Recommendations of the Brazilian Society of Rheumatology

Recommendations from the Brazilian Society of Rheumatology on the diagnosis and treatment of intestinal parasitic infections in patients with autoimmune rheumatic disorders

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ARTICLE INFO

Keywords:
Parasitarian enteropathy
Diagnostic
Therapeutics
Autoimmune diseases
Rheumatic diseases

ABSTRACT

Intestinal parasites – helminths and protozoa – are cosmopolitan diseases which are most prevalent in tropical regions. Patients with diagnoses of autoimmune rheumatic diseases have, due to the underlying disease or its treatment, an increased risk of occurrence of severe manifestations of intestinal parasites. Although the prevalence of these parasitic infections is very high in our environment, not always is the rheumatologist attentive to the need for investigation and treatment of helminthiasis and protozooses before the use of immunomodulatory, immunosuppressive therapies, and of biological drugs that are modifiers of the course of the disease. In this document, the Brazilian Society of Rheumatology establishes general recommendations on the diagnosis and treatment of intestinal parasitic infections in Brazil in patients with autoimmune rheumatic diseases, highlighting rheumatoid arthritis, systemic lupus erythematosus and spondyloarthritis.

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Recomendações da Sociedade Brasileira de Reumatologia sobre diagnóstico e tratamento das parasitoses intestinais em pacientes com doenças reumáticas autoimunes

RESUMO
As parasitoses intestinais – helmintíases e protozooses – são doenças cosmopolitas com maior prevalência em regiões tropicais. Pacientes com diagnóstico de doenças reumáticas autoimunes apresentam, em função da própria doença de base ou de seu tratamento, um maior risco de ocorrência de manifestações graves das parasitoses intestinais. Embora a prevalência dessas parasitoses seja bastante elevada em nosso meio, nem sempre o reumatologista está atento à necessidade de investigação e tratamento das helmintíases e protozooses antes do uso de terapias imunomoduladoras, imunossupressoras e dos medicamentos biológicos modificadores do curso da doença. Neste documento, a Sociedade Brasileira de Reumatologia estabelece recomendações gerais sobre o diagnóstico e tratamento das parasitoses intestinais no Brasil em pacientes com doenças reumáticas autoimunes, com destaque para a artrite reumatoide, o lúpus eritematoso sistêmico e as espondiloartrites.

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INTRODUCTION

Intestinal parasitic infections – helminthiasis and protozooses – are cosmopolitan diseases with more prevalence in tropical regions. Intestinal parasites more often found in humans are: Ascaris lumbricoides, Trichuris trichiura and ancylostomides: Necator americanus and Ancylostoma duodenale. Among the protozoa Entamoeba histolytica and Giardia intestinalis are highlighted.1

Patients with diagnoses of autoimmune rheumatic diseases present, due to the underlying disease or its treatment, an increased risk for severe manifestations of intestinal parasites. Although the prevalence of these parasites is very high in our environment, not always is the rheumatologist aware of the need for search and treatment of helmintiasis and protozooses before the use of immunomodulatory, immunosuppressive therapies, and immunobiological medications. The non-recognition of these conditions can lead to serious consequences.

The Brazilian Society of Rheumatology (SBR) considered that it would be appropriate to make general recommendations on the diagnosis and treatment of intestinal parasitic infections in Brazil in patients with autoimmune rheumatic diseases, highlighting rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and spondyloarthritis (SA).

OBJECTIVE

To provide a document that represents the opinion of experts based on literature review of aspects related to the management of intestinal parasites in Brazil in patients with autoimmune rheumatic diseases, identifying potential interference of this concurrence in the diagnosis and treatment of autoimmune diseases.

METHOD

The method for document preparation included a literature review, performed by rheumatology experts who are members of the SBR. Specialists from the Committee on RA, Committee on Endemic and Infectious Diseases, Committee on SLE, Committee on SA, and Committee of Epidemiology were invited, among others. A bibliographic survey included publications in MEDLINE, SciELO, PubMed and EMBASE databases up to February 2014. The recommendations were written and reassessed by all participants during multiple rounds of questions and corrections made via Internet.

This document is part of the SBR initiative to make recommendations on the diagnosis and treatment of endemic and epidemic diseases in Brazil in patients with autoimmune rheumatic diseases. In a previous document, recommendations were given on Chagas disease, syphilis, dengue, schistosomiasis, leishmaniasis and filariasis. The other selected endemic diseases will be addressed in separate documents.

GENERAL CONSIDERATIONS ON HELMINTHIASIS AND PROTOZOSES

Helminthiasis and protozooses are diseases of spectral manifestation, ranging from asymptomatic cases to mild to severe forms. In the most common presentations, symptoms are nonspecific, such as anorexia, irritability, sleep disturbances, nausea, vomiting, abdominal pain, and diarrhea. Severe cases occur in patients with higher parasite load, and in immunocompromised and malnourished individuals.2 The onset or exacerbation of malnutrition occurs through mucosal injury (G. intestinalis, N. americanus, Strongyloides stercoralis, coccidiosis), change of biliary salts metabolism (G. intestinalis), competition for food (A. lumbricoides), intestinal exsudation (G. intestinalis,
S. stercoralis, N. americanus, T. trichiura), bacterial proliferation facilitation (E. histolytica) and hemorrhages (N. americanus, T. trichiura).\(^3\)

Parasitic diseases are the leading cause of morbidity and mortality in the population with billions of people infected worldwide. Of these, 300 million suffer from severe clinical forms of parasitic infections, and 155,000 die each year from these diseases.\(^4\) Many infections occur throughout the world, even in countries where there are infection prevention measures, requiring considerable investment in public health infrastructure.\(^5\)

Ascariasis, trichuriasis and ancylostomoides infections, among other intestinal helminthiasis, are concentrated amongst the poorest population and have high morbidity. It is estimated that 20-30% of the population in America is infected by A. lumbricoides, T. trichiura or ancylostomoides and Schistosoma mansoni.\(^6\) These parasites affect respectively more than 1.2 billion, 795 million, and 740 million of people in the world, and can be considered the most prevalent human intestinal infections.\(^7\)

The reports made in the literature of prevalence of intestinal parasites in Brazil are scarce and very specific. They are usually described considering specific populations (school-aged children, elderly or immunocompromised patients), only reflecting the reality of small towns. Thus, you cannot have a comprehensive picture of the prevalence of these parasitic infections at national level.

The article by Basso and colleagues stands out. They have studied the variation for 35 years (1969–2004) on enteral parasitic infections’ prevalence in school-aged people from the city of Caxias do Sul, in the state of Rio Grande do Sul, evaluating 9787 parasitology fecal tests. These authors showed that the general prevalence of intestinal parasitic infections decreased from 89% to 37% and that there was a reduction in the prevalence of A. lumbricoides from 61% to 26% and of T. trichiura from 38% to 18%. For Giardia lamblia there was no significant change. The prevalence of Entamoeba coli increased from 29% to 46%.\(^8\)

Barbosa and colleagues made an ecological study for geo-helminths analysis by secondary data from Zona da Mata de Pernambuco (ZMP) covering 43 municipalities and more than 1100 million inhabitants. These authors demonstrated that there was a higher distribution of cases of A. lumbricoides and T. trichiura in the south of ZMP, and higher incidence of tapeworms in the north and center of this region. They concluded that although several studies revealed cases of geo-helminths in the ZMP, no effective preventive measure to reduce these health risks has been implemented in this endemic area.\(^4\)

**Giardiasis**

Giardiasis is an intestinal parasitic disease caused by the flagellate, extracellular protozoan, parasite of the small intestine, G. lamblia (synonyms: G. intestinalis, Giardia duodenalis). It is an important cause of world enteric diseases.\(^9\)

In Brazil, the prevalence varies from 5.5% in children from 0 to 5 years in the city of São Paulo\(^10\) to 24% in school-aged children in Caxias do Sul,\(^8\) achieving 32.8% in children below 7 years of age in day care centers in the city of São Paulo, and 75.2% in the rural areas of state of Pernambuco.\(^11,12\)

The transmission of G. lamblia occurs through water; consumption of vegetables and fruit contaminated by cysts; food handlers; inter-human direct contact (fetal–oral), especially in nursing homes, day care centers and psychiatric clinics. Cysts may remain viable in a wet environment for a period of 3 months and resist to usual chlorination of water. We also consider the transmission by arthropods through their stools or re-regurgitation.\(^13\)

Infections by G. lamblia may be presented in varied forms, from asymptomatic cases to infections with acute diarrhea followed by abdominal distension and pain. There may also be chronic diarrhea followed by steatorrhea, weight loss, and intestinal malabsorption in 30-50% of infected patients.\(^1\) Malabsorption of sugars, fats, and vitamins A, D, E, K, B12, folic acid, iron, or zinc are also described.\(^3\) Skin manifestations, allergies, and hives can also be described in patients with giardiasis.\(^14\)

Nitroimidazoles are drugs used to treat giardiasis and include metronidazole, secnidazole, tinidazole and ornidazole.\(^15\) Other drugs such as benzimidazoles, quinacrine, furazolidones, paromycin and nitazoxanide are often used.\(^16\)

Metronidazole is the most frequently used drug for the treatment of human giardiasis; however, its use can cause headache, dizziness, nausea, and metallic taste. A comparative study of albendazole and metronidazole showed that albendazole is an alternative drug to metronidazole for the treatment of giardiasis.\(^17\)

Nitazoxanide is a broad spectrum antiparasitic drug effective to treat helminths and protozoan.\(^18\) It is given orally; it shows a good bioavailability and is an alternative drug for the treatment of giardiasis in children younger than one year.\(^19\)

**Amoebiasis**

Amoebiasis or amebic dysentery is classically defined as an infection (symptomatic or asymptomatic) caused by the protozoan E. histolytica.\(^2\) Among the species of amoebae found in the gastrointestinal tract E. histolytica is the only one to cause an invasive disease, designated intestinal or extra-intestinal amoebiasis.\(^20\) In 1925, Brumpt suggested the existence of another species of amoeba, Entamoeba dispar, with symptomatic infection, but only during the 1990’s accumulated evidence confirmed the existence of two morphological identical amoebae, with E. dispar being non-pathogenic and the other, the pathogenic form (E. histolytica).\(^21\) The two species can be differentiated by molecular biology, biochemical or immunological methods.\(^22\) The parasitological diagnosis of intestinal amoebiasis is obtained by the search of parasites in stool samples, with the search for cysts being performed in consistent stools, and trophozoites in diarrheal stools. However, the technical inexperience, intermittent elimination of the cyst of E. histolytica/E. dispar and no morphological differentiation with other intestinal amoebae, and artifacts can provide microscopic misdiagnosis.\(^23\)

E. histolytica is widely distributed throughout the world. Its prevalence is higher in countries of tropical and subtropical areas where the population is poor, with low sanitation.\(^21\) However, the increasing migration of people from developing countries to developed countries favored the spread of the
parasite throughout the world. There are large numbers of people infected in regions with cold climate such as Canada, north of the United States and Europe.24

The infection with E. histolytica is the cause of death in approximately 100,000 people per year, second only to malaria in number of deaths by protozoa.25

Regarding national data on amoebiasis, its prevalence ranges from 3.4% in the population of the city of Salvador26 reaching 6.2% in students from the city of Bambuí (state of Minas Gerais)27 and reaching 20% also in school-aged children in the city of Caxias do Sul (state of Rio Grande do Sul).8

The life cycle of the parasite has the following morphological stages: trophozoites, precyst, metacyst and cysts. The transmission of amoebiasis is accomplished by the ingestion of mature cysts that contaminate food and water through a fecal–oral cycle. Less common forms of transmission include oral and anal sex.1

E. histolytica is a parasite of the large intestine. It can remain as a commensal parasite, or cause tissue invasion, leading to intestinal or extraintestinal forms of the disease. Clinically, amoebiasis can be asymptomatic, with most individuals belonging to this group. The infection is detected by finding cysts in the stool, a fact that makes the carriers asymptomatic disseminators of the disease.28

The intestinal amoebiasis associated with E. histolytica is characterized by the presence of colon, sigmoid and rectum ulcers. Occasionally, the individuals develop amoebic colitis with profuse bloody diarrhea, fever, leukocytosis, frequent abdominal pain with peritoneal signs, and extensive involvement of the colon. Amoebic abscesses may occur, but the dominant clinical picture in more than 75% of the patients with fulminant amoebic colitis consists of intestinal perforation. Pregnant women, immunocompromised individuals, patients with diabetes mellitus, alcoholics or those who are on corticosteroids are at high risk for the fulminant disease.24

Regarding extraintestinal amoebiasis, the most common form consists of amoebic abscess due to the migration of trophozoites through the superior mesenteric vein to the liver.29,30 The invasion of the respiratory tract is usually secondary to liver abscess after being ruptured through the diaphragm (7–20% of patients). However, brain abscess is rare and also occurs after rupture of hepatic abscess. The symptoms are abrupt and characterized by headache, vomiting, seizures and behavioral changes.31

The drugs used for treating amoebiasis vary in effectiveness and according to the site where parasites are often settled.32 Basically they fall into two classes: amoebicides working in the intestinal lumen and those working in the tissues.32

Nitroimidazoles comprise the main class of drugs, among which: secnidazol, metronidazole, tinidazole and ornidazole. They act in the intestinal lumen and tissues. Luminal amoebicides include: teclozan and etofamid.33

Metronidazole is the drug of choice for the treatment of hepatic amoebiasis, followed by a luminal agent. However, patients may remain symptomatic with significant risk of rupture of the abscess into the peritoneum. In this case, for patients who have failed treatment of 5 or 7 days, percutaneous aspiration may be necessary, although this indication remains controversial.34,35 Reported cases demonstrate the successful use of metronidazole for patients with rheumatic disease.36 The standard treatment for amoebiasis with metronidazole is 500–750 mg three times daily for 7–10 days for adults and 30–50 mg/kg/day for children for 5–10 days.32

Nitazoxanide was effective in the treatment of intestinal and tissue amoebiasis.37 In Mexico, a comparative study of nitazoxanide (200 mg for 3 days) with mebendazole (200 mg for 3 days) and/or quinbamid (100 mg per 1 day) for several intestinal parasitic infections showed 73.9% cure rates for giardiasis and 80% for amoebiasis.38 In Egypt, a prospective, randomized, double-blind, placebo-controlled study was performed to evaluate nitazoxanide efficacy in treating diarrhea caused by G. lamblia and E. histolytica/E. dispar. The results showed an 81% overall cure of nitazoxanide compared to 40% of the placebo group. For giardiasis, a cure of 91% versus 36% of the placebo was observed. In cases of E. histolytica/E. dispar, results showed 80% versus 48% of placebo and in mixed infections, 67% versus 25% of placebo.37 In Egypt, nitazoxanide was also investigated in the treatment of intestinal and hepatic amoebiasis in outpatients, in a double-blind, prospective, randomized, placebo-controlled study. The results showed 94% clinical and parasitological cure of the patients analyzed.29

**Ascariasis**

Ascariasis is an intestinal parasitic infection caused by the helminth A. lumbricoides, the most common species of nematode in humans, popularly known as “lombriga” (worm) in Brazil.40

Data about the prevalence of ascariasis are very heterogeneous in Brazil, ranging from 4.4% in children of São Paulo under five years of age,10 and 4.8% in students from the city of Bambuí (state of Minas Gerais),27 to 47% of the students in the city of Caxias do Sul (state of Rio Grande do Sul)9 and 48.8% of individuals from zero to 86 years of age living in the state of Minas Gerais.41

The symptomatology is directly related to the parasite load. Infections by A. lumbricoides may be asymptomatic (3–4 worms), but the adult worms can cause predatory, toxic or mechanical action (average of 30–40 worms). Massive infections (100 or more worms) are also described, potentially causing liver damage evolving to fibrosis. Patients infected with this helminth have a risk of progressing to malnutrition, especially at childhood, due to a large consumption of protein, vitamins, lipids and carbohydrates by the parasites.1

Other manifestations described include allergic reaction to parasite antigens and lesions caused by the worm larvae, pneumonic disease and intestinal obstruction. The main characteristics of this obstruction are diarrhea followed by constipation, abdominal pain, vomiting, history of elimination of the parasite in the stool or by vomiting. The obstructive or semiobstructive cases can cause death, especially in malnourished children.1

**Ancylostomiasis**

Ancylostomiasis is defined as an intestinal parasitic disease caused by nematodes of Ancylostomidae family: An. duodenale and N. americanus. In Brazil, the disease is popularly
known as “amarelão” (skin yellowing), “opilação” or “Jeca Tatu’s disease”.¹

The ancylostomides have widespread geographic distribution and high prevalence, being an infection that is more common in rural areas.² On this parasite group, the study published by Mudenda and colleagues stands out, in which risk maps were elaborated on a national scale (980 municipalities) through the application of known biological information on N. americanus using data on climate conditions appropriate for this species of ancylostomiasis.³ The average prevalence of ancylostomiasis among the municipalities obtained by the model was 5% (range = 0–70.2%; standard deviation [SD] = 8.9%). These researchers also included data from 30 independent articles published between 1990 and 2010 by several other authors in the study, in order to validate risk prediction in the developed models. Such articles covered 16 of the 26 states of Brazil. The prevalence of ancylostomiasis in these articles was calculated according to the model ranging from 0% (city of São Paulo/state of São Paulo) to 80.2% (city of São Lourenço da Mata/state of Pernambuco), with an average of 20.3% (SD = 22, 3%).⁴

Although the primary signal of ancylostomiasis is anemia, its symptoms depend on the intensity of parasitism. The ancylostomides’ eggs are eliminated in human feces and when they find a proper environment, with good oxygenation, high humidity and high temperature, they evolve to the larval form. These filaroid larvae penetrate the skin, conjunctiva, mucous membranes, or can be swallowed. After penetrating the skin, they reach the blood and lymph circulation and lodge in the heart and lungs. The skin condition is manifested by an itching dermatitis at the site of penetration of the larvae. Pulmonary manifestations are nonspecific and there may be long- or short-term cough, sputum and mild fever. Intestinal involvement is accompanied by epigastric pain, nausea, vomiting and diarrhea or constipation.¹

Treatment for nematodes transmitted in soil such as A. lumbricoides and ancylostomides include benzimidazoles, broad-spectrum agents, especially albendazole, mebendazole and thiabendazole. Mebendazole and albendazole are better tolerated. Thiabendazol is clinically less used because of its clinical toxicity, as it causes significant nausea, vomiting and anorexia at therapeutic doses.⁴

Benzimidazoles are selective agents for β-tubulin of nema- todes conferring a selective drug action to the parasite protein. For the treatment of ascariasis and ancylostomiasis, therapy regimens will vary depending on the drug of choice.⁴⁵,⁴⁶ For adults and children over 2 years of age with ascariasis and ancylostomiasis, the treatment with albendazole is accomplished with a single dose of 400 mg orally and for mebendazole 100 mg, twice daily orally, for 3 days, or a single dose of 500 mg orally.⁴⁷ Cure rates show to be varied according to the therapeutic regimens. A single dose of albendazole and mebendazole showed high cure rates for A. lumbricoides. In ancylostomides infections, a single dose of albendazole was more effective than mebendazol.⁴⁸–⁵⁰

Nitazoxanide is a nitrothiazole derivative used for the treatment of intestinal protozoa and helminths, including A. lumbricoides and ancylostomides. A clinical trial was conducted of nitazoxanide 200 mg twice a day for 3 days, which showed efficacy of 89% in ascariasis compared to albendazole single dose with 91% efficacy.⁵¹ However, later, a controlled, double-blind, randomized clinical trial was performed in poly- parasitized patients to evaluate the efficacy of nitazoxanide (twice daily for 3 days, 15 mg/kg/day for children and 500 mg for adults), compared to other antiparasitic drugs (albendazole, thiabendazole, praziquantel and secnidazole). The cure rate observed was 32.4% for nitazoxanide and 38.7% for conventional medication.⁵² The results showed that the effectiveness pattern for both treatments was considered low in comparison to studies performed to evaluate monoparasitism treatment.

**Strongyloidiasis**

S. stercoralis is an intestinal nematode found all over the world in moist soils contaminated with human feces.⁵³,⁵⁴ Although S. stercoralis infections occur almost all over the world but the northern and southern end, estimates of its prevalence are often little more than suppositions. Schär et al. published a systematic review of literature including 354 articles on the global distribution of the disease in 78 countries.⁵⁵ These authors showed that, although the disease is endemic in many regions of the world, their infection rates in many countries in these regions are very heterogeneous. In Africa they range from 0.1% in Central Africa Republic to 91.8% in Gabon, while in South and Central America they range from 1% in Haiti to 75.3% in Peru. In Southeast Asia they range from 0.02% in Vietnam to 23.7% in Thailand. It is believed that S. stercoralis infections are underreported.⁵⁶

With regard to prevalence data on S. stercoralis in Brazil, we highlight the review published by Paula and Costa-Cruz.⁵⁶ These authors showed that, when parasitological methods are used, the prevalence of strongyloidiasis was 5.5%, characterizing the country as hyperendemic for this parasitic infection.⁵⁶ They stressed that the occurrence increases with age, with 12.1% for persons aged over 60 years, suggesting that it is an epidemiological condition of concern for the elderly. From seroepidemiological studies of the general population, the average positivity ranged from 21.7% (immunofluorescence) to 29.2% (enzyme-linked immunosorbent assay – ELISA).⁵⁶

S. stercoralis has two types of larvae, the rhabditiform and the filariform. In autoinfection rhabditiform larva becomes infective filariform, and can penetrate both the intestinal mucosa (internal autoinfection) and perianal area skin (external autoinfection). In both cases, the filariform larvae can follow the previously described route, being successively carried to the lungs, respiratory tract, pharynx and small intestine, where they mature into adult worms or can spread throughout the body.⁵⁷ Depending on the host immune response, autoinfection and/or hyperinfection may occur. The autoinfection allows the parasite to survive for a long time in the usually asymptomatic human host. Hyperinfection consists of an intense autoinfection process, a stage in which larvae can be found in fresh feces. In the disseminated infection resulting from hyperinfection, larvae can be found anywhere, particularly in the sputum and skin.⁵⁷

Clinically, larval dermatitis in the feet, hands, buttocks, or in the anogenital region may occur. Other manifesta-
Intestinal parasitic infections in patients with autoimmune rheumatic diseases

Systemic lupus erythematosus

Most of the literature data relating to the occurrence of intestinal parasites in SLE patients include case reports from several countries, mainly related to S. stercoralis and Entamoeba. In general, these patients generally progress to severe, or even fulminant cases, especially in patients with active disease, with glomerular renal impairment, chronic corticosteroid users and/or those who used high doses of these drugs (>0.5 mg/kg/day of prednisone).

The occurrence of severe opportunistic infections by S. stercoralis in a patient with SLE was described by Wachter et al. At the time the patient developed fever and coma, with examination consistent with vasculitis, the therapy with high doses of corticosteroids failed. Larvae of S. stercoralis were found in feces and sputum. Treated with thiabendazole, the patient recovered quickly.

In 1988, Livneh and colleagues described a case of hyperinfection syndrome by S. stercoralis simulating flare in a patient with SLE. Six years later, Hayden and Atlas reported, in the United States, a case of strongyloidiasis simulating inflammatory bowel disease. Later, in 2006, Yoshida et al. described recurrent episodes of paralytic ileus due to S. stercoralis in a patient with SLE and a host for human T-cell lymphotropic virus type I (HTLV-I) on steroid therapy. The patient came from an endemic area and had a history of strongyloidiasis eight years before. After treatment with ivermectin she improved and showed no recurrence.

Deaths due to S. stercoralis presence have been described by several authors. In Japan, Setoyama and colleagues reported a case of death due to disseminated strongyloidiasis in patients with SLE and alveolar hemorrhage induced by filariform larva. In another report, a young patient with SLE, glomerulonephritis and chronic use of corticosteroids from the endemic rural area of Bosnia and Herzegovina had severe gastric and pulmonary symptoms, associated with weight loss of 13 kg in 3 months. Search for larvae in the feces, sputum and urine confirmed the presence of nematodes, also observed in the histopathological examination of the intestinal mucosa.

In Lima (Peru), Mora, Segami and Hidalgo reported two cases of SLE and anti-phospholipid syndrome (APS) that developed hyperinfection by S. stercoralis – a woman of 34 years and a man of 37, with one of them progressing to death. Both had glomerulonephritis and were treated with immunosuppressants in high doses for initial suspicion of necrotizing vasculitis. The first one had a stroke, being hospitalized many times due to infection, vomiting and diarrhea with suspected vasculitis of the digestive tract. Gastric biopsy revealed S. stercoralis and the patient improved after the use of ivermectin. In the second case, the patient developed recurrent thrombosis and digital necrosis. He progressed with alveolar hemorrhage and respiratory failure, septic shock and death. The bronchoalveolar lavage studies confirmed the presence of Strongyloides larvae. The authors concluded by suggesting that hyperinfection with S. stercoralis may exacerbate cases of SLE and APS, predisposing to infection by Gram-negative bacteria, sepsis and death. A similar case of SLE and APS complicated by disseminated strongyloidiasis was again described in 2010.

In 2013, Wang and colleagues evaluated the reports of 106 cases of strongyloidiasis that occurred in China between 1973 and 2012 in subjects aged 5–88 years. Among the 106 cases of strongyloidiasis found, 68% had other diseases or were taking immunosuppressive drugs. Five patients (5.3%) had a diagnosis of SLE.

Caramaschi et al. described a case of SLE complicated by strongyloidiasis in which the patient received ivermectin (18 mg/day for 2 consecutive days, two cycles in 2 weeks), with remission of diarrhea, polyarthritis and normalization of eosinophilia. It is recommended that before starting treatment with corticosteroids in patients with SLE, the presence of S. stercoralis, and subsequent treatment with ivermectin, is evaluated.

The cases described in the literature about the association between SLE and amebiasis reflect the occurrence of severe opportunistic infections, central nervous system involvement, and fulminant cases of colitis, often simulating severe systemic disease activity, and culminating in patients’ death (Table 1).

Rheumatoid arthritis

In a similar manner to that shown in relation to SLE, studies that relate the occurrence of intestinal parasites in patients with RA are scarce, basically restricted to case reports and case series, mainly of strongyloidiasis. We highlight two recent studies published recently. In the first, a systematic review of case reports on the hyperinfection syndrome and disseminated strongyloidiasis published by Buonfrate et al., studies published between 1991 and 2011 are researched. The study included 231 full articles related to 244 patients. A high
Table 1 – Reports of severe cases of amoebiasis – patients with systemic lupus erythematosus.

<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Therapy used</th>
<th>Event</th>
<th>Etiological agent/isolated material</th>
<th>Manifestations/evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grunnet al. (1981)</td>
<td>SLE/immunosuppressor SLE/immunosuppressor</td>
<td>Fulminant meningoencephalitis Fulminant colitis</td>
<td>Acanthamoeba castellanii (Trophozoites in the lung) Entamoeba histolytica (Trophozoites in intestinal mucosa)</td>
<td>Possible primary focus in the lung/death Intestinal amoebiasis complicated by Salmonella/Sepsis and death</td>
</tr>
<tr>
<td>Tai and Fong (1997)</td>
<td>SLE/immunosuppressor SLE/immunosuppressor</td>
<td>Granulomatous encephalitis Meningoencephalitis</td>
<td>Acanthamoeba encephalitidis (Trophozoites in the lung) Entamoeba histolytica (Trophozoites from the species Naegleria fowleri in the cerebrospinal fluid)</td>
<td>Possible primary focus in the lung/death Death</td>
</tr>
<tr>
<td>Okusawa et al. (1998)</td>
<td>SLE/immunosuppressor SLE/immunosuppressor</td>
<td>Encephalitis</td>
<td>Acanthamoeba mitochondrial (Neuropathological exam) Acanthamoeba meningoencephalitis (Neuropathological exam)</td>
<td>Death Multiple hemorrhagic foci in leptomeninges/death Behavioral change, coma and death Multiple intestinal perforations, respiratory failure Improvement with antiparasitic therapy</td>
</tr>
<tr>
<td>Shrestha et al. (2003)</td>
<td>SLE/immunosuppressor SLE/immunosuppressor</td>
<td>Meningoencephalitis</td>
<td>Acanthamoeba encephalitidis (Trophozoites in cerebral biopsy) Entamoeba histolytica (Trophozoites in resected colon)</td>
<td>Behavioral change, headache. It improves with treatment</td>
</tr>
<tr>
<td>Shirwadkar et al. (2006)</td>
<td>SLE/immunosuppressor Juvenile SLE/immunosuppressor</td>
<td>Encephalitis</td>
<td>Acanthamoeba encephalitidis (Neuropathological exam) Acanthamoeba meningoencephalitis (Neuropathological exam)</td>
<td>Death Multiple hemorrhagic foci in leptomeninges/death Behavioral change, coma and death Multiple intestinal perforations, respiratory failure Improvement with antiparasitic therapy</td>
</tr>
<tr>
<td>Lange et al. (2008)</td>
<td>SLE/immunosuppressor Juvenile SLE/immunosuppressor</td>
<td>Meningoencephalitis</td>
<td>Acanthamoeba encephalitidis (Trophozoites in cerebral biopsy) Entamoeba histolytica (Trophozoites in resected colon)</td>
<td>Behavioral change, headache. It improves with treatment</td>
</tr>
<tr>
<td>Castillo et al. (2012)</td>
<td>SLE/immunosuppressor SLE/immunosuppressor</td>
<td>Meningoencephalitis</td>
<td>Acanthamoeba encephalitidis (Trophozoites in cerebral biopsy) Entamoeba histolytica (Trophozoites in resected colon)</td>
<td>Behavioral change, headache. It improves with treatment</td>
</tr>
<tr>
<td>Lee et al. (2012)</td>
<td>SLE/immunosuppressor SLE/immunosuppressor</td>
<td>Meningoencephalitis</td>
<td>Acanthamoeba encephalitidis (Trophozoites in cerebral biopsy) Entamoeba histolytica (Trophozoites in resected colon)</td>
<td>Behavioral change, headache. It improves with treatment</td>
</tr>
<tr>
<td>Alkhunaizi et al. (2013)</td>
<td>SLE/immunosuppressor SLE/immunosuppressor</td>
<td>Meningoencephalitis</td>
<td>Acanthamoeba encephalitidis (Trophozoites in cerebral biopsy) Entamoeba histolytica (Trophozoites in resected colon)</td>
<td>Behavioral change, headache. It improves with treatment</td>
</tr>
</tbody>
</table>

SLE – systemic lupus erythematosus.

percentage of these patients (67% or 164/244) were on use of corticosteroids, but only 4 (2.4%) had a diagnosis of RA. In another review, Wang et al. reviewed the reports of 106 cases of strongyloidiasis (5–88 years old) occurring in China between 1973 and 2012. Of these, 72 patients (68%) also had other diseases or were taking immunosuppressive drugs, and only 7 (9.7%) were patients diagnosed with RA. Besides these two reviews, we found some case reports. Later, in Table 2, we present the most serious cases recently reported in the literature.

There were no RA case reports with infections with other parasitic diseases, including the last BiobadaBrasil report.89

Spondyloarthritis

Similarly to what has been reported for SLE and RA, there is a shortage of epidemiological studies about concomitant SA and intestinal parasitic infections. The articles are usually case reports and, in most cases, show the role of parasites as triggers of reactive arthritis. Thus, it is believed that cases of strongyloidiasis, ascariasis, giardiasis and amebiasis can present with oligoarthritis and must be appropriately treated.90,91 Moreover, patients with SA, such as ankylosing spondylitis, and psoriatic arthritis, may exhibit asymptomatic parasitic infections and, when receiving immunosuppressive therapy, they become susceptible to developing serious infectious conditions.92

Diagnosis of intestinal parasitic infections in patients with autoimmune rheumatic diseases

The diagnosis of an opportunistic infection by intestinal parasites in patients with autoimmune diseases is often hampered by the low level of suspicion, lack of eosinophilia and specific

Table 2 – Reports of severe cases of strongyloidiasis – patients with rheumatoid arthritis.

<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Event</th>
<th>Drugs used</th>
<th>Manifestations/evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koh et al. (2004)</td>
<td>Pneumonia</td>
<td>Metotrexate and prednisolone</td>
<td>Lung hemorrhage/death</td>
</tr>
<tr>
<td>Boatright and Wang (2005)</td>
<td>Abdominal pain and diarrhea</td>
<td>Etanercept and prednisone</td>
<td>Late abdominal infection Resolution after treatment</td>
</tr>
<tr>
<td>Miguel-Fraile et al. (2006)</td>
<td>Diarrhea, vomiting and malaise</td>
<td>Metotrexate, prednisone and paracetamol</td>
<td>Gastritis due to parasite/Resolution after treatment</td>
</tr>
<tr>
<td>Das et al. (2007)</td>
<td>Diarrhea and anorexia</td>
<td>Prednisone</td>
<td>Duodenitis due to parasite/Resolution after treatment</td>
</tr>
<tr>
<td>Al tintop et al. (2010)</td>
<td>Weakness, dyspepsy, dysnea and cough</td>
<td>Metotrexate and deflazacort</td>
<td>Gastritis and duodenitis due to parasite/Resolution after treatment</td>
</tr>
</tbody>
</table>
Table 3 – Characteristics and clinical picture of parasitic infections.

<table>
<thead>
<tr>
<th>Parasitic infection</th>
<th>Etiological agent</th>
<th>Transmission</th>
<th>Characteristics</th>
<th>Clinical picture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giardiasis</td>
<td>Giardia lamblia</td>
<td>Cysts ingestion, orally</td>
<td>Monoxenic cycle; parasite of the small intestine; absence of a pulmonary cycle; no tissue invasion of trophozoites; waterborne disease and responsible for diarrhea outbreaks; zoonosis; important cause of diarrhea in children.</td>
<td>Asymptomatic or symptomatic forms; acute or chronic diarrhea; steatorrhea; abdominal discomfort; nausea; weight loss; vomiting; flatulence; malaise.</td>
</tr>
<tr>
<td>Amoebiasis</td>
<td>Entamoeba histolytica</td>
<td>Cysts ingestion, orally</td>
<td>Monoxenic cycle; parasite of the large intestine; likelihood of tissue invasion; extraintestinal amebiasis; absence of a pulmonary cycle; asymptomatic patients are an important source of infection; food handlers play an important role in the transmission; morphologically similar to Entamoeba dispar.</td>
<td>Asymptomatic or symptomatic forms; dysenteric and non-dysenteric colitis; mucous and bloody stools; amebic appendicitis; extraintestinal amebiasis; hepatic abscesses; fever; hepatomegaly.</td>
</tr>
<tr>
<td>Ascarisis</td>
<td>Ascaris lumbricoides</td>
<td>Eggs ingestion, orally</td>
<td>Monoxenic cycle; infects uniquely humans; parasite of the small intestine; pulmonary cycle in the larval stage, erratic parasite.</td>
<td>Asymptomatic or symptomatic forms which are determined by the number of parasites; abdominal symptoms, pulmonary symptoms; elimination of adult worms; intestinal occlusion or obstruction; Loeffler's syndrome.</td>
</tr>
<tr>
<td>Ancylostomiasis</td>
<td>Ancylostoma duodenale/Necator americanus</td>
<td>Infective larvae penetration in the skin or mucosas</td>
<td>Monoxenic cycle; parasite of the small intestine; pulmonary cycle; parasite blood spoliation that causes anemia in the host proportional to the parasite load</td>
<td>Abdominal and pulmonary symptoms; transient cutaneous manifestations; iron deficiency anemia; hypoalbuminemia; fecal occult blood; Loeffler's syndrome.</td>
</tr>
<tr>
<td>Strongyloidiasis</td>
<td>Strongyloides stercoralis</td>
<td>Infective larvae penetration in the skin or mucosas, possible autoinfection</td>
<td>Monoxenic cycle; parasite of the small intestine in which the female parasite lodges in the intestinal villi; pulmonary cycle; eggs hatch still within the intestine; hyperinfection and disseminated forms described in immunocompromised patients.</td>
<td>Asymptomatic or symptomatic forms; skin, lung and intestinal symptoms; epigastric pain is a frequent report; Loeffler's syndrome; cases of hyperinfection and disseminated forms in immunocompromised patients.</td>
</tr>
</tbody>
</table>

signs of infection – all of which can be associated with the use of immunosuppressants, in particular the use of corticosteroids. Signs and symptoms of spread may be as fast as 20 days after initiation of steroid therapy, or late – appearing years after the start of treatment. In addition, eosinophilia is often absent in disseminated infections and in patients receiving corticosteroids. Intestinal parasites can mimic the diseases and the use of corticosteroids may be associated with normal serum levels of eosinophils, delaying diagnosis and facilitating the progression to serious and fatal forms.93

Immunosuppression interference in the progression of intestinal parasitic infections in patients with autoimmune rheumatic diseases

Although in most patients E. histolytica occurs asymptptomatically in immunocompromised patients receiving chemotherapy or corticosteroid therapy, or in transplant patients, there is high risk of fulminant amoebic colitis development. The mechanism by which amoebiasis is exacerbated in cases of immunosuppression remains undetermined.94–97

Corticosteroids are widely used in SLE patients and have been associated with hyperinfection with S. stercoralis in animal and human models. Some mechanisms have been proposed. One of them consists of the hypothesis that corticosteroids stimulate the virulence of the nematode through activation of its receptors. The other states impaired immunity mediated by T cells, facilitating the spread of S. stercoralis.98

Another related theory is based on the assumption that corticosteroids could reduce local inflammation. That would undermine intestine ability to contain parasites. With the increase in the number of larvae completing the autoinfection cycle, large numbers of larvae could reach the systemic circulation, producing hyperinfection and even sepsis or meningitis with high morbidity and mortality in immunocompromised patients.99

Disseminated infections by S. stercoralis have been reported in people with a wide variety of immunological changes: hematopoietic malignancies or connective tissue diseases...
### Table 4 – Recommendations regarding management of parasitic infections in patients with autoimmune rheumatic diseases.

<table>
<thead>
<tr>
<th>Parasitic infections</th>
<th>Parasitological tests</th>
<th>Complementary diagnostic tests</th>
<th>Treatment options</th>
<th>Prophylaxis</th>
<th>Recommendations for patients with autoimmune rheumatic diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giardiasis</td>
<td>Spontaneous sedimentation; Ritchie’s method/cysts and trophozoites search</td>
<td>Intermittent elimination of parasitic forms may require the collection of stools every seven days; evaluation of duodenal content for search of trophozoites; search for antigen in stools</td>
<td><strong>Metronidazole</strong> 250 mg, (orally) PO, bid, for 3 to 5 days; <strong>secnidazole</strong> 2 g, PO, single dose; <strong>albendazole</strong> 400 mg, PO, once a day for 5 days; <strong>nitazoxanide</strong> 500 mg, PO, bid for 3 to 7 days.</td>
<td>Proper cleaning of fruits and vegetables; use of filtered or boiled water; control of mechanical vectors; health education.</td>
<td>Prophylaxis before the onset of immunomodulatory, immunosuppressive or immunobiological drugs with secnidazole, 2 g, orally, single dose. Repeat annually if patient's immunosuppression persists and he/she lives in endemic areas.</td>
</tr>
<tr>
<td>Amoebiasis</td>
<td>Spontaneous sedimentation; Ritchie’s method/search for cysts and trophozoites.</td>
<td>Serological methods; search for antigen in stools; ultrasonography in cases of amebic abscess</td>
<td><strong>Metronidazole</strong> 500–750 mg, PO, bid for 7–10 days; <strong>secnidazole</strong> 2 g, PO, single dose; <strong>tinidazole</strong> 2 g, PO, for 2 days; <strong>nitazoxanide</strong> 500 mg, PO, bid for 3 to 7 days.</td>
<td>Proper cleaning of fruits and vegetables; use of filtered or boiled water; control of mechanical vectors; health education.</td>
<td>Prophylaxis before the onset of immunomodulatory, immunosuppressive or immunobiological drugs with secnidazole, 2 g oral, single dose. Repeat annually if patient's immunosuppression persists and he/she lives in endemic areas.</td>
</tr>
<tr>
<td>Ascariasis</td>
<td>Spontaneous sedimentation; Kato-katz method/eggs search</td>
<td>Elimination of adult worm; eosinophilia</td>
<td><strong>Albendazole</strong> 400 mg, PO, single dose; <strong>mebendazole</strong> 100 mg, PO, bid, for 3 days or 500 mg, VO, single dose; <strong>nitazoxanide</strong> 500 mg, PO, bid for 3 to 7 days.</td>
<td>Health education; sanitation; hands and food washing.</td>
<td>Prophylaxis before the onset of immunomodulatory, immunosuppressive or immunobiological drugs, with albendazole, 400 mg orally, a single dose. Repeat annually if the patient's immunosuppression persists and he/she lives in endemic areas.</td>
</tr>
<tr>
<td>Ancylostomiasis</td>
<td>Spontaneous sedimentation; Willis method/eggs search</td>
<td>Investigate the presence of anemia</td>
<td><strong>Albendazole</strong> 400 mg, PO, single dose; <strong>mebendazole</strong> 100 mg, PO, bid, for 3 days or 500 mg, PO, single dose; <strong>nitazoxanide</strong> 500 mg, PO, bid for 3 to 7 days.</td>
<td>Health education; sanitation; hands and food washing; use of shoes.</td>
<td>Prophylaxis before the onset of immunomodulatory, immunosuppressive or immunobiological drugs, with albendazole, 400 mg orally, a single dose. Repeat annually if the patient's immunosuppression persists and he/she lives in endemic areas.</td>
</tr>
<tr>
<td>Strongyloidiasis</td>
<td>Baermann-Moraes method; Rugai method, Mattos and Brisola-use fresh stools/Search for larvae</td>
<td>Cases of hyperinfection; larvae are found in body fluids.</td>
<td><strong>Ivermectin</strong> 200 μg/kg, PO, 1 to 2 days; <strong>albendazole</strong> 400 mg/day PO, during 3 days; <strong>tiabendazole</strong> 25 mg/kg, PO, bid, for 2 days.</td>
<td>Health education; sanitation; hands and food washing; use of shoes.</td>
<td>Prophylaxis before the onset of immunomodulatory, immunosuppressive or immunobiological drugs, with ivermectin 200 μg/kg/day, orally, for 2 consecutive days, repeated within 2 weeks. Repeat prophylaxis each 6 months, if immunomodulation or immunosuppression persists, if patient lives permanently in endemic area.</td>
</tr>
</tbody>
</table>
treated with immunosuppressive drugs, and hosts with congenital or acquired hypogammaglobulinemias. Patients being treated with corticosteroids, transplanted, with chronic renal insufficiency, diabetes mellitus, chronic obstructive pulmonary disease, asthma, chronic skin diseases, chronic infections (leprosy and tuberculosis), neoplasias (lymphoma, leukemia and solid tumors), chronic alcoholism, human immunodeficiency virus syndrome and achlorhydria are at high risk for strongyloidiasis.53,100

The occurrence of hyperinfection with S. stercoralis is associated with the use of corticosteroids at high, moderate, or low doses, and the local injectable administration of high levels of adrenocorticotropic hormones (endogenous or pharmacologically administered). In addition to the above mentioned diseases, rheumatologic diseases associated with altered innate immunity are described in association with secondary spread of S. stercoralis: SLE, RA and polymyositis.54

Other commonly used immunosuppressive drugs for autoimmune rheumatic diseases have been associated with the occurrence of hyperinfection with S. stercoralis, such as cyclophosphamide, azathioprine, and methotrexate. However, in all cases the patients were concomitantly on corticosteroids. Thus, it becomes difficult to relate the occurrence of any other hyperinfection to any of those drugs.54,100

Both patients with SLE and those with RA and SA present higher risks than the general population to develop serious infections or infestations by parasites that are being carried, even if asymptomatically. The risks increase when these patients are on immunobiological drugs. We highlight the letter published by Boatright and Wang,85 where they report the role of prednisone combination with the biologic drug etanercept in the occurrence of a case of strongyloidiasis.

The mortality of patients with disseminated strongyloidiasis in RA is very high, between 87% and 100%. This is due to the difficulty of making early diagnosis and high potential for fatal complications.88

Tumor necrosis factor (TNF-α) plays an important role in cell-cell communication in invasive infections. The Th2 immune response is important in controlling various helminth infections, and can be modified by glucocorticoids and biological agents. The Th1/Th2 ratio in peripheral blood can be increased by treatment with anti-TNF-α antibodies. Thus, it is plausible that these drugs can alter the immune response allowing indolent intestinal parasites to be clinically manifested.85

Prevention of hyperinfection with parasites in patients with autoimmune rheumatic diseases

Among the published works on prevention of parasites’ hyperinfection, we highlight the systematic revision published by Santiago and Leitão.101 These authors pointed out that the symptoms of hyperinfection strongyloidsy syndrome may not be recognized early, simulating an exacerbation of underlying rheumatic disease such as SLE, leading to a disastrous increase in immunosuppressive dose. Thus, the importance of conducting a routine investigation for intestinal parasites becomes evident in patients from endemic areas such as Brazil before inducing immunosuppression, particularly in patients refractory to standard therapy.

It is important to use appropriate methods to search for parasites, trying to minimize false negative results. While there is some evidence on the usefulness of serological tests following chronic strongyloidiasis, as the performance of these tests in immunocompromised patients was not well established, it may not be safe to use them for therapeutic decisions.

Regarding ascariasis and ancylostomiasis, guidelines for the prescription of drugs used in emergency SLE recommend the use of albendazole 400 mg orally (PO), for 3 days and metronidazole 400 mg, PO, each 12 h, for 5 days before administration of cyclophosphamide, even with negative parasitological stool test. In cases of positive tests, cyclophosphamide should only be used after the parasite treatment.102

Santiago and Leitão found no specific study for immunocompromised patients with diagnosis of rheumatic diseases. However, based on experimental studies for other diseases such as hematologic malignancies, they suggested that before starting immunosuppressive treatments prophylaxis with ivermectin be performed. Although a definitive prophylactic regimen has not been set, the option of 200 μg/kg/day for 2 consecutive days, repeated within two weeks, seems to be a reasonable approximation. Such a regimen should be repeated every 6 months in case immunosuppression in permanent residents of endemic areas persists.101

Since biological therapies have become very important for the treatment of some rheumatic diseases such as RA and psoriatic arthritis it has been suggested that the recommendation of strongyloidiasis prophylaxis should be extended to this type of therapy in patients from the endemic areas of S. stercoralis.103

Recommendations on the diagnosis and treatment of intestinal parasitic infections in patients with autoimmune rheumatic diseases

Tables 3 and 4 respectively summarize the main features of parasitic diseases discussed in this document and the recommendations on the management of these conditions in patients with autoimmune rheumatic diseases, based on information available in literature and on authors’ experience.

Conclusions

There are no prospective studies relating the prevalence of intestinal parasites in patients with autoimmune rheumatic diseases from endemic areas. However, although a large number of severe cases is expected from these areas, only a few cases in the literature include this subject and, in clinical practice, such cases are rare.

Even considering the possible rarity of cases of serious parasitic infections in patients with autoimmune rheumatic diseases, their severity and even mortality can be very high, warranting specific measures to address these cases.

SBR experts established, in this document, recommendations for the management of the main parasites found
in Brazil, in patients with autoimmune rheumatic diseases, based on the information available in the literature and the authors’ experience.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

ERRATUM

On Table 1 of the article “Recommendations from the Brazilian Society of Rheumatology on the diagnosis and treatment of intestinal parasitic infections in patients with autoimmune rheumatic disorders” (Rev Bras Reumatol. 2015;55(4):368–380), where it reads:
Acanthamoeba castellanii, Acanthamoeba encephalitidis, Acanthamoeba mitochondrial and Acanthamoeba meningoencephalitis

it should read
Acanthamoeba spp.