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Mini-review

Strongyloides stercoralis and the immune response

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ABSTRACT

The immune system is a highly evolved network of cells and molecules that can distinguish between invading pathogens and the body's own cells. But helminths, in their complex forms, are capable of down-regulating host immunity, protecting them from being eliminated and also minimizing severe pathology in the host. This review focuses on *Strongyloides stercoralis* and the immune responses in immunocompetent and/or immunocompromised individuals. It also highlights the implications for diagnosis/treatment and draws attention to an emerging public health disease. The solution to reducing the prevalence of strongyloidiasis remains on the effectiveness of pre-emptive measures in endemic communities, increased awareness, prompt early diagnosis as well as timely treatment.

Contents

1. Introduction

Strongyloides stercoralis, which is the causative agent of strongyloidiasis, is an opportunistic intestinal threadworm parasite that infects man, cats, dogs, and can be passed from man to dog/cat or vice versa. Strongyloidiasis is accountable for about 60–85% mortality rate in immunocompromised persons, affecting an estimated 100 million people worldwide [1,2]. The mortality rate for patients requiring hospitalization with *Strongyloides* infection is about 16.7%. It is endemic in warm moist tropical and sub-tropical climates and is widespread in Eastern Europe, South and Southeast Asia, Central America, South America and sub-Saharan Africa. It has also been reported in a non-endemic area [3]. Strongyloidiasis is more commonly found in institutional settings, rural areas and lower socioeconomic groups [4–6].

The *Strongyloides* life cycle is complicated when compared with other nematodes alternating between a free-living cycle and a parasitic cycle. *Strongyloides* is the only helminthic parasite that secretes larvae (not eggs) in faeces, appearing approximately 1 month after skin penetration. The transformation of the rhabditiform larvae (L1, L2) into the free-living invasive filariform larvae (L3) is often needed for re-infecting the host through the invasion of the intestinal wall or the perianal skin [7]. The 3 major areas of *Strongyloides* infection involve the skin, lungs and intestine. Transmission can also be enhanced from increased exposure in occupations that involve handling of contaminated faeces and through increased contact with contaminated soil (e.g. farming, coal mining) [8,9]. The result of infection ranges from an

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asymptomatic condition to multiorgan failure. More commonly, the infection manifests as mild gastrointestinal symptoms with devastating effects in immunocompromised individuals. One significant feature of *Strongyloides* is its asexual autoinfection capacity that explains importunate infections in individuals who have not visited an endemic area or had prior exposure to the infection. Autoinfection occurs predominantly in humans, monkeys, dogs [10,11] but does not occur in immunocompetent gerbils [12]. It only occurs when gerbils are given the non-steroidal immunosuppressant tacrolimus [13]. In contrast, autoinfection has been seen in immunologically immature or immunosuppressed jirds (*Meriones unguiculatus*) [14].

Strongyloidiasis in warm moist climates, rural tropics and subtropics where HIV/AIDS prevalence is considerably high, continues to attract the interest of researchers. Furthermore, a condition such as the hyperinfection syndrome complicates clinical presentation in immunocompromised individuals. Factors that determine the risk of occurrence, the understanding of the immunopathology, protective immune response in humans and the biology of *S. stercoralis* are still not fully known. This review focuses on the immunology and immunopathology in immunocompetent/compromised hosts. It also highlights its clinical importance in association with increases in travel histories to endemic and non-endemic countries attributed to globalisation.

2. B-cell immunity against *S. stercoralis*

B lymphocytes are believed to be essential for the acquisition of resistance to larval *S. stercoralis*. Results in severe combined immunodeficiency (SCID) mice indicated that the parasite developed into reproductive adults [15] while in T-cell-deficient hypothymic mice; *Strongyloides* development was not altered [16]. Data from defective B-cell development [17,18], X-linked immunodeficient [19,20] knockout mice with deficiencies in the B-1 cell population [19,21] illustrated the importance of B cells in the acquisition of resistance to larval *S. stercoralis* and indicated that B-1 cells could play an integral role. However, B cells may not be required in the primary response, but most likely in secondary immune responses to larval *S. stercoralis* [17].

Animal studies have continued to provide us with a better understanding of the molecular and immunological mechanisms of disease development. But, *S. stercoralis* in most animal models may be unrepresentative of natural infection in humans notwithstanding the similar biology of parasite infection of different hosts. Protective immunity in mice to the infective third larvae (L3) of *S. stercoralis* has been shown to involve IgM [17], complement activation [22] and neutrophils [23] in antibody-dependent cell-mediated cytotoxicity (ADCC) type responses [24]. In humans, immunity to L3 is not protective against the autoinfection larvae (L3a), which is the causative agent of strongyloidiasis [25] and L3a seems to have a different antigenic recognition pattern [26]. A previous study showed that both IgM and IgG antibodies were protective against larval *S. stercoralis* but they recognize different antigens and utilize different killing mechanisms [27]. Increased *S. stercoralis*-specific IgG4 antibody titre has been associated with resistance to albendazole treatment in male patients when compared with their female counterparts in a Japanese study [28] and *HLA-DRB1*0901* is suggested as a possible genetic marker for resistance to treatment of *S. stercoralis* in this population [29]. In humans, a statistically significant decrease in IgM and IgG antibody levels were found in people with severe *Strongyloides* when compared with the levels in people with asymptomatic or mild symptomatic infections, signifying the influence of antibodies in defence mechanisms against *S. stercoralis* larvae [30]. Furthermore, infants in endemic areas can acquire IgA and IgG antibodies to *S. stercoralis* from breast milk [31]. Although patients with strongyloidiasis have specific serum IgA responses against filariform larval antigens, the role of IgA antibodies in the disease is still unclear as it correlates poorly with clinical disease [32].

3. The role of eosinophils in protective immunity

Eosinophils are one major component of the immune system responsible for combating infections, specifically parasitic infections. They are commonly associated with helminth infections. In addition, eosinophils have been shown to function as antigen presenting cells (APCs) in allergy [33]. Eosinophils gather anywhere where there is a parasitic infection or an allergic reaction, subsequently releasing toxins that kill the invading pathogen. Their induction is required during immunization [34]. Helminth infections generally induce the activation of Th2 lymphocytes characterized by the production of eosinophilia, IL-5 and IgE [35,36]. IL-5, however, is an essential cytokine for differentiation, activation and proliferation of eosinophils which are cells involved in helminth killings [2,37]. In general, helminths cannot be ingested by phagocytes due to their large size. However, when coated with antibody especially IgE, eosinophils can attack via the high-affinity FcεRI.

Eosinophils and antibodies play important roles in defence mechanisms against *S. stercoralis* larvae [28] during innate and adaptive immune responses [34,38]. *S. stercoralis* antigens activate eosinophils; induce the expression of major histocompatible complex (MHC) class II and T-cell co-stimulatory molecules. Activated eosinophils can stimulate T cells for antigen-specific immune responses [39]. Eosinophils are also believed to function as APCs for the induction of the primary and secondary Th2 immune responses to *S. stercoralis* [39,40] indicating an essential role for eosinophils in the interface between innate and adaptive immune responses. Recently, both eosinophils and neutrophils were found to be required in the protective innate immune response while only neutrophils were necessary for the protective adaptive immune response to larval *S. stercoralis* [23]. In individuals with severe strongyloidiasis, eosinophil levels were found to be lower than that of asymptomatic individuals [33]. Thus, eosinophil levels may likely play key roles in preventing *S. stercoralis* infection.

4. *Strongyloides* and Toll-like receptors (TLRs)

The Toll-like receptors (TLRs) are one of the most important pattern recognition receptors (PRR). These PRRs recognize pathogens through pathogen-associated molecular patterns (PAMPs), which are conserved groups of molecules from pathogens that are essential for microbial survival [41]. In humans, 11 TLRs have been identified based on their cellular localization: TLRs 3, 7, 8, and 9 are expressed in endosomes, while TLRs 1, 2, 4, 5, and 9 are present on the surface of many cells. Each TLR activates a distinct signalling pathway and induces specific biological responses against micro-organisms [42]. TLR4 is expressed on B cells and is essential for lipopolysaccharide (LPS)-induced signalling of B-cell activation [43]. Stimulation of TLR4 in dendritic cells (DCs) induces IL-12 production and also enhances surface expression of co-stimulatory molecules [44]. TLR4 has been linked with the activation of Th1 type immune response. Mice deficient in TLR4 are impaired in their ability to recruit neutrophils [45] and exhibit decreased immunity to *Onchocerca volvulus* infections [46]. A recent study established that TLR4 was not required in *S. stercoralis* larval killing during innate immune response, but was required in killing the larva during the adaptive immune response [47]. This adaptive mechanism may require the activation of neutrophils which mediates larval killing whereas TLR4 is not required for T- and B-cell function.

5. *S. stercoralis* and human T-lymphotropic virus type 1 (HTLV-1)

In immunocompetent host, *S. stercoralis* can cause a chronic, well synchronized and occasionally lasting infection since the worm has the unusual ability to multiply asexually [48]. Immediate hypersensitivity is the response of the immune system to *S. stercoralis* infection which could be attributed to protection or pathogenesis depending on the arm of the immune response being activated.

HTLV-1 is a human RNA retrovirus that causes T-cell leukaemia and T-cell lymphoma. It was first isolated from a patient with adult T-cell leukaemia lymphoma [7]. It is rife in Asia (especially Japan), the Caribbean, South America and Africa. The genome of the HTLV-1 virus is diploid and, following interaction with the immune system, HTLV-1 enables the transcription of the viral DNA by integrating into the host genome effectively evading immune surveillance without killing the host.

The human HTLV-1 largely infects T cells and induces spontaneous lymphocyte proliferation and secretion of elevated levels of type 1 cytokines [7]. Exacerbation of *S. stercoralis* has been correlated with HTLV-1 infection in the human host [49]. HTLV-1 in the infected host incites a biased Th1 response resulting in increased interferon-gamma (IFN-γ) production while decreasing levels of interleukin-4 (IL-4) and IgE antibodies [50,51]. The reduced levels of total serum IgE are characteristic of selective immunosuppression by the retrovirus, creating a lenient environment for the propagation of *Strongyloides* [2,7,52]. Co-infection with HTLV-1 decreases IL-5 and IgE responses in patients and switches the immune response from a Th2 to a Th1 type [53]. However, the exact mechanism of the immune response to strongyloidiasis is not fully understood. In human helminth infections, Th2 type cytokines, IgE antibodies, eosinophils and mast cells participate in their expulsion and killing of the invading pathogen. IL-4 induces activated B cells to class-switch, differentiate and produce IgE, IgG4 antibodies. Furthermore, both IL-4 and IL-13 increase intestinal fluid content which contribute to parasite rejection [54,55]. The decrease in IL-4, IL-5, IL-10, IL-13 and specific IgE antibodies in patients co-infected with HTLV-1 suggest that a decline in the Th2 type immune response, mediated by high significant levels of IFN-γ, may elucidate the immunological parameter for increased susceptibility of co-infected patients with the development of strongyloidiasis [7,53]. This persistent infection with HTLV-1 increases the expression of IFN-γ and tumour growth factor (TGF-β), decreases the serum levels of specific IgE and IgG4, affects *S. stercoralis*-specific immunity and reduces therapeutic efficacy [56]. Thus, the HTLV-1 virus is able to impair the host immune response against *S. stercoralis* in patients [57].

6. Does HIV contribute to widespread strongyloidiasis?

Co-infection with human immunodeficiency virus (HIV) and *S. stercoralis* have been reported [58–60]. It is thought that immunosuppression in patients due to advancing HIV may favour hyperinfection with *S. stercoralis*. But, HIV-infection appears not to augment the odds of developing systemic strongyloidiasis [61]. A study conducted among 35 immune adults and the development of *S. stercoralis* infections showed that in immunocompetent individuals, a direct development of *S. stercoralis* is favoured whereas in individuals with lesser immune function, an indirect development was observed [62]. The results also signified a significant negative rank correlation between $CD4^+$ cell counts and the proportion of free-living male and female worms indicating notably the absence of disseminated strongyloidiasis in advanced HIV disease. Similarly, in Uganda, *Schistosoma mansoni*, hookworm, *S. stercoralis* and *Mansonella perstans* were not associated with higher viral load [63]. Conversely, Olmos et al. [64] reported a case of *S. stercoralis* hyperinfection in a Spanish patient who had not travelled to an endemic area and in whom HIV-infection and long-term immunosuppressive treatment most likely led to the dissemination of strongyloidiasis. Furthermore, a progressive stage of AIDS in Iranian patients showing severe hyperinfection syndrome has been reported [65]. A similar study in Thailand also indicated a higher risk of *S. stercoralis* infection among HIV patients [66]. Nonetheless, the immunobiological and immunoregulatory mechanisms involving HIV and strongyloidiasis remain a subject of discussion.

7. Systemic strongyloidiasis

Systemic strongyloidiasis is an unusual but severe complication of intestinal *Strongyloides* occurring mostly in immunosuppressed patients [61]. It has a life-threatening consequence in immunocompromised patients on corticosteroid medications [67] or in post-transplantation immunosuppression [68]. Systemic strongyloidiasis can be present in individuals for many years subsequent to their departure from an endemic area, emphasizing the utmost need for the collection of patients' travel history. Chronically infected individuals only have mild or no symptoms but those who are immunocompromised may develop a hyperinfection syndrome [69]. Symptoms include gastrointestinal and pulmonary infiltrates often seen on chest radiography [69,70]. The increased use of immunosuppressive treatments elevates the lethal outcome of this infection. HIV-infection does not appear to increase the risk of developing systemic strongyloidiasis [61] but disseminated strongyloidiasis only arise when HIV-induced immunodeficiency is profound [70]. Glucocorticoid treatment, hypogammaglobulinemia and human HTLV-1 infection are a few other conditions most specifically associated with triggering hyperinfection [2,26,71]. Patients on corticosteroid therapy, hepatic transplantation, renal transplant, systemic lupus erythematosus, asthma, chronic dermatosis, tuberculosis, lymphoma, leukaemia, tumours, and AIDS, are also at higher risk for strongyloidiasis [2,68,71,72]. The increase in oviposition is deemed to be as a result of the direct action of corticosteroid on parthenogenetic female thereby hastening their transformation to filarioid larvae [73].

Thiabendazole remains the drug of choice, but due to unacceptable side effects, albendazole and ivermectin are preferred. In particular, ivermectin seems to be the more useful drug for the treatment of strongyloidiasis in immunocompetent individuals [74], immunosuppressed patients [75] and patients co-infected with HIV as the drug is better tolerated [76,77]. The importance of parasitological and serological testing for *S. stercoralis*, before and during immunosuppressive therapies in patients with gastrointestinal symptoms, especially in areas endemic with strongyloidiasis, has been emphasized in order to improve prompt treatment of patients [78,79]. Moreover, management of strongyloidiasis is a priority and serological monitoring is required to ensure complete eradication following treatment [80,81] given that individuals exposed for many years may have low larval excretion, thus rendering parasitological faecal examination ineffective.

8. Strongyloidiasis: an emerging global disease

In the past few years, the prevalence of *S. stercoralis* has been on the increase, especially in Southeast Asia and Africa. Poor personal hygiene, insufficient supply of safe drinking water and contemptible sanitary measures have made the spread of infection imminent [82]. The zoonotic transmission capacity makes it even more serious as domesticated small ruminants may act as reservoir hosts. The link between veterinary and medical officers is reportedly weak and the interactive inter-border traffic and migration becomes a big challenge [83]. In a survey to determine the prevalence and seasonal abundance of nematode parasites, *Strongyloides* species were encountered throughout the year irrespective of the season [84] and arid savannas were found less suitable for helminth transmission than in the forest zone [85]. Furthermore, in randomly selected children below 5 years, *S. stercoralis* were associated with possible complication of malnutrition in children who presented with diarrhoea [86]. There is also evidence supporting the hypothesis of a possible association between positive *S. stercoralis* serology and diabetes [87].

Epidemiological studies have also identified endemic rates of *Strongyloides* infection in developed countries and immigrants/travellers are at particular risks in developing *Strongyloides* hyperinfection syndrome [88]. A high prevalence of *S. stercoralis* has been observed among Sudanese refuges in the United States of America and could

persist for prolonged period in the absence of adequate treatment [89]. In a random and representative sample of farm workers in a tourist region of Spain, a high prevalence of *S. stercoralis* was observed [90]. Infection can in addition be maintained in a temperate climate and may become a hazard for kennel workers [91]. Due to its low incidence, most developed countries place strongyloidiasis patients in iatrogenic danger attributable to misdiagnoses. In addition, there is a risk of medical errors by health care providers resulting from a lack of familiarity with the parasite [92]. Furthermore, *S. stercoralis* has recently been found in urine, which is a particularly rare occurrence [93]. Clinicians therefore must be aware of this unexpected infectious parasitic disease that is acquired through international travel and immigration which can be potentially lethal [94–96]. Laboratory professionals must also be alerted to the importance of early detection of *S. stercoralis* in specimens from immigrants at risk and immunodeficient patients to reduce morbidity and mortality [97,98]. New diagnostic methods are needed since the popular Kato–Katz method for the diagnosis of *Strongyloides* has a low sensitivity with direct faecal smears [99]. Other traditionally employed methods for the diagnosis of *S. stercoralis* are the Rugai and Baermann sedimentation methods. The more recent agar plate method has been tested and compared with direct smears, formalin ethyl acetate, Harada Mori culture method, Baermann and may be the test of choice, especially in immunocompromised patients [100]. Recently, a real time PCR method targeting the small sub-unit of the rRNA gene was developed for the detection of *S. stercoralis* DNA in faecal samples, including an internal control to detect inhibition of the amplification process [101]. These emerging methodologies may hopefully enhance routine diagnosis of *S. stercoralis* infections in the future.

9. Summary

Strongyloidiasis is an emerging global infection that is underestimated in many countries. In humans, it is likely that *S. stercoralis* L3a down-regulate the host's protective immunity; the mechanism seen as its survival strategy to evade the immune response. Strongyloidiasis remains an imperative helminth disease due to increases in travel, migration to endemic and non-endemic countries, lack of adequate sewage disposal system especially in endemic countries and the risk of autoinfection which can lead to persistent disease for many years. Therefore, patients with a history of travel to likely endemic areas must be examined for strongyloidiasis before any immunosuppressive therapy. Also, an awareness of an increased predisposition to *S. stercoralis* is essential when signs of gastrointestinal or pulmonary symptoms are observed in immunosuppressed patients.

Individuals' resident where strongyloidiasis is endemic or persons with high-risk occupations need to be informed about the risk of infection. Given the increasing number of immunocompetent/immunocompromised individuals worldwide, persistent eosinophilia likely caused by *Strongyloides* infection, clinicians need to realize the risk factors involved with this neglected helminth disease and additionally have an index of this disease since early diagnosis as well as timely treatment leads to successful resolution. Furthermore, it is worth emphasizing that in warm moist climates in tropical and sub-tropical countries, where strongyloidiasis is endemic, the appropriate practical preventive measures remain stepping up of health education campaigns on the disease, proper sanitation, regular de-worming, behavioural change through proper disposal of faecal waste and the use of protective foot-wear. These measures for disease prevention are all readily achievable and remain important approaches to reducing the prevalence of strongyloidiasis.

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References

[1] Siddiqui AA, Berk SL. Diagnosis of *Strongyloides stercoralis* infection. Clin Infect Dis 2001;33(7):1040–7.
[2] Evering T, Weiss LM. The immunology of parasite infections in immunocompromised hosts. Parasite Immunol 2006;28:549–65.
[3] Rivero FD, Kremer LE, Allende L, Casero RD. *Strongyloides stercoralis* and HIV: a case report of an indigenous disseminated infection from non-endemic area. Rev Argent Microbiol 2006;38(3):137–9.
[4] Genta RM. Global prevalence of strongyloidiasis: critical review with epidemiologic insights into the prevention of disseminated disease. Rev Infect Dis 1989;11(5):755–67.
[5] Gyorkos TW, MacLean JD, Vien P, Chheang C, Kokoskin-Nelson E. Intestinal parasite infection in the Kampuchean refugee population 6 years after resettlement in Canada. J Infect Dis 1992;166(2):413–7.
[6] Loutfy MR, Wilson M, Keystone JS, Kain KC. Serology and eosinophils count in the diagnosis and management of strongyloidiasis in a non-endemic area. Am J Trop Med Hyg 2002;66(6):749–52.
[7] Carvalho EM, Da Fonseca Porto A. Epidemiological and clinical interaction between HTLV-1 and *Strongyloides stercoralis*. Parasite Immunol 2004;11–12:487–97.
[8] Wagenvoort JH, Houben HG, Boonstra GL, Scherpbier J. Pulmonary superinfection with *Strongyloides stercoralis* in an immunocompromised retired coal miner. Eur J Clin Microbiol Infect Dis 1994;13(6):518–9.
[9] Walzer PD, Milder JE, Banwell JG, Kilgore G, Klein M, Parker R. Epidemiologic features of *Strongyloides stercoralis* infection in an endemic area of the United States. Am J Trop Med Hyg 1982;31(2):313–9.
[10] Nolan TJ, Megyeri Z, Bhopale VM, Schad GA. *Strongyloides stercoralis*: the first rodent model for uncomplicated and hyperinfective strongyloidiasis, the Mongolian gerbil (*Meriones unguiculatus*). J Infect Dis 1993;168:1479–84.
[11] Nolan TJ, Schad GA. Tacrolimus allows autoinfective development of the parasitic nematode *Strongyloides stercoralis*. Transplantation 1996;62(7):1038.
[12] Nolan TJ, Bhopale VM, Rotman HL, Abraham D, Schad GA. *Strongyloides stercoralis*: high worm population density leads to autoinfection in jird (*Meriones unguiculatues*). Exp Parasitol 2002;100(3):173–8.
[13] Schad GA, Hellman ME, Muncey DW. *Strongyloides stercoralis*: hyperinfection in immunosuppresed dogs. Exp Parasitol 1984;57:1479–84.
[14] Genta RM. Dysregulation of strongyloidiasis: a new hypothesis. Clin Microbiol Rev 1999;5(4):345–55.
[15] Rotman HL, Yutanawiboonchai W, Brigandi RA, Leon O, Nolan TJ, Schad GA, et al. *Strongyloides stercoralis*: complete life cycle in SCID mice. Exp Parasitol 1995;81:136–9.
[16] Dawkins HJ, Grove DI. Attempts to establish infections with *Strongyloides stercoralis* in mice and laboratory animals. J Helminthol 1982;56(1):23–6.
[17] Herbert DR, Nolan TJ, Schad GA, Abraham D. The role of B cells in immunity against larval *Strongyloides stercoralis* in mice. Parasite Immunol 2002;24:95–101.
[18] Kitamura D, Roes J, Kuhn R, Rajewsky K. A B cell-deficient mouse by targeted disruption of the membrane exon of the immunoglobulin mu chain gene. Nature 1991;350:423–6.
[19] Khan WN, Alt FW, Gerstein RM, Malynn BA, Larsson I, Rathbun G, et al. Defective B cell development and function in Btk-deficient mice. Immunity 1995;3(3):283–99.
[20] Khan WN, Sideras P, Rosen FS, Alt FW. The role of Bruton's tyrosine kinase in B cell development and function in mice and man. Ann N Y Acad Sci 1995;764:27–38.
[21] Hayakawa K, Hardy RR, Honda M, Herzenberg LA, Steinberg AD. Ly-1 B cells: functionally distinct lymphocytes that secrete IgM autoantibodies. Proc Natl Acad Sci U S A 1984;81(8):2494–8.
[22] Kerepesi LA, Hess JA, Nolan TJ, Schad GA. Complement component of C3 is required for protective innate and adaptive immunity to larval *Strongyloides stercoralis* in mice. J Immunol 2006;176(7):4315–22.
[23] Galioto AM, Hess JA, Nolan TJ, Schad GA, Lee JJ, Abraham D. Role of eosinophils and neutrophils in innate and adaptive protective immunity to larval *Strongyloides stercoralis* in mice. Infect Immun 2006;74(10):5730–8.
[24] Nolan TJ, Rotman HL, Bhopale VM, Schad GA, Abraham D. Immunity to a challenge infection of *Strongyloides stercoralis* third larvae in the jird. Parasite Immunol 1995;17(11):599–604.
[25] Seet RCS, Lau LG, Tambyah PA. *Strongyloides* hyperinfection and hypogammaglobulinemia. Clin Diagn Lab Immunol 2005;12(5):680–2.
[26] Brigandi RA, Rotman HL, Nolan TJ, Schad GA, Abraham D. Chronicity in *Strongyloides stercoralis*: dichotomy of the protective immune response to infection and autoinfective larvae in a mouse model. Am J Trop Med Hyg 1997;56(6):640–6.
[27] Ligas JA, Kerepesi LA, Galioto AM, Lustigman S, Nolan TJ, Schad GA, et al. Specificity and mechanism of Immunoglobulin M (IgM)-and IgG-dependent protective immunity to larval *Strongyloides stercoralis* in mice. Infect Immun 2003;71(12):6835–43.
[28] Satoh M, Toma H, Kiyuna S, Shiroma Y, Kokaze A, Sato Y. Association of a sex-related difference of *Strongyloides stercoralis*-specific IgG4 antibody titer with the efficacy of treatment of strongyloidiasis. Am J Trop Med Hyg 2004;71(1):107–11.
[29] Satoh M, Toma H, Sato Y, Kikuchi M, Takara M, Shiroma Y, et al. Production of a high level of specific IgG4 antibody associated with resistance to albendazole treatment in *HLA-DRB1*0901*-positve patients with strongyloidiasis. Am J Trop Med Hyg 1999;61(4):668–71.
[30] Carvalho EM, Andrade TM, Andrade JA, Rocha H. Immunological features in different clinical forms of strongyloidiasis. Trans R Soc Trop Med Hyg 1983;77(3):346–9.
[31] Mota-Ferreira DM, Gonçalves-Pires MR, Júnior AF, Sopelete MC, Abdallah VO, Costa-Cruz JM. Specific IgA and IgG antibodies in paired serum and breast milk samples in human strongyloidiasis. Acta Trop 2009;109(2):103–7.

[32] Genta RM, Frei DF, Linke MJ. Demonstration and partial characterization of parasite-specific immunoglobulin A responses in human strongyloidiasis. J Clin Microbiol 1987;25(8):1505–10.
[33] Shi HZ. Eosinophils function as antigen-presenting cells. J Leukoc Biol 2004;76(3):520–7.
[34] Mir A, Benahmed D, Igual R, Borras R, O'Connor JE, Moreno MJ, et al. Eosinophil-selective mediators in human strongyloidiasis. Parasite Immunol 2006;28:397–400.
[35] Herbert DR, Lee JJ, Lee NA, Nolan TJ, Schad GA, Abraham D. Role of IL-5 in innate and adaptive immunity to larval *Strongyloides stercoralis* in mice. J Immunol 2000;165(8):4544–51.
[36] Urban Jr JF, Madden KB, Svetic A, Cheever A, Trotta PP, Gause WC, et al. The importance of Th2 cytokines in protective immunity to nematodes. Immunol Rev 1992;127:205–20.
[37] Hogarth PJ, Bianco AE. IL-5 dominates cytokine responses during expression of protective immunity to *Onchocerca linealis microfilariae* in mice. Parasite Immunol 1999;21(2):81–8.
[38] Rotman HL, Yutanawiboonchai W, Brigandi RA, Leon O, Gleich GJ, Nolan TJ, et al. *Strongyloides stercoralis:* eosinophil-dependent immune-mediated killing of third stage larvae in BALB/cByJ mice. Exp Parasitol 1996;82(3):267–78.
[39] Padigel UM, Lee JJ, Nolan TJ, Schad GA, Abraham D. Eosinophils can function as antigen-presenting cells to induce primary and secondary immune responses to *Strongyloides stercoralis*. Infect Immun 2006;6(74):3232–8.
[40] Padigel UM, Hess JA, Lee JJ, Lok JB, Nolan TJ, Schad GA, et al. Eosinophils act as antigen-presenting cells to induce immunity to *Strongyloides stercoralis* in mice. J Infect Dis 2007;196(12):1844–51.
[41] Janssen S, Beyaert R. Role of Toll-like receptors in pathogen recognition. Clin Microbiol Rev 2003;16(4):637–46.
[42] Uematsu S, Akira S. Toll-like receptors and innate immunity. J Mol Med 2006;84(9):712–25.
[43] Ogata H, Su I, Miyake K, Nagai Y, Akashi S, Mecklenbräuker I, et al. The toll-like receptor protein RP105 regulates lipopolysaccharide signaling in B cells. J Exp Med 2000;192(1):23–9.
[44] Akira S, Takeda K, Kaisho T. Toll-like receptors: critical proteins linking innate and acquired immunity. Nature Immunol 2001;2(8):675–80.
[45] Kirimanjeswara GS, Mann PB, Pilione M, Kennett MJ, Harvill ET. The complex mechanism of antibody-mediated clearance of *Bordetella* from the lungs requires TLR4. J Immunol 2005;175(11):7504–11.
[46] Kerepesi LA, Leon O, Lustigman S, Abraham D. Protective immunity to the larval stages of *Onchocerca volvulus* is dependent on Toll-like receptor 4. Infect Immun 2005;73(12):8291–7.
[47] Kerepesi LA, Hess JA, Leon O, Nolan TJ, Schad GA, Abraham D. Toll-like receptor 4 (TLR4) is required for protective immunity to larval *Strongyloides stercoralis* in mice. Microbes Infect 2007;9(1):28–34.
[48] Grove DI. Strongyloidiasis in allied ex-prisoners of war in South-east Asia. Br Med J 1980;280(6214):598–601.
[49] Nakada K, Kohakura M, Komoda H, Hinuma Y. High incidence of HTLV antibody in carriers of *Strongyloides stercoralis*. Lancet 1984;1(8377):633.
[50] Robinson RD, Lindo JF, Neva FA, Vogel P, Terry SI, Cooper ES. Immuno-epidemiologic studies of *Strongyloides stercoralis* and human T lymphotropic virus type I infections in Jamaica. J Infect Dis 1994;169(3):692–6.
[51] Neva FA, Filho JO, Gam AA, Thompson R, Freitas V, Melo A, et al. Interferon-γ and interleukin-4 responses in relation to serum IgE levels in persons infected with human T lymphotropic virus type 1 and *Strongyloides stercoralis*. J Infect Dis 1998;178(6):1856–9.
[52] Newton RC, Limpuangthip P, Greenberg S, Gam A, Neva FA. *Strongyloides stercoralis* hyperinfection in a carrier of HTLV-I virus with evidence of selective immunosuppression. Am J Med 1992;92(2):202–8.
[53] Porto AF, Neva FA, Bitterncourt H, Lisboa W, Thompson R, Alcantara L, et al. HTLV-1 decreases Th2 type of immune response in patients with strongyloidiasis. Parasite Immunol 2001;23(9):503–7.
[54] Finkelman FD, Shea-Donohue T, Goldhill J, Sullivan CA, Morris SC, Madden KB, et al. Cytokine regulation of the host defense against parasitic gastrointestinal nematodes: lessons from studies with rodent models. Annu Rev Immunol 1997;15:505–33.
[55] Barner M, Mohrs M, Brombacher F, Kopf M. Differences between IL-4Rα-deficient and IL-4-deficient mice reveal a role for IL-13 in the regulation of Th2 responses. Curr Biol 1998;8(11):669–72.
[56] Satoh M, Toma H, Sato Y, Takara M, Shiroma Y, Kiyana S, et al. Reduced efficacy of treatment of strongyloidiasis in HTLV-1 carriers related to enhanced expression of IFN-γ and TGF-β1. Clin Exp Immunol 2002;127(2):354–9.
[57] Hirata T, Uchima N, Kishimoto K, Zaha O, Kinjo N, Hokama A, et al. Impairment of host immune response against *Strongyloides stercoralis* by human T cell lymphotropic virus type 1 infection. Am J Trop Med Hyg 2006;74(2):246–9.
[58] Sarangarajan R, Ranganathan A, Belmonte AH, Tcherkoff V. *Strongyloides stercoralis* infection in AIDS. AIDS Patients Care STDS 1997;11(6):407–14.
[59] Ferreira MC, Nishioka SA, Borges AS, Costa-Cruz JM, Rossin IR, Rocha A, et al. Strongyloidiasis and infection due to human immunodeficiency virus: 25 cases at a Brazilian teaching hospital, including seven cases of hyperinfection syndrome. Clin Infect Dis 1999;28(1):154–5.
[60] Ohnishi K, Kogure H, Kaneko S, Kato Y, Akao N. Strongyloidiasis in a patient with acquired immunodeficiency syndrome. J Infect Chemother 2004;10(3):178–80.
[61] Hagelskjaer LH. A fatal case of systemic strongyloidiasis and review of the literature. Eur J Clin Microbiol Infect Dis 1994;13(12):1069–74.
[62] Viney ME, Brown M, Omoding NE, Bailey JW, Gardner MP, Roberts E, et al. Why does HIV infection not lead to disseminated strongyloidiasis? J Infect Dis 2004;190(12):2175–80.
[63] Brown M, Kizza M, Watera C, Quigley MA, Rowland S, Hughes P, et al. Helminth infections is not associated with faster progression of HIV disease in coinfected adults in Uganda. J Infect Dis 2004;190(10):1869–79.
[64] Olmos JM, Gracia S, Villoria F, Salesa R, Gonzalez-Macias J. Disseminated strongyloidiasis in a patient with acquired immunodeficiency syndrome. Eur J Intern Med 2004;15(8):529–30.
[65] Meamar AR, Rezaian M, Mohraz M, Hadighi R, Kia EB. *Strongyloides stercoralis* hyper-infection syndrome in HIV^{+}/AIDS patients in Iran. Parasitol Res 2007;101:663–5.
[66] Vaiyavatjamai P, Boitano JJ, Techasintana PT, Tungtrongchitr A. Immunocompromised group differences in presentation of intestinal strongyloidiasis. Jpn J Infect Dis 2008;61:5–8.
[67] Schaeffer MW, Buell JF, Gupta M, Conway GD, Akhter SA, Wagoner LE. *Strongyloides* hyperinfection syndrome after heart transplantation: case report and review of the literature. J Heart Lung Transplant 2003;23(7):905–11.
[68] Patel G, Arvelakis A, Sauter BV, Gondolesi GE, Caplivski D, Huprikar S. *Strongyloides* hyperinfection syndrome after intestinal transplantation. Transpl Infect Dis 2008;10(2):137–41.
[69] Mahmoud AA. Strongyloidiasis. Clin Infect Dis 1996;23:949–52.
[70] Gompels MM, Todd J, Peter BS, Main J, Pinching AJ. Disseminated strongyloidiasis in AIDS: uncommon but important. AIDS 1991;5(3):329–32.
[71] Igra-Siegman Y, Kapila R, Sen P, Kaminski ZC, Louria DB. Syndrome of hyperinfection with *Strongyloides stercoralis*. Rev Infect Dis 1981;3(3):397–407.
[72] Longworth D, Weller P. Hyperinfection syndrome with strongyloidiasis. New York: McGraw-Hill; 1986.
[73] Andrade Neto JL, Assef MCV. Estrongiloidiase. In: Veronesi R, Focaccia R, editors. Tratado de Infectectologia São Paulo, Atheneu; 1996. p. 1371–8.
[74] Zaha O, Hirata T, Kinjo F, Sato A. Strongyloidiasis: progress in diagnosis and treatment. Intern Med 2000;39(9):695–700.
[75] Miller MA, Church LW, Salgado CD. *Strongyloides* hyperinfection: a treatment dilemma. Am J Med Sci 2008;336(4):358–61.
[76] Heath T, Riminton S, Garsia R, Macleod C. Systemic strongyloidiasis complicating HIV: a promising response to ivermectin. Int J STD AIDS 1996;7(4):294–6.
[77] Orem J, Mayanja B, Okongo M, Morgon D. *Strongyloides stercoralis* hyperinfection in a patient with AIDS in Uganda successfully treated with ivermectin. Clin J Infect Dis 2003;37(1):152–3.
[78] Machado ER, Teixeira EM, Gonçalves-Pires MR, Loureiro ZM, Araújo RA, Costa-Cruz JM. Parasitological and immunological diagnosis of *Strongyloides stercoralis* in patients with gastrointestinal cancer. Scand J Infect Dis 2008;40(2):154–8.
[79] Agrawal V, Agarwal T, Ghoshal UC. Intestinal strongyloidiasis: a diagnosis frequently missed in the tropics. Trans R Soc Trop Med Hyg 2009;103(3):242–6.
[80] Sudarshi S, Stumpfle R, Armstrong M, Ellman T, Parton S, Krishnan P, et al. Clinical presentation and diagnostic sensitivity of laboratory tests for *Strongyloides stercoralis* in travellers compared with immigrants in a non-endemic country. Trop Med Int Health 2003;8(8):728–32.
[81] Karunajeewa H, Kelly H, Leslie D, Leydon J, Saykao P, Giggs B. Parasite-specific IgG response and peripheral blood eosinophils count following albendazole treatment for presumed chronic strongyloidiasis. Int J Travel Med 2006;13(2):84–91.
[82] Singh S. Human strongyloidiasis in AIDS era: its zoonotic importance. J Assoc Phys India 2002;59:415–22.
[83] Coker AO, Isokpehi RD, Thomas BN, Fagbenro-Beyioku AF, Omilabu SA. Zoonotic infections in Nigeria: overview from a medical perspective. Acta Trop 2000;76(1):59–63.
[84] Nwosu CO, Madu PP, Richards WS. Prevalence and seasonal changes in the population of gastrointestinal nematodes of small ruminants in the semi-arid zone of north-eastern Nigeria. Vet Parasitol 2007;144(1–2):118–24.
[85] Yapi YG, Briet OJ, Vounatsou P. Prevalence of geohelminths in savannah and forest of Cote d'Ivoire. West Afr J Med 2006;25(2):124–5.
[86] Dada-Adegbola HO, Bakare RA. Strongyloidiasis in children five years and below. West Afr J Med 2004;23(3):194–7.
[87] Mendonça SCL, Gonçalves-Pires MRF, Rodrigues RM, Ferreire Jr A, Costa-Cruz JM. Is there an association between positive *Strongyloides stercoralis* serology and diabetes mellitus? Acta Trop 2006;99(1):102–5.
[88] Marcos LA, Terashima A, DuPont HL, Gotuzzo E. *Strongyloides* hyperinfection syndrome: an emerging global infectious disease. Trans R Soc Trop Med Hyg 2008;102(4):314–8.
[89] Franco-Paredes C, Dismukes R, Nicolls D, Hidron A, Workowski K, Rodriguez-Morales A, et al. Persistent and untreated tropical infectious diseases among Sudanese refuges in the United States. Am J Trop Med Hyg 2007;77(4):633–5.
[90] Román-Sánchez P, Pastor-Guzmán A, Moreno-Guillén S, Igual-Adell R, Suñer-Generoso S, Tornero-Estébanez C. High prevalence of *Strongyloides stercoralis* among farm workers on the Mediterranean coast of Spain: analysis of the predictive factors of infection in developed countries. Am J Trop Med Hyg 2003;69(3):336–40.
[91] Dillard KJ, Saari SAM, Anttila M. *Strongyloides stercoralis* infection in a Finnish kennel. Acta Vet Scand 2007;49(1):37.
[92] Boulware DR, Stauffer WM, Hendel-Paterson BR, Rocha JL, Seet RC, Summer AP, et al. Maltreatment of *Strongyloides* infection: case series and worldwide physicians-in-training survey. Am J Med 2007;120(6):545.e1–8.
[93] Pasqualotto AC, Zborowski MF, Dos Anjos M, Poloni JA, Dos Santos AP, Torelly AP. *Strongyloides stercoralis* in the urine. Trans R Soc Trop Med Hyg 2009;103(1):106–7.
[94] Lagacé-Wiens PRS, Harding GKM. A Canadian immigrant with coinfection of *Strongyloides stercoralis* and human T-lymphotropic virus 1. CMAJ 2007;177(5):451–3.

[95] Nuesch R, Zimmerli L, Stockli RS, Gyr N, Hatz CFR. Imported strongyloidosis: a longitudinal analyses of 31 cases. J Travel Med 2005;12:80–4.
[96] Keiser PB, Nutman TB. *Strongyloides stercoralis* in the immunocompromised population. Clin Microbiol Rev 2004;17(1):208–17.
[97] Greiner K, Bettencourt J, Semolic C. Strongyloidiasis: a review and update by case example. Clin Lab Sci 2008;21(2):82–8.
[98] Galimberti R, Pontón A, Zaputovich FA, Velasquez L, Galimberti G, Torre A, et al. Disseminated strongyloidiasis in immunocompromised patients—report of three cases. Int J Dermatol 2009;48(9):975–8.
[99] Steinmann P, Zhou XN, Du ZW, Jiang JY, Wang LB, Wang XZ, et al. Occurrence of *Strongyloides stercoralis* in Yunnan Province, China, and comparison of diagnostic methods. PLoS Negl Trop Dis 2007;1(1):e75.
[100] Blatt JM, Cantos GA. Evaluation of technique for the diagnosis of *Strongyloides stercoralis* in Human Immunodeficiency Virus (HIV) positive and HIV negative individuals in the city of Itajai, Brazil. Braz J Infect Dis 2003;7(6):402–8.
[101] Verweij JJ, Canales M, Polman K, Ziem J, Brienen EA, Polderman AM, et al. Molecular diagnosis of *Strongyloides stercoralis* in faecal samples using real-time PCR. Trans R Soc Trop Med Hyg 2009;103(4):342–6.