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**Review Article** 



# Hookworms in Emergency Department: The "Vampire" Within

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Hookworms infection is a soil-transmitted helminthic disease particularly endemic in developing counties of tropical regions. It is attributed mainly to two human pathogens nematodes namely *Necator americanus* and *Ancylostoma duodenale*. Although the disease has been characterized as "neglected" is very difficult to be eliminated and the economic consequences are great. Worms are fed with blood of hosts in small intestine and cause typically iron deficiency anemia with relevant symptoms as well as eosinophilia. Patients admitted in emergency department claim often diffuse general symptoms, whereas cases with obscure gastrointestinal bleeding can be seen. Within this brief review, after introducing some basic elements of hookworms' epidemiology, taxonomy and socioeconomic problem is emphasized, pathogenesis, and life cycle of parasite are concisely explained. Furthermore, clinical manifestations often or rarely seen in emergency department are described. Therapeutic options are also enclosed. Awareness of the problem and critical thinking of patients coming from endemic regions could result to identifying more hookworm cases and their therapy will efficiently alleviate not only the patients *per se* but health system and societies as well.

Key words: hookworm, emergency department, Ancylostoma, Necator, anemia

#### Introduction

Soon after birth, the human body is colonized in the intestine by a community of bacteria with relatively simple composition, which grow in number and complexity with age. It has been shown that, in connection with a beneficial impact on gastrointestinal function and host health, intestinal microbiota is associated with dietary habits, physiological factors such as age, gender and body mass index as well as disorders, such as inflammatory bowel disease (IBD) and obesity. Beyond intestinal microbiota, certain pathogens including soil-transmitted helminths (STH) appear to co-exist in the human intestine. Currently,

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there is considerable interest to define whether STH affect the gut microbiome and whether the effects of hookworms on human health is mediated through modification in the microbiome composition.<sup>1</sup> In this regard, relative data indicate that there is relationship between the intestinal microbiome and intestinal STH.<sup>1</sup>

STH have been identified as a major burden, especially in the less developed and tropical countries (Fig. 1);<sup>2,3</sup> they considered to be debilitating rather than lethal infections with a significant socioeconomic and public health impact;<sup>4</sup> and they cause impairments in physical, intellectual, and cognitive development.<sup>1</sup>

STH infect 1.5 to 2 billion people worldwide (in the majority of developing countries and mostly children) and cause an assessed burden of 3.3 million disability-adjusted life years.<sup>1,5</sup> According to World Health Organization, about one quarter of world's population is infected by STH.<sup>6</sup> Women in the reproductive age and children are included to the more susceptible groups<sup>3</sup> and heavy infections to such population may have serious outcomes like the mentioned growth retardation, intellectual and cognitive impairments; in pregnant women, they are also linked to adverse maternal-fetal outcomes.<sup>7</sup>

STH are mainly represented by Ascaris lum-

bricoides, whipworm Trichuris (T.) trichiura, and hookworm such as Necator (N.) americanus and Ancylostoma (A.) duodenale.<sup>1,8</sup> The latter have been characterized as "The Great Infection of Mankind" as they perform damage "silent and insidious" and are resistant to be "pushed back" compared to other global burdens like malaria.<sup>7</sup> These organisms are characteristically transmitted via the fecal-oral route indirectly by ingestion of contaminated food, water, soil, or fomites. Likewise, direct transmission through person-to-person or animal-to-person contact is conceivable for several species.<sup>4</sup> Climate conditions, the appropriate quality of the soil and poor sanitary regimes constitute an ideal substrate that favors the survival of parasitic eggs outside host and completion of their life cycle;<sup>3</sup> there is a complex and frequently inconsistent or unpredictable association between hand-washing station with water available and hookworm.9 Although great endeavors have been made globally over the last century for the elimination of the disease, the problem remains significant in less industrialized, developed societies; the incidence of human intestinal parasitoses has continued to increase in recent years, despite the concerted efforts at reduction.<sup>10</sup> Failure of eradication of hookworm infection in low-income countries has been attributed to the variable efficacy



Fig. 1. Topographic distribution of hookworm infestation around the globe. A distinction of human pathogen species has not been made. Endemic regions at descending order include Oceania, sub-Saharan Africa, Southeast Asia, South Asia, East Asia, Latin America and the Caribbean. Modified from Loukas et al.<sup>3</sup>

of mass drug administration and the rapid reinfection along with the aforementioned favorable factors.<sup>3</sup>

The initial description of hookworm (Fig. 2) belongs to the Italian physician Dubini and dates back to 1838.<sup>11</sup> Human hookworm infections are attributed mainly to the mentioned two different nematodes (round worms); A. duodenale and N. americanus.<sup>2,11-16</sup> The first one is more endemic in Mediterranean area, North Africa, India and China. The latter species is considered to be the most common causative factor worldwide. It is especially predominant in regions of Southeast Asia, South America and Africa and accounts for the majority of documented human cases.<sup>3,7,17</sup> Specifically, N. americanus is endemic in several rural areas of the global South, as well as in poor areas of the United States and its global control remains a distant prospect.<sup>18</sup> Another species which is pathogen for both human and dogs is A. ceylani $cum^{2,3,17}$  and its prevalence is high in Southeast Asia and particularly in Indonesia and Malaysia. A co-infection with N. americanus is also common.<sup>3</sup> Additional noteworthy species that infect dogs include A. caninum, A. braziliense and Uncinaria stenocephala,

whereas feline species include *A. tubaeforme* as well as the mentioned canine ones.<sup>19-21</sup> Interestingly, experimental human infection with *A. caninum* has been successfully performed in the past<sup>22</sup> and there are reports associating this pathogen etiologically with aphthous ileitis and eosinophilic enteritis syndromes;<sup>17</sup> dogs with spontaneous IBD have similar symptoms and clinical presentation to humans with the disease,<sup>3,23,24</sup> though the underlying mechanisms of these disorders have not been identified.<sup>25</sup>

The most "blood sucking" hookworm is *A. du-odenale*, which consumes up to tenfold more blood than *N. americanus*. The daily quantity of blood loss ranges from 0.05 to 0.3 mL per adult for *A. duodenale* and respectively 0.01 to 0.04 mL for *N. americanus*.<sup>26</sup> Hookworms depend nutritionally almost exclusively on ingestion of intact red blood cells, which are later hemolyzed in the parasitic gut by relevant proteins.<sup>3,7</sup> Hookworms are ranked as the second most common cause of associated iron deficiency anemia (IDA) after malaria as far as parasitic causative spectrum is concerned and in cases of co-infection with plasmodium they may provoke a severe anemia;<sup>3</sup> hookworms



Fig. 2. (A) Microphotograph of *Ancylostoma* species eggs identified in a stool probe. Courtesy of Professor of Parasitology Papadopoulos Elias, Greece. (B–D) Endoscopic images of a patient with overt gastrointestinal bleeding and iron deficiency anemia. In duodenum was evident the presence of multiple hookworms. Courtesy of Professor of Gastroenterology Vishal Sharma, India.

are globally one of the most significant contributors to IDA;<sup>27</sup> and IDA represents a public health concern among pregnant women in Africa and the factors associated with IDA include hookworm infection.<sup>28</sup>

Over the last decades, the increasing population movement worldwide has become a key factor in reshaping epidemiology of tropical diseases.<sup>13,29</sup> Therefore, parasitic diseases like hookworm infection should also be considered in cases of travelers or immigrants/refugees from endemic regions, who are admitted to emergency department claiming complaints of varying severity.

## Life Cycle and Pathogenesis

The first biological (life) cycle of hookworms was originally described by Loose in 1901.<sup>17</sup> Hookworms are considered to have a direct life (Fig. 3). Acquisition of worms by human host takes place once the infective so-called "third stage" (L3) larvae are ingested (A. duodenale) or penetrate through intact skin (both main human species). The about 600 µm long L3 larvae can survive in environment with favorable conditions for weeks but they are developmentally in a "hibernation." Once they enter human body, they receive signals from host, which resume further development. This signaling is cyclic guanosine monophosphate (cGMP)-dependent and is mediated via a muscarinic neuronal pathway. L3 larvae reach blood vessels and migrate through bloodstream to heart and lung capillaries. A further ascending migration route from lung parenchyma up to pharynx occurs. Through cough and swallow mechanism larvae end up in small intestine, where they molt two times before they grow to adults. Specifically, the life cycle of *N. americanus* demands that eggs excreted in human feces are deposited in warm, moist soil. Once hatched and in the existence of a naked foot, the larvae crawl through the skin and travel via blood vessels, heart, lungs, mouth, and throat to return to the gut. Thus successful reproduction demands situations with suitable climate and soil, frequent human defecation, and occasions for skin contact.<sup>18</sup> An elapse of about two months is required, till the infective L3 larvae reach sexual maturity and mate. Eggs are produced daily and are excreted with feces, the quantity of which determines the severity of infection. Hatching and release of larvae occurs in one to two days. After twice molting the L3 larvae are developed. They can survive for several weeks in appropriate environment, till their lipid reserves run out.7,12,17,24

Infection has been associated with less rigorous hygiene regiments.<sup>12</sup> Moreover, favorable climate conditions like appropriate soil, humidity and temperature are found in many coastal tropical regions that have among the highest prevalence of hookworm infection.<sup>24</sup>

In such regions, the prolonged exposure of human skin to L3 larvae (human species) causes the socalled "ground itch" lesion, which is an erythematous papular rash that appears locally on feet and hands and is characterized by pruritus.<sup>3,24,30,31</sup> The penetration of L3 larvae is facilitated through production of hydrolytic enzymes, such as proteases and hyaluronidases.<sup>3,17</sup> The zoonotic species A. braziliense can also cause a self-limited skin condition, the "creeping eruption" (known also as cutaneous larva migrans) through the cutaneous invasion and migration of larvae, resulting in the appearance of serpiginous tunnels, more often on feet, buttocks or abdomen. Travelers and personnel of armed forces belong to vulnerable populations. Although the disease is in the majority of cases limited to cutaneous manifestation, there are rare case reports of pulmonary migration of A. braziliense causing the so-called Loeffler's syndrome.<sup>3,21,24,30,32</sup> A. duodenale has the unique mentioned feature to bypass cutanopulmonal migration of other species and reaches directly intestine after been swallowed. The caused disease with the name Wakana, is characterized by vomiting, nausea, cough, hoarseness, pharyngitis and dyspnea.<sup>30,33</sup> Noteworthy, A. secreted protein 2, which is a cysteine rich secretory protein and shows allergenic properties, contributes to the development of pneumonitis as well as Wakana disease.<sup>3</sup>

Some data indicate that, following the migration of infective larvae (L3) through rodent tissues, N. brasiliensis induces a T helper type 2 (Th2) lymphocyte response in the lungs, skin, and intestinal mucosa,<sup>34</sup> features also present in human hookworm infections, including cluster of differentiation 4 (CD4+) T lympthocyte-dependent immunoglobulin E (IgE) production, mastocytosis, eosinophilia, and mucus production.3 Moreover, hookworm infections are characterized by the generation of an immune-regulatory environment with the anti-inflammatory cytokines including interleukin (IL)-10 and transforming growth factor (TGF)- $\beta$ , and regulatory T cells, type 2 innate lymphoid cells, tolerogenic dendritic cells, and M2 macrophages to inhibit possibly dangerous pathologies.<sup>35,36</sup> Due to the exquisite immunomodulatory capacity of hookworm infections, STH may act as a



- **Fig. 3.** Life cycle of human hookworms. *Necator americanus* and *Ancylostoma duodenale* are the main human pathogens. Eggs (A) once they find favorable climatic conditions give birth to rhabditiform larvae (B) in 24 to 48 hours. At this stage, larvae are not infectious and grow further to filariform or 3rd stage larvae (C) in feces—soil. They can survive up to a month. Through percutaneous route, often via bare feet, they enter human body (D). Larvae migrate further through blood vessels (E) to heart and lungs (F) and via bronchial tree (G) ascending to pharynx (H) where they can be swallowed and enter thus gastrointestinal tract. Once they reach small intestine (I) they grow to adults (J) and ingest blood, causing anemia to the host. They also reproduce and live up to several years.
- \*Ancylostoma duodenale is known to have alternatively a direct fecal-oral transmission route, bypassing thus the lung migration phase.
- \*\*Ancylostoma duodenale larvae might also become dormant in the muscle or intestine.

\*\*\*Ancylostoma ceylanicum can be excreted by cats and dogs and is also infectious to human.

potential treatment for inflammatory diseases, such as celiac disease, asthma, multiple sclerosis, and IBD.<sup>37-40</sup>

Other findings that are regarded as typical of hookworm infections due to Th2 cell polarization are the mentioned mastocytosis and IgE production.<sup>3,17,31</sup> The latter is strong and is induced by both specific to parasitic epitopes and nonspecific IgE stimuli, presumably due to release of pro-allergic mediators by hookworms.<sup>17</sup> In this respect, the Th2 immune response, culminating in eosinophilia and IgE production, is not only characteristic of allergy but also of hookworm infection.<sup>41</sup> Since STH may cause several pathologies such as the mentioned Loeffler's syndrome,<sup>3,17,32</sup> aphthous ileitis likely IBD and eosinophilic enteritis syndromes,<sup>17</sup> further studies are warranted to elucidate aforementioned contradictory data.

Besides, nematode roundworm extracellular vesicles (EVs) may suppress potentially threatening type 2 innate responses and eosinophilia and induce a regulatory and/or suppressive immune response that is beneficial for parasite's long-term survival.<sup>42</sup> Interestingly, EVs have also been related to Platyhelminth flatworms;<sup>43</sup> schistosome EVs impact macrophage differentiation;<sup>44</sup> and liver fluke EVs are internalized by human cholangiocytes and promote cell proliferation thereby potentially contribute to the development of liver malignancy.<sup>45</sup> In this respect, proteins and microRNAs (miRNAs) contained within helminth EVs hold potential application in development of drugs to treat helminth infections and chronic non-infectious diseases attributed to a dysregulated immune system, such as IBD<sup>46</sup> and thus further studies are necessary.

The pathophysiology of STH-induced gastrointestinal bleeding is multifactorial. A great component of host's IDA is attributed to ingestion of blood by the hookworms. Moreover, blood leakage after the mechanical injury of intestinal epithelium-vasculature is another well recognizable factor. The release of serine proteases, which inhibit clotting factors VIIa and Xa, tissue factor inhibitors and hookworm platelet inhibitor protein are also implicated in mechanism of blood loss.<sup>3,12</sup> N. americanus is believed to induce a blood loss of more than one ml per day. Heavy untreated infections (more than 4,000 eggs per gram feces) can lead long-term to hypoproteinaemia and hydropic decompensation with ascites and anasarca. The skin coloration of such patients turns yellowish, a condition previously known bibliographically as "chlorosis."<sup>3</sup>

## **Clinical Presentation in Emergency Department**

Hookworm disease's clinical manifestations are mainly subtle and insidious as well as often nonspecific, hampering therefore the early establishment of diagnosis. Patients claim usually general symptoms and conditions like itchy rash,<sup>2,47</sup> nausea, flatulence, abdominal pain, diarrhea, reduced absorption of micronutrients,<sup>2,4,11</sup> weight loss-stunted growth, intestinal obstruction and impaired development.<sup>2</sup> Occasionally unexplained eosinophilia might be a major clue usually in mild infection cases.<sup>11</sup> Individuals with mild infections may remain fully asymptomatic<sup>11</sup> and parasites can be accidentally diagnosed, as patients are admitted due to other reasons. Of note, cases with history of traveling or origin from endemic tropical regions should raise the suspicion of clinician. A summary of clinical presentations seen in an emergency setting and attributed to hookworms can be found in Table 1.

Gastrointestinal bleeding, the predominant hallmark, is more commonly occult and less often overt (Fig. 2) obscure gastrointestinal bleeding,<sup>11,12,59</sup> whereas there are very rare reports of massive bleeding under anticoagulants.<sup>58</sup> Prolonged blood loss leads longterm to IDA, the course of which is heavier after *A. duodenale* infection. The subsequent range of indirect urgent complaints that patients claim once admitted to emergency department include angina, dyspnea, fatigue, palpitations. Another slowly evolving condition is malnutrition and hypoproteinemia, which contribute secondary to mentioned lower extremities edema—anasarca.<sup>24</sup>

Children and pregnant are more susceptible to infection and the course might be more severe, because of the increased obstetric and perinatal morbidity<sup>60</sup> and the clinician in emergency department should be aware of this particularity. IDA seems to be more common and intense among affected females in gestation, causing maternal mortality, premature birth, underweight infant and reduced breastfeeding.<sup>24,60</sup> Vertical transmission through vaginal passage or colostrum to neonates remains is possible, affecting growth, memory, reasoning ability, and reading comprehension.<sup>24</sup>

Hookworms are also known in the literature to mimic acute surgical abdomen. Patients may present with loss of appetite, diffuse sharp and cramping pain, with tenderness and guarding during clinical assess-

								Hookwor	ms in Emerge	ency Departm
2	Treatment	N/Aª	N/A <sup>a</sup>	Ivermectin Mebendazole	Mebendazole	Albendazole + iron	Mebendazole	Mebendazole	Mebendazole	N/A <sup>a</sup>
	Diagnosis	Stool samples	Stool samples	Skin biopsy Colonoscopy	Stool samples	Capsule endoscopy	Single-balloon enteroscopy	ERCP <sup>b</sup>	Capsule endoscopy	Capsule endoscopy
	Related hookworm	Ancylostoma duodenale	$N/A^{a}$	N/A <sup>ª</sup> Ancylostoma duodenale	N/A <sup>a</sup>	N/A <sup>a</sup>	Ancylostoma ceylanicum	Ancylostoma duodenale	Ancylostoma duodenale	N/A <sup>a</sup>
	Clinical Manifestation	Vernal keratoconjunctivitis	Mooren's ulcer	Papules, pustules Acute Abdomen	Diarrhea and eosinophilia	Melaena, weakness	Abdominal pain, nausea	Pancreatitis	Melaena, abdominal pain	Hematemesis and melena
	No. of cases	12	Seven	One One	One	One	One	One	One	One
infection	Journal	J Natl Med Assoc	Opthalmology	Int J Dermatol Am J Med	J Microbiol Immunol Infect	Asian Pac J Trop Med	Gastrointest Endosc	Am J Emerg Med	Gastrointest Endosc	Indian J Gastroenterol
kworm	Year	2005	2007	2008 2009	2011	2012	2012	2014	2014	2015
ed emergencies caused by hool	Title	Vernal Keratoconjunctivitis and Intestinal Parasitic Infestations in Black Children	Hookworm Infestation as a Risk Factor for Mooren's Ulcer in South India	Hookworm Folliculitis Unusual Case of Hookworm Presenting as Acute Surgical Abdomen	Hookworm Infection in a Healthy Adult that Manifested as Severe Eosinphilia and Diarrhea	Overt Gastrointestinal Bleeding Because of Hookworm Infection	Diagnosis of Ancylostoma Ceylanicum Infestation by Single-Balloon Enteroscopy (With Video)	Hookworm Infestation as Unexpected Cause of Recurrent Pancreatitis	Overt Small-Intestine Bleeding Caused by Ancylostoma Duodenale	Gastrointestinal Bleeding in a Young Man: Think Outside the Box
Table 1. Publishe	Author	Ajaiyeoba <sup>48</sup>	Zelefsky et al. <sup>49</sup>	Rivera-Roig et al. <sup>50</sup> Baltz et al. <sup>51</sup>	Wang et al. <sup>30</sup>	Chen et al. <sup>52</sup>	Chung et al. <sup>53</sup>	Tseng et al. <sup>54</sup>	Chou et al. <sup>33</sup>	Nayak et al. <sup>55</sup>

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Author	Title	Year	Journal	No. of cases	Clinical Manifestation	Related hookworm	Diagnosis	Treatment	Doulberi
pongsathorn amath <sup>47</sup>	Iron-Deficiency Anemia With an Itch	2015	Mayo Clin Proc	One	Cutaneous larva migrans, anemia	$N/A^{a}$	Clinical	Albendazole + iron	s et al.
na et al. <sup>12</sup>	Gastrointestinal Bleeding in the Tropics: Look for the Hookworm	2017	Trop Doct	Three	Melaena, weakness	N/A <sup>a</sup>	EGD°	Albendazole + iron	
t al. <sup>56</sup>	Mating <i>Ancylostoma</i> <i>Duodenale</i> Under Magnifying Endoscopy	2016	Gastrointest Endosc	One	Anemia, occult bleeding	Ancylostoma duodenale	EGD <sup>¢</sup> , NBI <sup>d</sup>	Mebendazole	
t al. <sup>11</sup>	Hookworm Infection Caused Acute Intestinal Bleeding Diagnosed by Capsule: A Case Report and Literature Review	2017	Korean J Parasitol	One	Hematochezia	N/A <sup>a</sup>	EGD°, capsule endoscopy	Albendazole + transfusion + iron	
et al. <sup>57</sup>	Blood Sucking Hookworm Under Narrow Band Imaging	2017	Dig Liver Dis	One	Abdominal discomfort, anemia	Ancylostoma duodenale	EGD <sup>e</sup> , NBI <sup>d</sup>	Albendazole	
et al. <sup>58</sup>	Acute Major Gastrointestinal Bleeding Caused by Hookworm Infection in a Patient on Warfarin Therapy: A Case Report	2018	Medicine	One	Chest pain, shortness of breath	N/A <sup>a</sup>	EGD°, capsule endoscopy	Albendazole	
ailable by the r copic retrograd- agogastroduode v band imaging	publication. le cholangiopancreatography. enoscopy. 3.								

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ment, a tricky picture that could lead to unnecessary explorative laparotomies.<sup>51</sup> Rarely hookworms can cause established acute abdomen by inducing gut perforation.<sup>61</sup> Likewise, a rare, albeit documented complication of hookworm infestation is the development of pancreatitis, which can be the result of hookworms' migration into the ampulla of Vater and can even lead to chronic recurrent pancreatitis.<sup>54</sup>

Additionally, a substantial component of hookworm's clinical picture are also the skin lesions and particularly, atopic conditions. In returning travelers, the most frequent tropical skin disorder is hookworm-related cutaneous larva migrans though treating physicians might also face patients with localized cutaneous leishmaniasis.<sup>62</sup> In this respect, folliculitis is an unusual form of cutaneous larva migrans and affects travelers of tropical zones. When accompanied by fever, human immunodeficiency virus (HIV) co-infection should be excluded.<sup>21</sup> Allergic rhinoconjunctivitis and dermatitis in children are known to be related to parasites and mainly to hookworms.<sup>63</sup> The characteristic serpiginous skin lesions are recognized as larva migrans cutanea ("creeping eruption;" sandworm);<sup>64</sup> hookworm dermatosis seen in patients with invasion point(s) that is/are itchy and have erythematous appearance, with accompanying pustular linear or follicular serpiginous lesions is suggestive of larva migrans.<sup>3,65</sup> Rash may have dimensions up to three millimeter width and up to 20 cm length, migrating at a rate of 1–2 cm per day.<sup>50</sup>

Ophthalmological emergencies are not unswayed by STH. Allergic reaction of conjunctiva constitutes a relatively common complaint in African children and could conceal an intestinal worm infestation in children when associated with an exacerbation episode of a chronic vernal keratoconjunctivitis.<sup>48</sup> Furthermore, it has been suggested that hookworm penetration in the alimentary tract might be a risk factor for development of Mooren's ulcers. This ocular pathological entity is characterized by a painful peripheral ulceration of the cornea and acute projection of deepithelialized tissue.<sup>49</sup> Another less common neuro-ophthalmologic manifestation of hookworms includes the occurrence of diffuse unilateral subacute neuroretinitis caused by A. species and causality has been substantiated with molecular-based genetic identification.<sup>66</sup> Finally, a rare case of female hookworm (N. americanus) located in the eye has been associated with a reducing central vision.67

## Diagnosis

Initial assessment should include all these clinical and laboratory investigations, which help to clarify and triage an emergency situation. Detailed and focused history plays a key-role for establishing diagnosis. Targeted questions elucidating the main complaint could reveal anemia, weight loss, chronic diarrhea, atopy and compose the portrait of the present illness. Epidemiological data of hookworm distribution should not be underestimated, especially in cases of recent repatriation from endemic regions.

The gold standard diagnostic technique for assessment of worm infestation includes stool microscopy (Fig. 2) for direct hookworms' eggs detection and species identification.<sup>68</sup> It constitutes an economical and simple method, though it is confined by the difficulty (especially if the personnel is not very experienced) sometimes to distinguish, due to morphological similarities, among the eggs of different parasites species like N. americanus, A. species and other strongylid nematodes species, like Oesophagostoum and Trichostrongylus species<sup>2,69</sup> Kato-Katz is a widely known microscopic technique, which was originally developed for the detection of eggs Schistosoma species The currently recommended Kato-Katz method has already been in use for decades. The advantages of Kato-Katz method are its low cost, short sample preparation time, simple handling and the requirement of only basic equipment.<sup>70</sup> Nevertheless, the method has a low sensitivity for reduced STH infection intensities, hookworm eggs disappear after one hour, thereby needing immediate preparation and samples and slides for hookworm cannot be stored.<sup>71</sup> However, the sensitivity can be increased by analyzing multiple Kato-Katz thick smears from multiple samples<sup>72</sup> or by analyzing an augmented amount of stool as it is done by the FLOTAC (1 g) or Mini-FLOTAC (2/10 g) system.73

DNA-based diagnostic testing using quantitative real-time polymerase chain reaction (PCR) offers an ideal means for the sensitive and species-specific detection of STH infection.<sup>74</sup> In this respect, PCR-based diagnostic options of A. species have been developed. They target the so-called internal transcribed spacer regions of the ribosomal gene cluster. Furthermore, a novel, real-time PCR-based assay for detection of A. *ceylanicum* has also been lately developed. The latter offers a sensitive detection and targets a non-coding, highly repetitive genomic DNA element.<sup>20</sup> A further

diagnostic modality is the so-called Loop Mediated Isothermal Amplification (LAMP) technique for the detection of *N. americanus* in fecal samples. It is a promising solution, as it is characterized by simplicity, low cost, sensitivity, and specificity.<sup>75</sup>

Regarding blood tests, the most typical finding that is suggestive for parasitic infections is eosinophilia.<sup>13,22,30,69,76,77</sup> The predominance of eosinophils in peripheral blood is, however, not pathognomonic for STH-etiology, as it can be met in other entities like allergic and autoimmune disorders, malignant diseases, vasculitis, skin diseases, primary immunodeficiencies, endocrine conditions, drug reactions, and, occasionally, even in some non-helminthic infections like sarcocystosis or coccidioidomycosis.<sup>13</sup> Important to note that, in the case of eosinophilia in an individual who has lived in helminth endemic areas, it is advisable to introduce methods for detection the infection, irrespective of immigration type, length of stay, or the presence of symptoms.<sup>78</sup> Moreover, the absence of eosinophilia, cannot exclude the disease.

Other common laboratory findings include the mentioned IDA,<sup>11,57</sup> vitamin A deficiency,<sup>2</sup> and hypoproteinemia,<sup>11</sup> though they are also nonspecific. Regarding IDA, a mean corpuscular volume of about less than 83 fL is required for diagnosis along with low ferritin or serum transferrin receptor. Other etiologies of microcytic anemia which could also co-exist with IDA include thalassemia, anemia of chronic disease, leading poisoning, sideroblastic anemia<sup>79</sup> and pyridoxine (vitamin B6) deficiency.<sup>80</sup> Of note, a normal mean corpuscular volume does not exclude IDA, since the presence of a parallel macrocytic anemia (e.g., folate or B12 vitamin deficiency) could lead to a normal measured corpuscular volume and in the peripheral blood smear might be seen a mixed population of microcytic and macrocytic red cells with an elevated distribution width.<sup>81</sup>

Occult blood test can be often performed once a gastrointestinal bleeding with/or IDA is suspected, which is mostly positive, but required further clarification endoscopically.<sup>33,47,56,58</sup>

Upper light endoscopy is able, sometimes, to directly detect hookworms in mucosa of duodenum.<sup>11,56</sup> Narrow band imaging (NBI) has been suggested during endoscopy, to improve the technique's quality. Specifically, during white light endoscopy small, white and reddish punctate hookworms are detected and after NBI conversion the blood-filled structures, like intestine of the hookworm containing sucked blood, stand out more prominently in sharp contrast to surrounding nonvascular structures.<sup>57</sup>

Capsule endoscopy might also be considered as a diagnostic modality for intestinal hookworm infections, although it is not suggested in emergency setting by the current guidelines.<sup>11,15,33,55</sup>

Urgent gastrointestinal endoscopy is indicated, under certain circumstances, when acute bleeding reported, before targeted investigations to STH are performed. More advanced endoscopic procedures, such as double-balloon enteroscopy or endoscopic retrograde cholangiopancreatography, are carried out under specific indications and could act supplementary to hookworm infection diagnosis and management.<sup>59</sup> Colonoscopy does not offer diagnostic advantages, unless terminal ileum catheterization reveals the parasites.<sup>53,54</sup>

#### **Initial Management and Therapy**

Fundamental therapeutic approach of each patient being evaluated in emergency department is stabilization of vital signs and offering of a quick albeit efficient symptomatic therapy with parallel rough investigation of etiology. Conditions that jeopardize patient's life like hypovolemic shock or acute abdomen should be firstly addressed and once cardiopulmonal stability has been achieved, a further targeted management can be performed.<sup>82</sup>

A common treatment of hookworm is the usage of benzimidazole class of anthelmintics, mainly represented by albendazole and mebendazole.<sup>11,12</sup> The drugs eliminate adult worms by inhibiting microtubule polymerization in invertebrates. A single 400 mg dose of albendazole is more effective than a single 500 mg dose of mebendazole. Three consecutive daily doses of either drug improve both cure and egg reduction rates.<sup>11</sup> An alternative possibility could be the administration of a single dose of oral ivermectin 200 mg/kg. Nevertheless, there are studies claiming that ivermectin is less effective against hookworms compared to Ascaris lumbricoides or filariasis.8,17,32 Recent data, however, suggest a good tolerability and higher efficacy of ivermectin-albendazole against T. trichiura compared to the standard single-dose albendazole therapy, thereby supporting the use of this co-administration in preventive chemotherapy programs.<sup>5</sup> Large-scale relative randomized controlled trials are essential to confirm these findings.

The microbiome composition is possible to

change owing to interactions between helminth and anthelminthic treatment, though a direct impact of treatment on microbiome composition has not been observed; albendazole does not affect the microbiome composition.<sup>1</sup>

Interesting, antidepressant medications like sertraline and paroxetine, as well as antipsychotic ones like chlorpromazine, have been shown to appear an anthelmintic action. Particularly, they are attributed among other helminths to prevent both hatching and development of *A. caninum*.<sup>83</sup>

Of note, anthelminthic therapy is suggested in endemic countries during pregnancy and many studies showed a significant benefit in anemia treatment when iron supplements were combined with these drugs. Despite that, only Madagascar, Nepal and Sri Lanka did so systematically until 2008.<sup>60</sup>

Although sufficient chemotherapy exists, there is a high rate of re-infection in endemic regions. A recent review and meta-analysis tried to highlight this problem and correlate to water, sanitation, and hygiene deficiencies. Piped water usage, hand-washing and wearing shoes were associated with significantly lower odds of infection with hookworm, while no evidence of a statistically significant association between sanitation and hookworm were found.<sup>84</sup> Finally, recent data show that skin-penetrating human parasitic hookworms and threadworms display adaptive host-seeking behaviors that are based on their temperature experience, thereby opening up possibilities for new intervention strategies.<sup>85</sup>

#### Conclusion

Hookworms' infestation still remains a significant burden in many rising economies and large-populated countries. The financial consequences are also enormous. In spite of hookworm's classification as a "neglected tropical disease," its financial and health burden surpassed published estimates for a number of diseases that have received comparatively more attention than hookworm like rotavirus. Additionally, large countries that tend to evolve to higher income countries such as Brazil and China, still confront remarkable hookworm burden.<sup>86</sup>

Endeavors for elimination of the disease have, partially at least, failed. Vaccination is a promising idea that might be feasible in the future.<sup>87</sup> Alertness of physician along with clinical suspicion when patients from endemic areas with compatible picture admitted to emergent evaluation is one of the best investment for controlling the disease. IDA with eosinophilia, and obscure gastrointestinal bleeding should be further clarified and treated.

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## **Conflicts of Interest Statement**

Authors declare no conflicts of interest.

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