factors predisposing for eosinophilia and hypereosinophilia. The number of different helminth species present in stool increased the chance for hypereosinophilia (Table 3).

The median number of eosinophils was significantly higher in individuals presenting ectoparasitic infestation (median 1340/µl, IQR 990µl-2160µl) as compared to individuals without an ectoparasitic infestation (median 990/µl, IOR 530/µl-1585/µl; $p < 0.001$). However, individuals with ectoparasites, when coinfected with intestinal helminths, showed a significantly higher number of different helminth species (median 2, IQR 1-3) as compared to individuals with intestinal helminths but without ectoparasites (median 1, IQR 0-2, $p = 0.004$). Therefore, the median number of eosinophils between the two groups was compared, stratified by the number of different helminth species found. Table 4 shows that eosinophil counts were significantly higher when individuals were coinfected with intestinal helminths and ectoparasites, independent of the number of different helminth species found.

The PPVs of eosinophilia for infection with ectoparasites, intestinal helminths or co-infection was 20% (95% CI 15%-26%), 79.9% (95% CI 73%-84%) and 41% (95% CI 36%-45%), respectively. The PPV of hypereosinophilia for infection with ectoparasites, intestinal helminths, or coinfection with both was 16% (95% CI 9%-22%), 83% (95% CI 77%-90%) and 48% (95% CI 43%-54%), respectively. The PPV of eosinophilia and hypereosinophilia for infection with either intestinal helminths or ectoparasites was 87% (95% CI 84%-90.7%) and 91% (95% CI 88%-95%), respectively.

Leukocytosis was significantly correlated with the presence of intestinal helminthiases ($V = 0.12$; $p < 0.001$). Eosinophilia was significantly correlated with the presence of a parasitic infection in general ($V = 0.33$, $p < 0.001$), presence of an intestinal helminthic infection ($V = 0.27$, $p < 0.001$) and presence of an ectoparasitosis ($V = 0.08$, $p = 0.04$). Infection with intestinal helminths correlated significantly with ectoparasitic infestation ($V = 0.1$, $p = 0.01$). In addition, the presence of eosinophilia was significantly correlated with the number of different helminth species present ($V = 0.32$, $p < 0.001$).

There was a significant relation between eosinophil counts and the presence of *Ancylostoma duodenale* (Eta 0.85, $p < 0.001$), ectoparasites in general (Eta 0.6, $p < 0.05$), and the number of different helminth species (Eta 0.22, $p < 0.001$). The degree of anemia correlated significantly with the presence of *Ascaris lumbricoides* ($V = 0.14$, $p < 0.05$) but not with other helminth species.

Discussion

The data from this study show that eosinophilia, hypereosinophilia, and anemia are common in individuals living in a resource-poor rural community in Brazil where intestinal helminthiases and parasitic skin disease are frequent. In comparable settings, Hillyer *et al*. found a prevalence of eosinophilia of 52% and Cardoso *et al*. a prevalence of anemia in 28%. In other studies in similar settings, prevalence of intestinal parasites ranged form 26% to 99% [15,20,21]. For ectoparasitic infection, prevalences between 16% and 43% have been described [16,21].

In resource-poor settings, intestinal helminths are generally considered the main cause of eosinophilia [22-24]. This study underlines the predominant role of intestinal helminthiases in eosinophilia: in individuals with a helminthic infection (in the absence of ectoparasites), the prevalence of eosinophilia was over 60% and logistic regression revealed that the presence of intestinal helminthiases was the best predictor of eosinophilia. In comparison, ectoparasitic infestation by itself did not increase the chance of eosinophilia. Furthermore, when individuals were infected with more than one helminth species, the odds of hypereosinophilia increased by 24% per present species. In other words, the more abundant helminth species are in the intestinal tract, the higher the chance that eosinophilia is present.

Leukocytosis is a less reliable predictor of intestinal helminthiases. Even though it correlated with the presence of intestinal helminthiases, no association between leukocytosis and intestinal helminthiases could be found. Considering the fact that the hygienic situation in the study area was precarious and that leukocytosis is an unspecific immune response to infection, the high prevalence of leukocytosis could be due to concomitant or previous infections of bacterial or viral origin.

The relationship between chronic intestinal infection with helminths and anemia has been thoroughly investigated and confirmed in several studies [25,26]. In particular, infection with hookworm species can cause severe anemia due to continuous blood loss from blood-sucking adults and bleeding mucosal ulcer [27]. In this study, however, we could not show a significant relationship between presence of intestinal helminths and anemia. An explanation could be a rather low intensity of infestation with intestinal helminths resulting from repeated administration of antihelminthic drugs at the primary health center of Feliz Deserto. Anemia is only suspected to occur at a minimum amount of 500 eggs/g feces of hookworms [28].

Comparable to intensity of infestation with intestinal helminths, Speare *et al*. (2006) showed that only an infestation with head lice is unlikely to significantly contribute to anemia, only at extremely high parasite loads (more than 2500 head lice per individual) [12]. To what extent ectoparasitc infestation contributes to eosinophilia is difficult to correlate, since in impoverished communities co-infection with ectoparasites is common [14]. In a previous study from Brazil, eosinophil counts were higher in individuals co-infected with intestinal helminths and ectoparasites than in individuals with only intestinal helminths [14]. The data from the present study support this finding, showing that the median number of eosinophils was significantly higher in individuals co-infected with both types of parasites irrespective of the number of helminths species present. Prevalence of eosinophilia and hypereosinophilia was also higher in co-infected individuals compared to individuals with intestinal helminthiases only. This observation indicates an accentuation of eosinophilia in individuals with intestinal helminthiases by the presence of ectoparasites. In fact, clinico-pathological studies have shown that parasites embedded in the epidermis such as *Tunga penetrans* and *Sarcoptes scabiei* are surrounded by eosinophils and that patients with these conditions show elevated levels of IL-5, a cytokine needed for the production of eosinophils [29,30]. Cutaneous larva migrans has been associated with systematic eosinophilia [31-33].

It is generally believed that in a tropical environment the presence of eosinophilia is a better predictor for intestinal helminthiases than in industrial countries [14]. Travel clinics, for instance, consider eosinophilia only modestly helpful for the diagnosis of helminthic infections [2,6,8]. A study in Canada found that only 14% of patients with eosinophilia were infected with helminths, emphasizing the importance of factors other than helminthic infection that are responsible for eosinophilia [8]. In the current study, this value was considerably higher with almost 80% of patients with eosinophilia presenting intestinal helminthiases.

The low correlation indices between intestinal helminthiases and eosinophilia found in this study could indicate that even in a tropical environment other factors besides helminthic infection are important causes for eosinophilia. Among such causes allergic disorders, which can cause high eosinophilic counts [4], could play an important role. In this investigation, 12% of all study participants presented eosinophilia without any diagnosis of parasitic infection. On one hand this can be explained by erroneously categorizing infected patients parasite-free due to a limited sensitivity of the stool examination technique. In addition, attention has to be paid to the life cycle of the parasite [5]. Some helminths, such as *A. lumbricoides*, induce blood eosinophilia primarily during their tissue passage when no eggs are present in feces. A considerable day-to-day variation of egg excretion in stool can also account for false-negative diagnoses. Furthermore, other parasitoses not included in this study could have caused eosinophilia in the study population, such as toxocariasis and trichinosis [34-36]. *Ancylostoma caninum* is known to cause eosinophilic enteritis which can present peripheral eosinophilia [37].

On the other hand, eosinophilia may occur in parasite-free individuals. The development of eosinophilia depends on host immunocompetence in general and in particular on previous eosinophil-stimulating infections [1]. Probably frequent re-infection with multi-cellular parasites causes eosinophilia that persists during parasite-free episodes. In addition, eosinophil levels are known to be higher during morning hours when corticosteroid levels are low [37]. As blood samples were not

always collected at the same time, early collection during the day may have led to a diagnosis of eosinophilia in some individuals that would otherwise have shown normal results.

High PPVs are important to initiate a treatment after diagnosing a disease. In this study we found the highest PPV for infection with either helminths or ectoparasites. Since many intestinal helminths and ectoparasites can be treated with the same antiparasitic drug, such as ivermectin, eosinophilia could be used to initiate treatment with ivermectin in communities with a high degree of helmintho-ectoparsitic co-infection where the examination of stool samples is not feasible.

In conclusion, we have shown that in a polyparasitised rural population in northeast Brazil, eosinophilia was strongly associated with the presence of intestinal helminths and accentuated by ectoparasites. Factors other than infection with multicellular parasites seem to be more relevant causes of leukocytosis and anemia. We confirm the common practice that in populations with a high prevalence of intestinal helminthiases and co-infection with ectoparasites, eosinophilia can be used to initiate antiparasitic treatment without any further diagnosis.

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