Chapter 2

Strongyloidiasis Worldwide: Review and Literature Updates

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Strongyloides Stercoralis Overview

History

Strongyloides stercoralis is a widespread, soil-transmitted parasitic intestinal worm which infects millions of people worldwide [1]. It was first described in 1876 when the military physician Louis Normand had tested stool specimens taken from soldiers who returned from French colony in Vietnam and who suffered from severe diarrhea and other gastrointestinal symptoms [2], and at that time S. stercoralis was named as the military worm [3]. Thereafter, in 1902 and after several changes for name of this parasitic worm, Stiles and Hassal suggested giving it the name *Strongyloides stercoralis* [3]. *S. stercoralis* is regarded nowadays as a member of the phylum Nemathelminths, class Nematoda (nema: threadlike). The genus *Strongyloides* contains 52 species that infect gastrointestinal tracts of numerous vertebrates such as mammals, birds, reptiles and amphibians. Among the 52 species, only *S. stercoralis*, and *S. fulleborni*, are the most important/frequent species which are known to infect human, dogs and cats [4].
**Morphology and Function**

*Strongyloides stercoralis* possesses structures and systems which plays a vital role in maintaining the adaptation of this worm to various conditions and differentiate it from other helminthes. The outermost covering, the cuticle (or exoskeleton) of this parasitic worm contain a non-cellular substances such as collagens, lipids, carbohydrates, and glycoproteins which protect the parasitic worm from the harmful environmental conditions inside the host gastrointestinal tract maintain its structural integrity [4,5]. The digestive system begins with a mouth that contains lips, teeth, and dental plates. The esophagus extends to the intestine that ends in the rectum, which opens to the outside through the anal opening. The digestive system is well-adapted for active digestion of the host’s gut contents, cells, blood, or cellular breakdown products [3,6].

The reproductive system of *Strongyloides* is highly developed with separate-sexes. The female reproductive system consists of vulva, uterus, in which eggs can be readily seen, and oviducts. The male reproductive system encloses testis which is attached to a vas deferens and a seminal vesicle [3,5]. The secretory-excretory system which is responsible for the parasitic adaptation of this worm to different environmental conditions such as fresh and salt water, soil, and variant organic tissues, especially the intestinal tracts [5]. The muscular system permits body movement and internal system functions such as digestive and reproductive systems. The movement of muscles elsewhere in the body is controlled via highly organized nervous system [6].

**Strongyloides Stercoralis Life Cycle**

The life cycle of S. stercoralis consist of an egg, four larval (immature worm) stages and an adult stage, in which the reproductive and associated structures become fully developed and functional (figure 1). When larvae grow, they increase in size, and then modification on the old cuticle coat occurs to accommodate the new size. The cuticle must either grow or being replaced through a process known as molting. In general, nematodes grow between molts and after the final molt [7]

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**Figure 1:** *Strongyloides Stercoralis* Life Cycle. Adapted From P. F. Whitefield.,[8].
The adult females live in the tissue of the upper segments of the small intestinal (the duodenum and jejunum). There are apparently no adult males beside females because they are eliminated from the body in the early infection [9]. Adult female reproduce parthenogenetically (virgin birth), which is a form of asexual reproduction by which the adult female worm yields embryos without sexual mating with adult male worm, and those embryos grow and develop normally [6,10]. Therefore, *S. stercoralis* is unique among worms causing human disease in its ability to multiply asexually within the host, thus completing the entire life cycle within a single host [11]. The result of parthenogenetic reproduction is the deposition of more than 100,000 eggs per day [12]. The eggs of *S. stercoralis* are rarely seen in stool since they hatch in the intestine producing rhabditiform larvae (L1). The eggs of *S. fuelleborni* are shed in stool, and the species is so called egg-ly-ing *Strongyloides*. The eggs of the free-living and the parasitic females are morphologically identical (ellipsoidal and thin-shelled) and fully embryonated when laid, [3].

Rhabditiform larvae move slowly from the intestinal wall to the lumen. Some of them pass with feces to the external environment and can be detected in fecal samples, while others stay in the bowel for parasitic life cycle [13,14]. In the environment, the L1 rhabditiform larvae may either undergo 4 molts to become mature adult male and female worms; or directly molt into infective L3 filariform larvae which have the ability to to re-penetrate the skin of a new host [14]. L2 rhabditiform larvae are larger than L1 larvae. They are more mature and differentiated and being diagnostic for the infection from clinical samples. L2 larvae undergo major structural changes, molt and grow to become infective filariform L3 larva [3,15].

Infective L3 filariform larvae are more mature, cylindrical, and fast-moving worms. They have some features of adult worms, and they are able to initiate the infection [14,15]. In general L3 larvae are produced via two cycles of development:

**Direct Cycle**

L1 rhabditiform larvae stay in the bowel for parasitic life cycle, they directly molt twice to become infective L3 filariform larvae that re-infect the same host either by penetrating intestinal wall or skin of anal opening and circulate throughout the body until they reach the intestine again and continue molting into adult female that might survive up to 5 years [12,13].

**Indirect Cycle**

L1 rhabditiform larvae passed with feces to the external environment. Under warm moist conditions they continue growing and molting to become adult females that continue in the free-living stage, they mate with adult males and reproduce sexually to yield free-living genera-
tions of L1 rhabditiform larvae that either continue (under warm moist conditions) through free-living cycle; or molt directly (under harsh environmental conditions) to L3 filariform larvae that search for another host to penetrate and infect [12,16].

Routes of Transmission

There are several routes by which the human can get the infection with *S. stercoralis*. From the soil, the larvae can transmit to the host via active penetration of the skin (mainly hand palm and foot sole) [17]. The transmission within a community could be predominantly related to human habits in regard to eating, defecation, personal hygiene and environmental sanitation [18]. Vegetables and herbs that grow on grounds with high humidity near drainage areas serve as reservoir for the infection, since these are places with higher likelihood of harboring viable parasites. This was supported by a study in which fruits, vegetables, and herbs were separately washed by distilled water, and the used water samples were examined microscopically. Among the expected parasites, only *S. stercoralis* larvae were identified in the three different items. It was concluded that the vegetable sellers and the food handlers are at high risk of acquiring the infection [19]

However, still some unusual routes of transmission had been reported such vertical transmission (mother-to-child transmission) of *S. stercoralis* in dogs and other hosts, but not in human [20]. A person can be at risk of getting the infection when become in close contact with infected animals [12] or human, particularly hospitalized patients [21], handicapped persons [22] and donor-derived transmission[23]. However, the application of standard precautions is sufficient for preventing *S. stercoralis* passage from hospitalized patient to people in their surround, and once the infection is diagnosed, physicians should alert for person-to-person spread of *S. stercoralis*, regardless the clinical status of the infected person [24]. The trans-mammary transmission of *S. stercoralis* larvae has been demonstrated in several animals and it is possible to occur in man [25].

Strongyloidiasis Epidemiology

Strongyloidiasis is characterized by nonspecific symptoms which involve skin, lung and gastrointestinal tract. Strongyloidiasis was known for many years as Cochinchina diarrhea [2] and regarded as a common cause of morbidity and mortality throughout the world, particularly in developing countries [26].

The occurrence of strongyloidiasis varies widely among different countries, localities, and socioeconomic backgrounds with a prevalence that can be as high as 50% in endemic countries [27]. Tropical, temperate and heavy rainfall areas such as Southeast Asia, Latin America, sub-Saharan Africa, and parts of the Southeastern Unit-
ed States, are considered as endemic areas [16]. There is no precise estimation available on the global prevalence and distribution of strongyloidiasis, since the infection is sometimes misdiagnosed or difficult to be detected due to poor sensitivity of the applied diagnostic tests, as well as, the absence of gold standard method for its proper diagnosis. Therefore, *S. stercoralis* is considered to be the most neglected parasite among soil-transmitted helminths infections [28].

Worldwide the prevalence of *S. stercoralis* infection has been estimated as 30-100 million people, with increased infection prevalence in patients with compromised immunity [29]. However, recent works indicated severe underestimation for true prevalence of *S. stercoralis* and reported that at least 370 million infected people were probably infected worldwide. Moreover, the majority of previous gastrointestinal parasitic infection surveys were designed to investigate general parasites burden, rather than specific diagnosis for *S. stercoralis*. The Diagnostic method applied in these surveys was stool examination but not any of the techniques that enhance the detection of *S. stercoralis* (such as the Baermann method or agar culture plate); therefore, previous data were mostly built on the bases of diagnostic methods of suboptimal sensitivity [30].

The epidemiology of *S. stercoralis* infection has been studied in details in Thailand, especially among school-

children [31]. In a study, the prevalence of helminths infection among Southern Thai children from four primary schools was investigated. It was found that nearly 50% of the schoolchildren were infected. Fourteen (1.8%) children were positive for *S. stercoralis*; a percentage was 6-30 times greater than previous reports performed in the same country [32]. Other investigations in northern and central Thailand reported different prevalence rates ranging from 2.3% to 28.9% [31]. However, in highly endemic areas, *S. stercoralis* re-infection can occur as early as 2 months after treatment. However, 4 months post-treatment, recurrent infection might occur in the treated population [18].

Collectively, systematic reviews of the literature in the last 25 years (1989 to 2014) estimated a country-wide prevalence rates of strongyloidiasis for South-East Asia and summarized the risk factors and most commonly applied diagnostic methods (table 1) [28].

The infection with *S. stercoralis* is frequently imported from endemic to non-endemic areas by travelers and immigrants [33]. In England, the analysis of laboratory and clinical data from 192 patients with proven strongyloidiasis found that 64 of infected patients were travelers and 128 were immigrants from Africa, Asia, the Caribbean, and in South America [34].
Table 1: Strongyloidiasis Clinical Epidemiology in Southeast Asia. Adapted from F. Schar [32].

<table>
<thead>
<tr>
<th>Country(^{a})</th>
<th>Prevalence range</th>
<th>Risk factors</th>
<th>Applied diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand</td>
<td>0.05-57%</td>
<td>Rural areas/thiamine deficiency/AIDS</td>
<td>FECT, DS, KAP, ELISA</td>
</tr>
<tr>
<td>Cambodia</td>
<td>2.6-44.7%</td>
<td>Male/age&gt;20yrs/poor hygiene/CNS</td>
<td>KAP, BM, DS, PCR</td>
</tr>
<tr>
<td>China</td>
<td>0.04-17.9%</td>
<td>---</td>
<td>KAP, DS, BM</td>
</tr>
<tr>
<td>Indonesia</td>
<td>0.8-5.4%</td>
<td>Wet areas</td>
<td>KAP, DS, FECT, HM, KK, PCR</td>
</tr>
<tr>
<td>Laos PDR</td>
<td>1.4-41%</td>
<td>Male/age&gt;20yrs</td>
<td>KK, KAP, FECT, BM</td>
</tr>
<tr>
<td>Malaysia</td>
<td>1.2-39%</td>
<td>---</td>
<td>FECT, PCR, ELISA</td>
</tr>
<tr>
<td>Vietnam</td>
<td>0.1%(^{b})</td>
<td>---</td>
<td>DS</td>
</tr>
</tbody>
</table>

\(^{a}\)No data were available from Brunei, Singapore, Philippines and Myanmar. \(^{b}\)This is the estimated prevalence, since only single study was reported.

CNS: Childhood nephrotic syndrome. BM: Baermann test; DS: direct smear; ELISA: enzyme-linked immunosorbent assay; FECT: formalin-ether concentration technique; HM: Harada Mori filter paper technique; KAP: Koga Agar plate culture; KK: Kato-Katz technique; PCR: polymerase chain reaction.

Strongyloidiasis is becoming an important parasitic disease in the United States [35], where 347 cases of strongyloidiasis-associated deaths occurred between 1991 and 2006, in which deaths had occurred primarily in the southeastern states among elderly, white colored, Hispanic race, and male gender [36]. Moreover, during the 1990s in Los Angeles state, 40 to 50 strongyloidiasis cases were reported yearly and turned into 5 cases per year. In the 20th century and thereafter, strongyloidiasis was removed from the reportable disease list in that state. However, during 2013-2014, an unusual disease occurrence was reported with new 43 cases and caused unexpected relapse for the increased incidence of strongyloidiasis in the same state. That peak was attributed to the application of strongyloidiasis screening guidelines that was recommend for all persons with a history of *Strongyloides* exposure that was at risk for *Strongyloides* hyper infection and disseminated syndromes. Thus the change in screening protocols, rather than an actual increase in disease prevalence, was behind the relapsed incidence [37].

**Pathology, Pathogenesis and Risk Factors for Strongyloidiasis**

Strongyloidiasis is caused by two species of the intestinal nematodes; *S. stercoralis* and *S. fuelleborni*. *S. stercoralis* is the most common and globally distributed species of medical importance however, other species, *S. fuelleborni* is less prevalent and cases are found sporadically in Africa and New Guinea especially in monkeys and may produce limited infections in humans[2]. *S. stercoralis* is the fourth most clinically significant and important intestinal nematode infection in the world, but still the infection is not believed to be one of the leading causes of morbidity worldwide. *S. stercoralis* is unique among other intestinal helminths in its ability to cause infections...
which persist for long time, which can be life-long in human host. Strongyloidiasis might result in asymptomatic dormant infection, mild symptomatic disease or fatal disseminated infection [48].

Table 2: Worldwide Studies of Strongyloidiasis in The Recent Five Years.

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of Specimens Analyzed</th>
<th>S. stercoralis Prevalence</th>
<th>Year (References)</th>
<th>Applied diagnostic method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honduras</td>
<td>712</td>
<td>5%</td>
<td>2016 [38]</td>
<td>BM</td>
</tr>
<tr>
<td>Lao PDR</td>
<td>327</td>
<td>41%</td>
<td>2016 [39]</td>
<td>KK, APC, Sequencing</td>
</tr>
<tr>
<td>Poland</td>
<td>90</td>
<td>7.78%</td>
<td>2011 [40]</td>
<td>DM</td>
</tr>
<tr>
<td>Cambodia</td>
<td>302</td>
<td>24.2%</td>
<td>2014 [41]</td>
<td>KAP, HM</td>
</tr>
<tr>
<td>Spain</td>
<td>231</td>
<td>19%</td>
<td>2012 [42]</td>
<td>FECT, APC, ISM, RT-PCR</td>
</tr>
<tr>
<td>USA</td>
<td>189</td>
<td>15%</td>
<td>2012 [43]</td>
<td>ELISA</td>
</tr>
<tr>
<td>Spain</td>
<td>157</td>
<td>26.8%</td>
<td>2014 [44]</td>
<td>ELISA</td>
</tr>
<tr>
<td>Australia</td>
<td>249</td>
<td>11.6%</td>
<td>2015 [45]</td>
<td>ELISA</td>
</tr>
<tr>
<td>Malaysia</td>
<td>192</td>
<td>5.7%</td>
<td>2014 [46]</td>
<td>FECT, RT-PCR, ELISA</td>
</tr>
<tr>
<td>USA</td>
<td>378</td>
<td>1.9%</td>
<td>2014 [47]</td>
<td>ELISA</td>
</tr>
</tbody>
</table>

BM: Baermann test; DS: direct smear; ELISA: enzyme-linked immunosorbent assay; FECT: formalin-ether concentration technique; HM: Harada Mori filter paper technique; KAP: Koga Agar plate culture; KK: Kato-Katz technique; PCR: polymerase chain reaction; APC: agar plate culture.

The third-stage filariform larva L3 is the infective stage that can initiate the infection with S. stercoralis and the clinical signs and symptoms of the infection are accompanied with every site and organ involved during the parasite pathological cycle [49]. Within 12-18 hours of the penetration of L3 filariform larvae into intact skin it passes through the dermis, a phenomenon termed larva currens, from which it will reach the blood stream. During this phase, transient itchy, linear and urticarial rash-like manifestation, and skin lesions accompanied with edema will be evident at the site of penetration [50,51]. After that, L3 filariform larvae migrate into cutaneous blood capillaries and successfully carried to the lungs; where they enter the alveoli and go up to the respiratory tree and stay for 1 week. The host immune response may delay the progress of the larvae, so the will be greater for the larvae to mature to adult worms which have the capability to invade the bronchial epithelium causing pulmonary symptoms (Loeffler’s pneumonia) such as dry cough, throat irritation, bronchopneumonia and wheezing [52]. Thereafter the worms are swallowed and continue their way to the stomach then to the duodenum and jejunum where they mature into egg-lying adult females and stay 2 weeks before symptoms started. The total incubation period of S. stercoralis in human body is around 1 month [12,13,25,49]. In rare and severe infections, duodenal obstruction might occur [53]. Diarrhea, abdominal pain, nausea, and anorexia are common gastrointestinal symptoms [54]. Strongyloidiasis encompasses four clinical syndromes: i) acute infection; ii)
chronic intestinal infection and autoinfection; iii) hyperinfection syndrome; iv) dissemination syndrome [27].

**Acute Strongyloidiasis**

In the acute infection with *S. stercoralis*, the early migration of the running filariform larvae throughout the host's body during the parasitic life cycle causes non-specific symptoms which involve the skin (itchy), pulmonary system (pneumonia) and gastrointestinal tract (abdominal discomfort) [16]. Risk factors and predisposing conditions have been described for the primary acute infection, including people with socioeconomic conditions that make them risky for fecal-oral contact and the exposure to *S. stercoralis* reservoirs [17]. Symptomatic autoinfection occurs in people living in endemic areas and those with diabetes, malnutrition, alcoholism, or any immunodeficiency condition. However, it is extremely uncommon to see acute infection in clinical practice; reports are mainly among volunteers [35].

**Chronic Strongyloidiasis and Autoinfection**

Chronic strongyloidiasis and autoinfection develop when the acute infection is not completely treated. Chronic infection is probably maintained by a relatively low and stable number of adult worms that reside within the intestine and survive by means of well-regulated autoinfection [14,27]. Autoinfection occurs when some L1-rhabditiform larvae, transform into invasive L3-filariform larvae through direct development cycle and re-enter the mucosa of the intestine or penetrate the peri-anal skin to finally enter blood circulation [27]. Autoinfection allows the worms to build-up in the host, enabling them in maintaining themselves in the absence of any other infection from an external source. Autoinfection results in the intermittent recurrence of the symptomatic episodes [25]. Chronic infection is occasionally seen in immigrants, travelers, and refugees, while it is seen mainly in endemic countries [35]. In normal circumstances, the autoinfection does not seem to be a problem, and the infection may present as asymptomatic or minimally symptomatic chronic infection through autoinfection cycles in the normal host and persist for decades [49]. In addition, since the host immunity is not protective against the autoinfective-stage larvae, this explains the development of advanced stages of the disease in certain clinical conditions that facilitate autoinfective larvae activation [55].

**Hyperinfection Syndrome (HS)**

Hyperinfection describes the syndrome of uncontrolled accelerated autoinfection manifested by acute or insidious symptoms [16]. Disruption in the controlling role of immune system elements will trigger and increase parasitic transformation from rhabditiform larvae into filariform larvae, followed by replication and migration from the small intestine to the pulmonary and gastrointestinal tracts [56]. Clinically, the HS is characterized by the exacerbation of the gastrointestinal and pulmonary
symptoms that are attributed to the increased larval migration throughout the same organs involved in the pulmonary autoinfection cycle (i.e. GI tract, lungs, and skin) [26]. The distinction between HS and autoinfection is quantitative and still not strictly defined. The detection of increased numbers of rhabditiform and filariform larvae in stool and/or sputum is the hallmark of HS [16,57].

In France, Geri et al., [58] had performed a major retrospective multicenter study to review cases of HS admitted to the intensive care unit over 40 years (1970-2010). The study reported 133 cases, the median age was 53 years and 72.2% were males. Immunosuppressive medications were given to 127 patients of them, mostly long-term corticosteroid treatment (83.5%). The common underlying immune disorders were autoimmune diseases (24.8%), hematological malignancies (20.3%) and AIDS (10.7%). Fever, respiratory and gastrointestinal symptoms were the most common reported clinical manifestation, whereas the mortality was 60%. The study concluded that the HS was associated with poor outcome, in particular, when associated with septic shock and mechanical ventilation.

**Disseminated Infection (DI)[SH]**

The term disseminated infection is often used to describe the widespread dissemination of larvae to organs outside the *S. stercoralis* is autoinfection cycle. Filariform larvae can be visualized in many organs including the lungs, liver, spleen, the gall bladder and pancreas. Clinically, DI of *S. stercoralis* is more severe and difficult to be controlled [13,16].

HS and DI are usually accompanied by secondary bacteremia, which is the primary cause of death [26]. Intestinal microbial commensals may be collected on the surface of autoinfective filariform larvae or they may gain access to the circulation through intestinal ulcers and find their way to the circulation [16,59]. Hyperinfection syndrome is frequently misdiagnosed as Gram-negative sepsis or acute respiratory syndrome [26,60]. In addition, some case reports documented mixed microbial infections in patients with strongyloidiasis [61-64]. Table 3 summarizes worldwide case reports for strongyloidiasis in the past few years.

The alternation in the immune status of the host is thought to be the leading risk factor for the development of hyperinfection and disseminated syndromes, in spite of the few case reports that documented DS in patients with normal intact immunity [16,78].

Immunosuppression conditions associated with HS and DS include: viral infections (such as human T-lymphotropic virus type-1 (HTLV-1) and human immunodeficiency virus (HIV)); hypogammaglobulinemia syndrome; debilitated conditions (such as malnutrition and alcoholism) and exposure to immune suppressive agents (such as chemotherapy and total body irradiation) [16].
The association of HTLV-1 and the development of HS is more frequent and critical than the HIV infection, this is attributed to immunological aspects [16]. In Japan, Hirata et al.,[80] had evaluated the relationship between strongyloidiasis and infection with HTLV-1 in a prospective study over a period of 11 years. The study concluded that co-infection with HTLV-1 impairs the immune response against *S. stercoralis*. Furthermore, a very recent study reported that co-infection with HTLV-1 can cause normal or lower levels of serum IgE during *S. stercoralis* infection [81]. On the other hand, Zali et al.,[82] had performed a study in Iran to determine the prevalence of intestinal parasitic infections among 206 HIV-positive patients. The overall prevalence was 18.4%. Among detected parasites, *S. stercoralis* was reported in two cases only (0.9%).

A retrospective analysis was performed between 1971 and 2003 on cancer patients of various age groups at a comprehensive cancer center in the United States. Patients were under various types of chemotherapy regimens. It was found that the overall frequency of strongyloidiasis infestation was 0.8 per 10000 patients. It means that only 25 patients were found to have strongyloidiasis. Among those infected patients, 52% of them had solid organ malignancy (e.g. breast, lung, and colon cancers) and the remaining had hematologic malignancy (e.g. leukemia and lymphoma). It was concluded that strongyloidiasis was uncommon in patients with cancer in that country [83].

### Table 3: Reported Cases on All Stages of Strongyloidiasis.

<table>
<thead>
<tr>
<th>Strongyloidiasis type/ Risk factor</th>
<th>No. of cases</th>
<th>Age (years)/ Gender</th>
<th>Country</th>
<th>Treatment/Outcome</th>
<th>Diagnosis</th>
<th>Year/Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic/immune suppressive agents</td>
<td>2</td>
<td>3, male / 3, male</td>
<td>Malaysia</td>
<td>Albendazole/cured</td>
<td>Real-time PCR ELISA IgG, IgG4, stool microscopy</td>
<td>2012/65</td>
</tr>
<tr>
<td>Acute/ poor hygiene, contact domestic animals</td>
<td>1</td>
<td>87, female</td>
<td>USA</td>
<td>Albendazole/cured</td>
<td>Stock microscopy</td>
<td>2014/66</td>
</tr>
<tr>
<td>Chronic/ immune suppressive agents</td>
<td>8</td>
<td>4, 14, 43, male, 38, 38, 41, female</td>
<td>Malaysia</td>
<td>Stock treated/undiagnosed</td>
<td>Real-time PCR ELISA IgG, IgG4, stool microscopy</td>
<td>2016/85</td>
</tr>
<tr>
<td>Disseminated/ immune suppressive agents</td>
<td>1</td>
<td>Male</td>
<td>China</td>
<td>Albendazole/death</td>
<td>Histology/radiology/microscopy</td>
<td>2016/66</td>
</tr>
<tr>
<td>Hyperinfection/ immune suppressive agents</td>
<td>1</td>
<td>59, female</td>
<td>India</td>
<td>Ivermectin/death</td>
<td>Microscopy</td>
<td>2016/66</td>
</tr>
<tr>
<td>Hyperinfection/ immune suppressive agents</td>
<td>1</td>
<td>50, female</td>
<td>Ethiopia</td>
<td>Ivermectin/death</td>
<td>Histology/stool microscopy</td>
<td>2015/70</td>
</tr>
<tr>
<td>Acute/immune suppressive agents</td>
<td>1</td>
<td>67, male</td>
<td>Korea</td>
<td>Albendazole/cured</td>
<td>Stock microscopy/expanding</td>
<td>2015/71</td>
</tr>
<tr>
<td>Hyperinfection/ immune suppressive agents</td>
<td>1</td>
<td>76, male</td>
<td>Brazil</td>
<td>Ivermectin/death</td>
<td>Histology</td>
<td>2014/72</td>
</tr>
<tr>
<td>Hyperinfection/ immune suppressive agents</td>
<td>1</td>
<td>76, male</td>
<td>USA</td>
<td>Ivermectin/death</td>
<td>Stock microscopy</td>
<td>2015/72</td>
</tr>
<tr>
<td>Acute/immune suppressive agents</td>
<td>1</td>
<td>62, female</td>
<td>Japan</td>
<td>Ivermectin/death</td>
<td>Intrathoracic discharge microscopy</td>
<td>2015/74</td>
</tr>
<tr>
<td>Acute/ malnourished</td>
<td>1</td>
<td>39, female</td>
<td>Turkey</td>
<td>Albendazole/cured</td>
<td>Stock microscopy</td>
<td>2015/75</td>
</tr>
<tr>
<td>Acute/ immune suppressive agents</td>
<td>1</td>
<td>74, male</td>
<td>China</td>
<td>Albendazole/cured</td>
<td>Bronchoalveolar lavage fluid/stool microscopy</td>
<td>2015/61</td>
</tr>
<tr>
<td>Chronic/ immune suppressive agents</td>
<td>1</td>
<td>27, female</td>
<td>Germany</td>
<td>Albendazole/death</td>
<td>Stock microscopy</td>
<td>1999/11</td>
</tr>
<tr>
<td>Hyperinfection/ immune suppressive agents</td>
<td>9</td>
<td>38, 47, male</td>
<td>Singapore</td>
<td>Ivermectin/cured</td>
<td>Histology/ELISA/thrombocytopenia microscopy</td>
<td>2009/66</td>
</tr>
<tr>
<td>Hyperinfection/ immune suppressive agents</td>
<td>1</td>
<td>79, male</td>
<td>Malaysia</td>
<td>Albendazole/cured</td>
<td>RT-PCR/ELISA/thrombocytopenia</td>
<td>2012/76</td>
</tr>
<tr>
<td>Disseminated/ immune suppressive agents</td>
<td>1</td>
<td>69, male</td>
<td>Korea</td>
<td>Albendazole/cured</td>
<td>Histology</td>
<td>2003/77</td>
</tr>
<tr>
<td>Disseminated/not presented</td>
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<td>61, male</td>
<td>Taiwan</td>
<td>Albendazole/cured</td>
<td>Pericardial fluid/stool microscopy</td>
<td>2002/78</td>
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<tr>
<td>Disseminated/ immune suppressive agents</td>
<td>1</td>
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<td>Malaysia</td>
<td>Albendazole/death</td>
<td>Stock microscopy</td>
<td>2010/79</td>
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<tr>
<td>Hyperinfection/ immune suppressive agents</td>
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<td>64, female</td>
<td>USA</td>
<td>Albendazole/cured</td>
<td>Bronchoalveolar lavage microscopy</td>
<td>2005/89</td>
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However, still some cases of DS were diagnosed in patients with normal immunity. In the case reported by Lai et al., [78] on the patient with mild symptomatic DS, the patient was immunocompetent in spite of the presence of S. stercoralis larvae in the pericardial fluid and stool samples. The same finding was reported by Lahn et al.,[84] in immunocompetent woman with central nervous system strongyloidiasis after being in Sri Lanka for one month. In both cases, it was postulated that DS in immunocompetent patients was attributed to the prolonged administration of steroid which activate the worms and facilitate their migration to other organs.

Steroids are the most common drugs which are associated with strongyloidiasis hyper infection [85]. Hyper infection was resulted from low or high dose steroids, locally injected steroids, pharmacologically administered adrenocorticotropic and high levels of endogenous adrenocorticotropic [16]. The explanation for the ability of steroids in inducing strongyloidiasis hyper infection is attributed to their suppression effect on eosinophil’s and reduction of their levels in the circulation. In addition, steroids act on specific receptors available on the cell membrane of T lymphocytes called glucocorticoid receptors (GCRs) causing T lymphocytes dysfunction and induce cell death in immature lymphocytes. Some authors have suggested that exogenous and endogenous steroids may also have a direct effect on the parasites themselves by increasing the level of ecdysteroid-like substances (parasitic molting and sex hormones) in the body tissues, including the intestinal walls where the worms reside. These substances signal to rejuvenate the reproductively latent adult females and to accelerate the eggs hatching and the transformation of rhabditiform to invasive filariform larvae leading to increased number of filariform larvae and their output [14,16,27,86].

While steroids induce HS by causing immune suppression, as well as direct activating effect on the adult worms; vinca alkaloids chemotherapy (such as vincristine) was reported to enhance larval molting and transformation by decreasing and slow-down the intestinal motility, thus giving a chance for the transformation of rhabditiform to filariform larvae [16]. Many case reports attributed the onset of acute episode of S. stercoralis are actually associated with the intake of steroids doses [59,78,84,87-90].

**Host Immune Response**

During the primary stage of infection, the presence of S. stercoralis larvae in the tissues of skin, lungs, and the small intestine, beside their released secretions initiate immune response which is directed against all stages of the parasite. S. stercoralis larvae induce excessive immune response more than adult worms because of their metabolic activity, thus producing more proteins and secretions that are recognized by the host immune system as foreign bodies [14].
IgG is the most abundant circulating antibody which is produced against *S. stercoralis* and its level increase in 95% of patients during the acute infection and remains elevated during the chronic state. However, the production of IgG in patients with strongyloidiasis might be suppressed in certain clinical conditions such as infection with HTLV-1 [3]. There are four subclasses of IgG: IgG1, IgG2, IgG3, and IgG4 (which participate in the humoral response against *S. stercoralis*). It was reported that the subclasses IgG1 and IgG4 were the major ones of IgG response, and they differ in the timing of production during the infection [91]. Genta et al., [92] had assessed the role of these subclasses by analyzing the response of each subclass in immunocompetent patients with uncomplicated infection and in immune-suppressed patients with DS. It was found that IgG4 response was the most prominent in both patients groups due to its ability to recognize more antigens than other three subclasses. In addition, IgG1 levels increased upon the early infection and then declined, while IgG4 level is usually elevated in cases of chronic and treatment-resistant patients, especially in males. The study also reported that IgG4 and IgG2 levels increased in immunocompetent more than in immunocompromised patients.

Another study investigated the host factors which might be associated with the response to treatment. Patients with proven strongyloidiasis were examined for *S. stercoralis*-IgG4 and the effect of treatment on its level. It was found that the cure rates were slight, but not significantly, lower in males than in females, and a significantly higher level of *S. stercoralis*-specific IgG4 antibody was observed in males than in females. In addition to significant difference in IgG4 antibody titer between cured and non-cured male patients. These results suggested that elevated *S. stercoralis*-specific IgG4 antibody titer would be associated with resistance to treatment of *S. stercoralis* infection, especially in males [93].

Along with IgG1, the level of IgE increased in 90% of patients during the course of acute infection, but declined later in chronic infection and co-infection with HTLV-1 [3]. A study performed to evaluate total IgG, IgG1, IgG4, and IgE antibody responses in human strongyloidiasis. One hundred serum samples were withdrawn from three groups of volunteers: patients who were shedding *S. stercoralis* larvae in feces (group I), patients with other intestinal parasites (group II), and intact subjects (group III). They found that levels of total IgG, IgG1, IgG4, and IgE were significantly higher in patients of group I than in groups II and III, with a significant positive correlation between IgE versus IgG4; and IgG1 versus IgG4. In addition, the detection of specific IgG1 and IgE antibodies was more specific when compared to the detection of total IgG and IgG4 antibodies in patients with strongyloidiasis. They concluded that the detection of specific IgE, IgG1, and IgG4 subclasses rather than total IgG would improve the serodiagnosis of human strongyloidiasis.
study also concluded that the antibody levels detected in patients may be correlated with the disease status. For example, single-positive IgE+/IgG4− patients might represent a more recent infection, whereas those with single-positive IgE−/IgG4+ more likelihood related to a chronic infection. On the other hand, patients with single-positive IgE−/IgG1+ or IgG1+/IgG4− might be associated with a longer-standing chronic infection [94].

IgA is responsible for mucosal immunity in respiratory and gastrointestinal tracts [95]. It was reported that the IgA response is more significantly elevated in occult infection (i.e. no larvae detected in stool) [96]. Serum IgA level was measured in 104 presumably immunocompetent individuals with chronic uncomplicated strongyloidiasis and in 15 immunocompromised patients with proven S. stercoralis infection. It was shown that most patients with strongyloidiasis mount specific IgA responses against filariform larval antigens, and these antigens differ from those recognized by IgG [97]. However, the immune response is not protective since it would not eradicate all parasitic stages in the host's body. Therefore, screening of cured individuals, as well as follow-up diagnosis in treated patients are required [55].

There are several suggested mechanisms by which S. stercoralis can suppress host immune response. S. stercoralis larvae that reside in the tissues exert a strong anti-inflammatory effect that inhibits the response of both eosinophils and neutrophils by releasing chemicals such as glycans and lectins (block eosinophil migration to the site of infection), parasitic proteases (degrade chemical signals between immune cells), serpins (block neutrophil proteases); and parasitic antioxidants that inhibit eosinophil lethal attack [98]. On the other side, infective filariform larvae present during hyper infection syndrome have the ability to modify their body and evade the host immune response [35].

**Laboratory Diagnosis**

Strongyloidiasis is suspected in individuals with unexpected eosinophilia, suggestive serologic findings, or having clinical signs and symptoms typical to those observed in strongyloidosis in the skin, lungs, and gastrointestinal tracts [2,14]. In addition, screening for strongyloidiasis can be done for asymptomatic travelers and immigrants who visited endemic areas [34], as well as immune-suppressed patients in endemic areas [99].

S. stercoralis is one of the most difficult helminths to diagnose since the definitive diagnosis needs direct visualization of the parasite from clinical samples, in addition to the absence of agreeable gold standard test and ideal screening strategy to investigate the parasite [100]. Therefore, several detection methods including microscopy, culture methods, specific antibody detection, and molecular techniques were applied in various combinations [101].
Microscopic Examination

Stool Microscopy

Microscopic examination of stool samples is the routine method which is used for the diagnosis of *S. stercoralis* since it is non-invasive and easy to be performed as an initial screening procedure [3]. *S. stercoralis* rhabditiform larvae are diagnostic for acute, chronic, and autoinfection, while the recovery of filariform larvae and adult females, and occasionally males and eggs, occurs in hyper infection and disseminated syndromes [49,102]. The rhabditiform larvae in stool can be directly examined by microscopy in wet mounts preparation by suspending the stool sample with physiological saline or with Lugol's iodine stain [2]. The rhabditiform larvae are 220 to 260 µm in length and can be differentiated from hookworms by their typical esophageal structure which is club-shaped in the anterior portion, short bucal cavity, and a posterior bulb [11,15]. *S. stercoralis* filariform larvae are 540 to 570 µm in length and can be differentiated from hookworm filariform larvae by their long esophageus and notched tail [11]. *S. stercoralis* adult worm is slenderical, non-segmented and thread-like with an average of 37 µm in diameter of. The adult male is less than 1.2 µm in length; with a bent tail which gives the worm its J-shaped appearance. Parasitic females are 2-2.8mm long and transparent in nature, making them difficult to be seen with the naked eye, even when they are purified from stool material [3].

Direct microscopic examination of stool specimens is not sensitive in asymptomatic individual due to decreased larval output (<25 larvae per gram of stool) [49]. To improve this sensitivity, investigators have recommended the followings: (1) the examination of three or seven consecutive daily stool specimens (2) collection of alternative specimens, such as duodenal and lungs fluids (3) using a combination of methods for diagnosis (4) apply additional processing procedures for stool samples such as formalin-ethyl acetate concentration; Harada-Mori filter paper culture technique; Baermann funnel technique and agar plate culture [2]. Comparative studies were heavily done to determine the best sensitivity performance for different sample processing techniques. A study performed in Thailand to determine the efficacy of formalin-ethyl acetate concentration (FAC), Harada-Mori culture, and agar plate culture methods in the detection of *S. stercoralis* and hookworm infection. Out of 475 subjects, the total positive cases for *S. stercoralis* by the three methods were 95. *S. stercoralis* infection was best detected by agar-plate culture method; since the detection rate was 94.7%, while Harada-Mori and formalin-ethyl acetate concentration showed only 50.5% and 3.2%, respectively. The study recommended that agar-plate culture can be performed after negative results of suspected cases obtained by routine laboratory methods and it is useful in strongyloidiasis researches and in epidemiological surveys [103].
The sensitivity of detection by agar plate culture could be further increased after repeated stool examinations done by the agar plate culture method. That conclusion was suggested when Hirata et al.,[104] cultured 4071 stool samples and reported positivity in 86/2406 samples at the first examination. While the estimated detection rate after examination of three stool samples was 2-fold higher than that after a single examination. Recently, a modification for agar plate culture method was proposed and has confirmed the improvement of the detection upon its comparison with other conventional methods and, on the other hand, added the advantage of preservation and identification of larvae at different stages, adult worms and eggs of *S. stercoralis*. The preserved larvae, worms and eggs can be used for antigen extraction and serology based research [105].

Overall, a systematic review with meta-analysis was performed on the existing literature on strongyloidiasis in the Latin America over a period 1980-2013 to evaluate four parasitological methods for their efficiency to detect *S. stercoralis* infection. The overall literature included 9025 individuals and the sensitivities of the BM, APC, DM and FECT were 72%, 89%, 21%, and 48%; respectively. The specificity was 100% in all tests. The study pointed the APC and BM as the best suited methods of strongyloidosis diagnosis[106].

Since only small numbers of larvae are shed in the feces, conventional parasitological methods have low diagnostic sensitivity, even with repeated examinations. Although the Baermann technique and fecal culture are more sensitive, they are time-consuming and must be performed on fresh stool sample [107].

**Examination of Samples Other Than Stool**

*S. stercoralis* is often recovered from samples other than stool, including gastrointestinal secretions and pulmonary tissues during hyper infection syndrome, while in case of disseminated infection, the larvae can be seen in other organs such as tissue biopsies obtained from different organs and urine samples[108, 109]. Lung samples (sputum, bronchoscopy and bronchoalveolar lavage) are the best samples in which *S. stercoralis* larvae are often recovered and can be visualized by microscopic examination of wet mounts and Gram-stained smears. Although the respiratory tract is a part of the normal path of larval migration, lung samples remain negative for the parasite unless hyper infection developed[3]. Many case reports had documented the detection of *S. stercoralis* rhabditiform and filariform larvae [49,110-113], *S. stercoralis* eggs [114], and adult worms [115,116] in various lung samples and were considered diagnostic for hyper infection syndrome.

Duodenal aspirate samples also provide another choice for diagnosis. Some studies declared the diagnostic sensitivity of duodenal aspirate [2]. Direct microscopic examination of a single sample of duodenal aspirate was
found to be more sensitive than direct wet mount microscopy of stools samples for the detection of larvae [117]. However, this invasive method is not practical and not routinely made and it is usually recommended only for children for rapid demonstration of parasites [2,107].

**Peripheral Blood Microscopy**

Eosinophil count can be performed by microscopic examination of peripheral blood samples withdrawn from the patient. Eosinophil count is requested in uncomplicated cases of chronic strongyloidiasis in which the intestinal worm output is often very low [2,118]. Absolute eosinophil count could serve as an alternative indicator for the investigation of *S. stercoralis* infection and presented as mild eosinophilia (0.4-1.5×10³ cells/µl) [2].

In a study, blood samples were obtained from chronic strongyloidiasis-confirmed patients and were introduced for specific-antibody testing and eosinophil count. Mild eosinophilia was seen in 82.6% of the patients at the first examination before treatment. Eosinophil count decreased within three months upon treatment, but instead, remained elevated in 44.8% of patients and required additional months for decline. However, after 24 months of follow-up, all re-treated patients had eosinophil counts < 400 cells/µL. In conclusion, eosinophil counts decreased after therapy, suggesting good prognosis [107]. However, still eosinophil count does not provide sufficient diagnosis of strongyloidiasis because the elevation in count is mild and is not specific, especially in cancer patients. In addition, eosinophilia may not develop in immunocompromised hosts, and thus it is not helpful in excluding strongyloidiasis in the differential diagnosis [108].

**Immunological Diagnosis**

Immunological diagnosis of strongyloidiasis is often based on investigating the presence of anti-*strongyloides* antibodies which circulate in patient’s blood [107]. Serological test has shown a correlation between the *S. stercoralis* infection and the level of antibody in all the infection stages including acute, chronic, hyper infection, treatment follow-up, and cure [94,119].

Several immunologic principles had been applied for *S. stercoralis* diagnosis and had shown satisfactory results [2]. IgG and IgE ELISA is the most commonly used immunoassay for serological diagnosis of strongyloidiasis since it is a reliable and cost-effective method [3].

ELISA exhibits variable sensitivity and specificity ranging between 83-93% and 95-97.7%, respectively, depending on the antigen preparation used (obtained from larvae lysate), the immunoglobulin isotypes and the population tested [119,120]. Koosha et al.,[121] had evaluated the indirect ELISA and indirect immunofluorescence assay (IFA) for the serological diagnosis of human strongyloidiasis. The study tested serum specimens obtained from 46 individuals infected with *S. stercoralis*, 37 healthy
subjects and 381 patients with other parasitic infections. The sensitivity and specificity for ELISA were 93.5% and 96.1%, respectively; and those for IFA were 87%, 90.1%, respectively. The study concluded that indirect ELISA method reported good sensitivity and specificity, and may be preferable to IFA. Another study reported that the ELISA specificity was higher than gelatin particle agglutination test (GPAT), when applied agar plate culture test (APCT) as a gold standard. But in contrast, the sensitivity of GPAT had been slightly higher than that of ELISA [122].

In another study, ELISA for IgG and stool microscopy was used to screen 177 participants in a village in an area endemic for strongyloidiasis. 11% of the villagers had *S. stercoralis* present on stool examination and 45% had antibodies detected by ELISA. The level of IgG decreased 42 days after successful treatment in 14 villagers. These results suggested that ELISA is sensitive and specific method for strongyloidiasis surveying in an endemic area [123].

At present, many researchers tend to develop ELISA protocols in their laboratories and compare their performance with ready-prepared commercial ELISA kits, as well as other detection methods in order to improve the diagnostic value. Van Doorn *et al.*, [33] had evaluated laboratory-based ELISA with two commercial ELISA kits. The sensitivities of the laboratory-based ELISA and the other two commercial ELISAs were 93, 89, and 83%, respectively, whereas the specificities were 95.0, 97.2, and 97.2%, respectively. Later on, Bunofrate *et al.*, [124] has guaranteed the usefulness of commercial ELISA and other sero-assays for treatment follow up, particularly, in non-endemic countries. In addition, another study has recommended the application of ELISA for different immunoglobulins as screening test panel in cancer patients [67]. A recent study compared sensitivity and specificity of 5 serologic tests, namely, in-house IFAT, NIE-ELISA, NIE-LIPS, Bordier-ELISA and IVD-ELISA using 399 cryopreserved serum samples and fecal results, as well as, combination of tests the primary reference standard. Results reported that the most sensitive test was IFAT, with 94.6% sensitivity (91.2–96.9), followed by IVD-ELISA (92.3%, 87.7–96.9). Whereas the most specific test was NIE-LIPS, with specificity 99.6% (98.9–100), and IVD-ELISA (97.4%, 95.5–99.3) [125].

Sudarshi *et al.*, [34] had reported that immigrants with chronic asymptomatic infection are significantly more likely to be positive by ELISA than travelers after a study performed in England on 64 travelers and 128 immigrants from endemic countries with microscopically-proven strongyloidosis. The sensitivity of ELISA in travelers was 73% while in immigrants was 98%. In addition, the same study reported that eosinophil count and stool microscopy are insufficiently sensitive to be used alone for screening. Another study reported that serum IgE levels can remain within the normal range for some patients infected with *S. stercoralis* [81].
However, there are some limitations for ELISA that may affect their results including: cross-reactions with other nematode infections; variable sensitivity and specificity because of lost gold standard; and inability to differentiate between acute or chronic infection [2]. In addition, the sensitivity of serology is good in individuals with chronic infection but is lower in those who become infected after travelling to endemic areas [120]. Therefore, continuous efforts for the improvement of sero-assays performance is steadily carried on in different research institutes [124,126-130].

**Molecular Diagnosis**

Several conserved regions in *S. stercoralis* genome were recognized and successfully targeted and showed good sensitivities and specificities, including cytochrome c oxidase subunit I gene [131], 28S rRNA gene [132], the 18S rRNA gene sequence [42,131], and Internal Transcribed Spacer (ITS) [89,120]. Recently, the detection of parasitic DNA in fecal samples using real-time PCR proved to be a sensitive and specific method for the diagnosis of intestinal protozoan and helminth infections [120, 133, 134]. The efficacy was evaluated for real-time PCR to detect *S. stercoralis* from fecal samples. Three sequences from genomic DNA were targeted, including cytochrome c oxidase subunit I gene, *S. stercoralis*-specific repeated sequence, and the 18S rRNA gene sequence. The comparison performed with Baermann method and culture methods. The study showed that the detection sensitivity was 21.2, 10.4, and 21.7% for real-time PCR, Baermann method, and culture, respectively. In addition, 18S rRNA gene sequence found to have better detection rate when compared with other gene targets. The study concluded that *S. stercoralis* real-time PCR could be a useful alternative to the commonly used Baermann method, offering a two-fold increase in the detection rate. [120].

PCR has proved to be a highly specific and sensitive technique for intestinal parasites diagnosis in individuals with or without clinical symptoms. Real-time PCR is a preferred over other PCR variants due to its improved rapidity, sensitivity, reproducibility and the considerably reduced risk of contamination [135].

**Treatment and Avoidance**

The treatment for strongyloidosis is made by antihelminth drug that targets circulating L3 filariform larvae during the autoinfection cycle, which are being highly drug resistant [2]. Thiabendazole has been the drug of choice for the treatment of strongyloidiasis, despite the associated gastrointestinal side effects and a high relapse rate [117,136]. Albendazole has an important role in the treatment of chronic strongyloidiasis. The side-effects of albendazole are few and it is increasingly being used without serious problems in older children. However, albendazole should be avoided if possible in pregnancy and during lactation. [137]. Ivermectin is the best drug for the
treatment of *S. stercoralis* infection [138]. In comparing with albendazole and thiabendazole, ivermectin is much better tolerated, shows better rates of larval clearance from stool, and has a higher cure rate [137-139]. In addition, Ivermectin has been found to be the most effective drug in treating acute infection, as well as disseminated strongyloidiasis and hyper infection in patients with chronic intestinal disease [2,16,138]. Therefore, ivermectin has been registered as the drug of choice in the World Health Organization’s (WHO) list of essential drugs for the treatment of *S. stercoralis* [140] and was recommended for treating strongyloidiasis as the first choice therapy, while albendazole and thiabendazole are the second therapeutic options [137].

Adenusi et al., [138] had performed a study to compare ivermectin efficacy and safety with that of thiabendazole in 252 individuals with proven uncomplicated strongyloidiasis. Subjects were administered orally with ivermectin in a single dose or thiabendazole for 3 consecutive days. Stool samples were examined after treatment by 7, 21 and 30 days. The study showed that the cure rate for ivermectin was 84.07% and for thiabendazole was 78.64%; as patients had stool positive for larvae 30 days post-treatment. In addition, the clinical adverse reactions were mild and transient in subjects treated with ivermectin, while they varied from mild to severe in those treated with thiabendazole. Therefore, single-dose ivermectin provides efficacy comparable with standard, multiple-dose thiabendazole, with a much reduced incidence of adverse effects and consequently better patient compliance.

Another study compared between ivermectin and albendazole efficacies in treatment and their side effect. 78 subjects were treated with single-dose ivermectin and 33 with albendazole, the cure rates were 98.7% and 78.7%, respectively. The study concluded that the efficacy of single dose and mild side effects suggest ivermectin as drug of choice for strongyloidiasis treatment [141].

The primary infection of strongyloidiasis is prevented by avoiding contacting with sources of the infection such as animals (dogs and cats), infected humans, and contaminated soil in endemic countries, in addition to avoid consumption of contaminated food or drinks [108]. Strongyloidiasis can be controlled by improved sanitation and provision of clean water, which reduces or prevents transmission [20]. The best strategy for avoiding hyper infection development and filariform larvae dissemination in complicated strongyloidiasis is to diagnose and treat chronically infected patients who are at risk for developing immune suppression and under steroids treatment. Serology, absolute eosinophil count, and stool sampling for microscopy and PCR are the best screening strategies [101].

Another sort of avoidance of treatment resistance has to take place in diabetic patients who were diagnosed with strongyloidiasis and were treated with ivermectin. This group of patients must be highly considered by the treating clinicians for the state of treatment resistance to insure the optimal treatment and careful follow up. This conclusion was made by Hays and colleagues who found
that diabetes mellitus type 2 was an independent risk factor that significantly associated with treatment failure through different suggested mechanisms including drug interactions between diabetes medications and ivermectin, hyperinsulinaemia that slows gastric emptying which impairs absorption of ivermectin, or altered gut biota that occur in diabetic patients that could influence the absorption of ivermectin [142,143].

References


15. Grove D I, Lumsden J, Northern C. Efficacy of albendazole against Strongyloides ratti and S. ster-


29. Azira NM, Abdel Rahman MZ Zeehaida M. Review of patients with Strongyloides stercoralis in-


40. Zukiewicz M, Kaczmarski M, Topczewska M, Sidor K Tomaszewska BM. Epidemiological and


51. Tous Romero F, Delgado-Marquez AM, Gargallo-Moneva V, Burillo-Martinez S, Martin Diaz A, et


64. Praharaj I, Sujatha S, Ashwini MA Parija SC. Co-infection with Nocardia asteroides complex and


114. Kennedy S, Campbell RM, Lawrence JE, Nichol GM Rao DM. A case of severe Strongyloides ster-


126. Goncalves AL, de Araujo KC, Carvalho EF, Ueta MT, Costa-Cruz JM. Specific IgG and immune


