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REVIEW

Current pharmacotherapeutic strategies for Strongyloidiasis and the complications in its treatment

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ABSTRACT

Introduction: Strongyloidiasis, an infection caused by the soil-transmitted helminth *Strongyloides stercoralis*, can lead immunocompromised people to a life-threatening syndrome. We highlight here current and emerging pharmacotherapeutic strategies for strongyloidiasis and discuss treatment protocols according to patient cohort. We searched PubMed and Embase for papers published on this topic between 1990 and May 2022.

Areas covered: Ivermectin is the first-line drug, with an estimated efficacy of about 86% and excellent tolerability. Albendazole has a lower efficacy, with usage advised when ivermectin is not available or not recommended. Moxidectin might be a valid alternative to ivermectin, with the advantage of being a dose-independent formulation.

Expert opinion: The standard dose of ivermectin is 200 µg/kg single dose orally, but multiple doses might be needed in immunosuppressed patients. In the case of hyperinfection, repeated doses are recommended up to 2 weeks after clearance of larvae from biological fluids, with close monitoring and further dosing based on review. Subcutaneous ivermectin is used where there is impaired intestinal absorption/paralytic ileus. In pregnant or lactating women, studies have not identified increased risk with ivermectin use. However, with limited available data, a risk-benefit assessment should be considered for each case.

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1. Introduction

Strongyloidiasis is labeled as the most neglected of the Neglected Tropical Diseases (NTD), yet an estimated 614 million people are infected worldwide [1]. Categorized under Soil Transmitted Helminths (STH), human strongyloidiasis is usually caused by the remarkably persistent, microscopic helminth *Strongyloides stercoralis* [2]. The unique autoinfective lifecycle distinguishes *S. stercoralis* from other STHs. Rather than remaining within the gastrointestinal system, the auto-infective filariform larvae penetrate the intestinal mucosa or perianal skin, randomly migrating on various pathways to the small intestine where they mature to adult females [3–5]. The filariform larvae can transport enteric bacteria, with septicemia and meningitis considered complications of a hyperinfective phase.

The human host provides a habitat where the parasitic female can reproduce without a male (parthenogenesis) [6] and the auto-infective cycle enables the infection to continue for decades, potentially a lifetime, unless effectively treated. In immunocompromised hosts, all phases, including the auto-infective cycle, are accelerated, and the parasitic load increases notably, leading to the severe, life-threatening form of the infection: hyperinfection/disseminated infection [4,7,8]. In this advanced phase, all stages of the parasite (including the adult worm) can be found throughout the soft tissues of the body [8]. Unfortunately, due to the nonspecific manifestations of hyperinfection, e.g. pneumonits, sepsis, paralytic ileus, cases can be missed unless microscopy is performed in the stool or respiratory samples [9].

Understanding the *S. stercoralis* lifecycle is key to addressing the challenges of diagnosis and treatment. The goal of therapy is eradication of all phases, including the auto-infective larvae, as one remaining larva could potentially reestablish a patent infection. This differs from other STH, which don't have an auto-infective cycle, where reducing the worm load may be sufficient to reduce morbidity.

The aim of this paper is to highlight current and emerging pharmacotherapeutic strategies for strongyloidiasis and various treatment protocols, according to patient cohort.

We searched PubMed and Embase for papers published on this topic between 1990 and May 2022. The detailed search strategy is reported in the Supplementary File.

2. The diagnostic issue and its impact on the evaluation of treatment efficacy

There is no single, high sensitivity and high specificity reference test for the diagnosis of *S. stercoralis* infection [10]. Direct

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Article highlights

- Strongyloidiasis is a neglected disease that infects hundreds of millions of people worldwide, which can lead to chronic, decades-long asymptomatic infection, with the risk of fatal hyperinfection associated with immunocompromise
- All diagnostic modalities have limitations, with serology having the greatest diagnostic yield in chronic infection, while a higher burden of disease increases the sensitivity of stool tests. These limitations affect individual diagnosis, test of cure and the accuracy of epidemiological studies.
- The goal of treatment is a complete cure rather than larval-load reduction and in uncomplicated infection in immunocompetent individuals, first-line treatment is a single dose of 200 µg/kg oral ivermectin, which has a higher efficacy than albendazole.
- For immunocompromised persons, repeated doses of ivermectin are recommended, although no definite evidence is available in support of a specific dosing schedule
- Priorities for further research include medication safety in pregnancy, breastfeeding, and young children, optimal regimens for immunocompromised persons, and the role of moxidectin in mass drug administration

stool microscopy has a low sensitivity (around 21% according to a systematic review) [11], which can be improved with repeated stool examination [10]. Other parasitological techniques, such as the Baermann method and agar plate culture, demonstrate better sensitivity than direct microscopy, but this is still relatively low compared to combining methods for a composite reference standard and multiple collections. These techniques require good parasitological skills to differentiate the larvae, which could be cumbersome (Baermann in particular) in routine laboratory practice, and require viable larvae from fresh stool (ideally produced within 24 hours) [10]. In referral laboratories with molecular diagnostic capacity, polymerase chain reaction (PCR) has become increasingly available in the last decade. PCR assays do not require fresh stool, so samples can be preserved either in ethanol or frozen and sent with less time constraints to referral sites. Based on a systemic review, PCR can also have limited sensitivity (around 61.8%, 95% CI 42–78.4) [12], which is likely due to the effect of nucleases, inhibitors and sampling error, depending on local protocols for nucleic acid extraction and in-house assays.

Due to the low and fluctuating larval output in chronic infection, fecal-based methods cannot be totally reliable for the assessment of post-treatment clearance from infection: a negative test might be either indicative of missed detection or parasitological cure [13]. In an untreated cohort, Dreyer et al. [14] demonstrated that weekly examination of stool samples with Baermann technique over an 8-week period, resulted in alternating positive and negative results from the same individual. It is interesting to notice that 76% of individuals who tested positive on at least one sample, showed negative results in all following follow-up tests, although never treated. If these people were enrolled in a clinical trial aimed at estimating the efficacy of a drug against *S. stercoralis*, they would erroneously be classified as cured. The use of fecal-based techniques for the post-treatment evaluation can hence cause an overestimation of therapeutic efficacy in clinical trials.

Ideally, a more sensitive marker for the assessment of cure in strongyloidiasis would be identified, due to the risk of severe disease even in cases of reduced or undetectable parasitological load.

Serological assays have demonstrated the highest diagnostic yield for strongyloidiasis, though specificity is variable due to possible cross-reaction with other nematodes. Some assays demonstrate sero-reversion following treatment, though this can take months. Alternative criteria to define response to treatment have been proposed, such as halving the optical density ratio at follow up; however, this will vary according to the host antibody response [15,16]. The usefulness of serology as a marker of cure would also be decreased in endemic areas, where there is the potential for *Strongyloides* re-infection and the potential for other nematode infections. Only a few randomized controlled clinical trials have included serology among the diagnostic tests for the estimation of treatment efficacy against *S. stercoralis* infection [17,18].

3. The use of benzimidazoles for the treatment of strongyloidiasis

3.1. Albendazole

Albendazole is a benzimidazole drug with a broad-spectrum activity against helminth infections, including many nematodes and cestodes. Its mode of action is not entirely clear, although the drug probably causes metabolic disruption in the parasite through inhibition of the beta-tubulin polymerase [19]. It has been extensively used in mass administration campaigns for the control of the other STH (i.e. hookworm, *Ascaris lumbricoides* and *Trichuris trichiura*) in endemic areas [20]. In that context, albendazole is used as a single dose of 400 mg, which proved extremely well tolerated. Few gastrointestinal adverse events have been reported over time with the use of this drug [19]. For the treatment of *S. stercoralis* infection, a single dose demonstrated exceedingly low efficacy (around 69% cure) [19], so different researchers tested repeated doses of 400 mg twice a day for three to 7 days (Table 1). A subsequent systematic review with meta-analysis showed that the efficacy of albendazole, given either for three or 7 days, was significantly lower than that of ivermectin for the parasitological cure of strongyloidiasis (RR 1.79, 95%CI 1.55 to 2.08), while there was no significant difference in the frequency of adverse events caused by the two drugs [21]. For this reason, albendazole is now considered a second-line treatment for *S. stercoralis* infection, limited to cases of unavailability or contraindications to ivermectin.

3.2. Thiabendazole

Thiabendazole was the first benzimidazole licensed for human use [19]. Like albendazole, it has a broad-spectrum activity against helminth infections, at the recommended dose of 50 mg/kg/day divided every 12 hours (maximum 3 g/day) for 2 days [19,21]. Different doses have been used in randomized controlled trials (RCT) (Table 1). However, while its demonstrated efficacy was similar to that of ivermectin for the treatment of strongyloidiasis,

Table 1. Main characteristics of selected randomized controlled trials for the treatment of strongyloidiasis.

Study	Drug regimens	Efficacy %(95%CI)	N Participants For assessment of cure	Age Range - Years	Country	Test(s) used for assessment of cure			
						Direct microscopy	Baermann and/or APC	PCR	Serology
Adenusi 2003 [22]	(1) IVM 200 µg/kg single dose (2) TBZ 50 mg/kg/day for 3 days	(1) 84.07 (2) 78.64	216	5–66	Nigeria		Y		
Barda 2017 [85]	(1) IVM 200 µg/kg single dose (2) MOX 8 mg single dose	(1) 95.1 (86.5–99) (2) 93.6 (84.5–98.2)	127	12–60	Lao People's Democratic Republic		Y		
Bisoffi 2011 [18]	(1) IVM 200 µg/kg single dose (2) TBZ 2 doses of 25 mg/kg/day for 2 days	(1) 56.6, up to 85.7 when cure assessed with fecal tests only (2) 52.2, up to 94.6 when cure assessed with fecal tests only	198	5–95	Italy		Y		Y
Buonfrate 2019 [17]	(1) IVM 200 µg/kg single dose (2) IVM 200 µg/kg/day for 2 consecutive days, repeated 2 weeks apart	(1) 86 (79–91) (2) 85 (77–90)	309	5–95	Italy Spain England		Y	Y	Y
Datry 1994 [23]	(1) IVM 150 to 200 µg/kg single dose (2) ALB 400 mg/day for 3 days	(1) 83 (2) 38	53	5–70	France	Y	Y		
Gann 1994 [24]	(1) IVM 200 µg/kg single dose (2) IVM 200 µg/kg for 2 days (3) TBZ 2 doses of 25 mg/kg/day for 3 days	(1) 100 (2) 100 (3) 94.7	53	5–70	United States		Y		
Marti 1996 [25]	(1) IVM 150 to 200 µg/kg single dose (2) ALB 400 mg/day for 3 days	(1) 82.9 (2) 45	301	9–22	Tanzania	Y*	Y		
Supputtamongkol 2008[§] [67]	(1) IVM 150 to 200 µg/kg single dose[#] (2) ALB 800 mg/day for 7 days	(1) 76.2 (2) 38.1	42[§]	>14	Thailand	Y			
Supputtamongkol 2011[§] [32]	(1) IVM 150 to 200 µg/kg single dose (2) IVM 150 to 200 µg/kg/day for 2 days (3) ALB 800 mg/day for 7 days	(1) 96.8 (2) 93.1 (3) 63.3	90[§]	>18	Thailand	Y	Y		
Zaha 2002 [26]	(1) IVM 200 µg/kg single dose repeated 2 weeks apart	(1) 98	50	30–79	Japan		Y		

CI: confidence interval. APC: agar plate culture. PCR: polymerase chain reaction. IVM: ivermectin; TBZ: thiabendazole; MOX: moxidectin; ALB: albendazole. [§]included immunocompromised individuals.

tolerability was significantly lower, with nausea, malaise, and dizziness among the main adverse events [21]. Based on the high frequency of adverse events caused by thiabendazole, and the availability of anthelminthic drugs of comparable efficacy, the product is no longer in the market in many countries [21].

4. Ivermectin

Ivermectin is the drug of choice for the treatment of strongyloidiasis. It is a semi-synthetic drug belonging to the avermectin class. It has a broad spectrum of action against parasitic infections, and it is the first "endectocide', meaning that it acts both against ectoparasites (such as small arthropods, insects) and endoparasites (nematodes) [27]. It was first registered for veterinarian use, then registration for human use followed in the 1980's.

In helminths, ivermectin acts selectively on glutamate-gated chloride channels, blocking neurotransmission and thus causing paralysis of the somatic muscles and consequent death. In humans, ivermectin stimulates the release of gamma-amino butyric acid (GABA) in neurons. However, the blood–brain barrier prevents the drug from reaching the GABA channels, which are present in the central nervous system only, resulting in safe administration [27,28].

The drug is metabolized by the liver through the enzyme CYP3A4, and it is excreted almost completely in the feces, with less than 1% of the drug excreted in the urine [29].

Bioavailability increases when ivermectin is taken with food; in particular absorption was 2.5 times higher after high-fat meal in a study on healthy volunteers [29].

Ivermectin has been extensively used in mass drug administration (MDA) campaigns aimed at the elimination of onchocercosis and lymphatic filariasis. In that context, the drug proved to be safe, though caution was recommended in areas where *Loa loa* is endemic, as a potentially fatal encephalopathy might occur in people with high *Loa loa* parasitemia [30,31].

In the absence of loiaisis, the main adverse events include dizziness, somnolence, myalgia, gastrointestinal symptoms, pruritus, and these are usually mild to moderate with spontaneous resolution [31]. Moreover, the safety of doses up to 10 times higher than the licensed 200 μg/kg was assessed in healthy volunteers in a double-blind, placebo-controlled trial. Even the highest doses were well tolerated, with no evidence of central nervous system signs [29]. Given the importance of ivermectin in the fight against the debilitating neglected diseases infecting hundreds of millions impoverished persons, the 2015 Nobel Prize in Medicine was awarded jointly to the scientists who discovered the drug, William C. Campbell and Satoshi Ōmura [28].

The administration of multiple doses of ivermectin to treat strongyloidiasis did not demonstrate higher efficacy than a single dose of 200 μg/kg in an RCT [17], where the latter regimen was compared to the administration of 200 μg/kg for two consecutive days, repeated 2 weeks apart. In this study, the authors stated that at 12 months follow-up, which included serology for the assessment of cure, the overall efficacy was around 86%. Another RCT compared one to two doses of ivermectin given 2 weeks apart, finding no significant difference in efficacy [32]. In this study, clearance from infection was assessed with parasitological methods, 12 months after treatment. The efficacy was around 97% and 93% for the single and the double doses of ivermectin, respectively. Discrepancy in the efficacy resulting from the two RCTs is presumably due to the different methods used to define clearance from infection, with parasitological methods possibly overestimating the efficacy of the drug, and serology underestimating it (Table 1).

4.1. Ivermectin in special categories

4.1.1. Pregnancy

Before the application of the US Food and Drug Administration Pregnancy and Lactation Labeling Rule, ivermectin was classified as pregnancy category C, as 'it has been shown to be teratogenic in mice, rats, and rabbits when given in repeated doses of 0.2, 8.1, and 4.5 times the maximum recommended human dose, respectively' [33]. Later evidence demonstrated that P-glycoprotein, an efflux pump expressed among which in placenta and blood–brain barrier, has a crucial role in preventing ivermectin toxicity. This protein has deficient expression in the mouse strain (CF-1) used during initial studies, while in humans the placental P-glycoprotein is present at an earlier stage and during the fetus development begins earlier and develops faster than in animal models [34–36]. Despite this insight, a clear evaluation of ivermectin safety in pregnancy is lacking, and pregnant women are usually excluded from treatment. However, a significant proportion of this sub-population is inadvertently exposed during MDA campaigns, particularly in the first trimester [37]. Nevertheless, limited information is available from these programs. In 2020, Nicolas et al. [37] conducted a systematic review and meta-analysis to evaluate safety of ivermectin during pregnancy: five case-control studies and one open-label RCT were finally included in the quantitative analysis. These studies enrolled 893 pregnant women with 899 pregnancy outcomes; of these women, 496 received ivermectin inadvertently during MDA campaigns and 397 purposely received ivermectin as part of open-label RCT. Overall, the rate of serious adverse events (i.e spontaneous abortions, stillbirths, and congenital anomalies) did not increase after ivermectin exposure (OR 1.15, 95% CI 0.75–1.78). However, the certainty of evidence was classified as very low using the GRADE approach, as all studies were underpowered, and the case-control studies were not designed with the specific aim of assessing safety in pregnancy.

4.1.2. Breastfeeding women

As reported in the product information leaflet, ivermectin is excreted in human milk in low concentrations, but nursing women are recommended to undertake therapy 'when the risk of delayed treatment to the mother outweighs the possible risk to the newborn' [33]. Indeed, data on safety of ivermectin in nursing women are scanty. To the best of our knowledge, breast-milk concentrations of ivermectin have been published for only four healthy volunteers [38] and one patient [39] treated for uncomplicated intestinal strongyloidiasis. Both case reports suggest that the excretion of ivermectin in breast-milk is low, with a calculated relative infant dosage (RID) of approximately 0.55%. This value is much smaller than the threshold of 10% below which breastfeeding is proposed to be acceptable by the World Health Organization (WHO) [40], and supports the current WHO policy, which excludes lactating women from IVM therapy only in the first week after delivery [41].

4.1.3. Pediatric use

At present, safety of ivermectin in children weighing less than 15 kg [33] or aged less than 5 years has not been established and administration is therefore not recommended. As highlighted above, ivermectin elicits some effects on GABA receptors, but these are restricted to the central nervous system and protected by the blood–brain barrier in humans. The relative immaturity of the blood–brain barrier in infants has led to concerns about the use of ivermectin in small children. However, recent studies indicate an earlier development of P-glycoprotein and prevention of neurotoxicity, than was historically thought [34,35].

Despite the official recommendation, it is likely that a large number of children have been exposed to ivermectin, particularly during MDA for onchocerciasis and lymphatic filariasis in Africa, where ivermectin dosing is usually based on height rather than on weight. In addition, a case series of infants as young as 3 months old who were treated with ivermectin has

been published [42]. In that case series, 15 children (median age 10 months – range 3–22 months) were enrolled. Two doses of ivermectin 200 mcg/kg were administered 14 days apart for scabies resistant to topic treatment. Two transient adverse events were reported: one infant seemed nervous and irritable, and the other one scratched intensely for several days after ivermectin intake.

Overall, two systematic reviews tried to answer the question of safety of ivermectin in children. In 2018, Wilkins et al [43]. retrieved 8 studies (1 RCT, 2 cohort studies, 3 case series and 3 case reports) in which ivermectin was administered to small children at the dosage of 150–200 µg/kg to treat various diseases (i.e. scabies, cutaneous larva migrans, and strongyloidiasis). Specifying the low quality of data due to the limited available literature, the authors suggested that ivermectin was well tolerated and no serious or long-term adverse effects was demonstrated in children. In 2021, Jittamala et al. [44] updated the research and added analyses of individual-level patient data. The authors found that ivermectin was administered to 1,088 children, with a median age of 36 months and median weight 13.0 kg. A notably high proportion of children (82.8%) received two doses of ivermectin. In total, 15 children reported 18 adverse events (specifically, diarrhea, eczema, headache, pruritus and vomiting), none of which was deemed severe. Notwithstanding the limited published data, ivermectin is routinely used for children weighing 10–15 kg with strongyloidiasis in some Australian health services [45].

Even assuming the tolerability of ivermectin in small children, some issues remain unresolved. First, there is no pediatric ivermectin formulation available and it can be difficult for children to swallow tablets. In most studies, ivermectin tablets were crushed and mixed with water to allow administration; nevertheless, the development of a specific pediatric formulation would be convenient and might permit a more precise dosing. Secondly, the pharmacokinetics of ivermectin in children is not well understood, and recent studies suggested a need for an increased dosage [46,47]. To answer these questions, a randomized, double-blind, placebo-controlled trial to assess the safety, pharmacokinetics, and efficacy of escalating doses (up to 800 µg/kg) of ivermectin in children weighing less than 15 kg is underway (NCT04332068).

4.1.4. Geriatric population

In general, geriatric patients may be a difficult-to-treat population, due to the frequent coexistence of underlying conditions and pharmacological therapies. In addition, the elderly are often excluded from clinical trials so less data are available.

In 1997, Barkwell et al [48]. reported 15 deaths among 47 nursing home residents after treatment with a single 200 µg/kg dose of ivermectin for scabies. Although causes of death were not provided, the authors suggested a causative link with ivermectin therapy. Subsequent data from other studies [49,50] has not confirmed an excess mortality in elderly populations following ivermectin administration. More recently, ivermectin raised the world interest due to the possible use in COVID-19 patients. A few trials enrolled geriatric patients [17,51–53]; in most cases, no adverse events or mild, self-limiting symptoms were reported. Only one trial [53] identified 4 serious adverse effects (i.e. 2 myocardial infarction, 1 severe anemia and 1 hypovolemic shock due to severe diarrhea) in 241 patients who received ivermectin treatment, compared with 1 adverse event (inferior epigastric arterial bleeding) among 249 patients in the control group. However, correlation with ivermectin and with other confounding factors (such as comorbidities) was not further analyzed.

4.2. Treatment of strongyloidiasis in the immunosuppressed host

Strongyloides hyperinfection is associated with a very high larval burden [54] and a mortality rate approaching 90% [8]. Iatrogenic immunosuppression, particularly the administration of corticosteroids, cytotoxic agents and immunomodulatory therapies, is a major risk factor for complicated strongyloidiasis [55,56]. However, infection with the human T cell leukemia virus type 1 (HTLV-1) may be a more common risk factor in some resource-limited areas [57]. Co-infection with HTLV-1 increases the risks of symptomatic [58] and complicated strongyloidiasis [59] and reduces treatment efficacy [57,60]. Limited epidemiological data suggest that HTLV-1 coinfected individuals are twice more likely to develop symptomatic strongyloidiasis [59,61,62] and nearly six-times more likely to develop hyperinfection than their HTLV-1 uninfected peers [59]. Symptomatic strongyloidiasis in individuals coinfected with HTLV-1 is associated with a high larval burden [58,61]. Such individuals could potentially function as 'core transmitters' in communities with poor health infrastructure and heavy environmental fecal contamination. Consistent with other complications of HTLV-1 infection, a high number of HTLV-1 infected cells in blood (HTLV-1 proviral load; PVL) predicts the larval burden and the risk of symptomatic strongyloidiasis [63]. These cells produce high levels of interferon gamma, which reduces levels of IL-4, IL-5 and IL13 and eosinophil counts [63,64]. HTLV-1 infection also increases rates of treatment failure when this is determined by detecting larvae in stool [61]. When defined by stool microscopy, cure rates are ≤50% for coinfected patients following treatment with albendazole [65]or ivermectin at a dose of 100 mcg/kg [61], but reach 90% following treatment with ivermectin at 200 mcg/kg [60]. Cure rates with higher doses of ivermectin therefore approximate those of HTLV-1 uninfected patients (Table 1). Our current understanding of the immune effects of HTLV-1 infection suggest that individuals with a higher HTLV-1 PVL may be at greater risk of treatment failure; however, no RCT to date has stratified risk by PVL.

Data supporting a possible role of HIV/AIDS as a trigger for severe strongyloidiasis are more limited. A small observational study [66] reported the outcome of nine patients with AIDS with abundant *S. stercoralis* larvae in stool. Seven out of nine patients were treated with the dose regimen of 200 µg/kg of ivermectin for 2 days, repeated 2 weeks apart, while the remaining two patients received a single-dose course of the drug. The authors reported clinical and parasitological cure up to 3 years after treatment in all but one patient, who worsened 30 days after the single-dose treatment and died without receiving a further course of antiparasitic therapy. This posed the question whether patients with AIDS should receive multiple doses of ivermectin, but there is no sufficient evidence yet.

Management of strongyloidiasis in this patient population is complicated by the absence of data from randomized controlled trials. Few RCT included immunocompromised

participants [32,67] (Table 1), and those that did were either underpowered or did not report sufficient information to allow estimates of efficacy to be calculated [21]. Consequently, whether the standard single-dose regimen of ivermectin is appropriate for chronic infection in immunosuppressed individuals without signs of hyperinfection/severe dissemination remains unclear. An observational study that will compare cure rates in immunosuppressed and immunocompetent individuals is ongoing [68].

The treatment of hyperinfection/severe dissemination is even more problematic. In the absence of any specific RCT, there are case reports/series only that can be used as guidance, but with obvious limitations [8]. Some experts [69] recommend repeated doses of ivermectin, up to 2 weeks after parasitological clearance demonstrated with microscopy examination of positive body fluids. Patients with serious illness might not tolerate oral administration of ivermectin, hence alternative routes have been tried (section 4.2).

Post-treatment monitoring of patients who are immunosuppressed or HTLV-1 infected is particularly important because some will fail therapy and suffer recurrent symptomatic disease including complicated strongyloidiasis [60,70], and others living in *Strongyloides* – endemic areas will become reinfected. Secondary anthelminthic prophylaxis has been suggested for such patients [60] .

4.3. Parenteral administration of ivermectin

Subcutaneous administration has been the most common administration route of ivermectin in case of intolerability to the oral formulation [71,72]. This may occur particularly in advanced infection due to paralytic ileus, vomiting, malabsorption. As the oral products are the only formulations licensed for human use, the parenteral formulations that were administrated subcutaneously were veterinary preparations [71,73]. Thus, there are no specific recommendations for the dose and the schedule for parenteral administration, and in literature many different dosages were reported [71]. While 200 µg/kg given in alternate days was a frequent choice, concerns have been raised about the adequacy of dosing, even when daily, based on drug levels [71,74]. The different baseline characteristics of the patients and the delay that is often reported for obtaining the veterinary formulation (and the authorization for its off-label use) hamper the evaluation of the effectiveness of subcutaneous treatment. Moreover, there are concerns about the optimal plasma concentration of ivermectin that should be achieved, considering a proper balance between treatment effectiveness and toxicity. Indeed, in some cases the authors had concerns about the possible cause(s) of observed neurotoxicity, that could be the disseminated infection itself, its complications (including meningitis, sepsis and multiorgan failure) or abnormal ivermectin levels [73–75].

While there is no controlled-trial evidence about the effectiveness of subcutaneous ivermectin, no reasonable alternatives are available for patients who cannot take the oral formulation.

A few cases in literature describe administration per rectum [72]. Even less evidence is available about this administration route compared to the subcutaneous administration.

5. Moxidectin for *Strongyloides stercoralis* infection in humans

Moxidectin is a macrocyclic lactone, licensed and widely used in the veterinary medicine as an anthelmintic agent [76]. This drug is a milbemycin and belongs to the same drug family of ivermectin that, however, is from the avermectin sub-family.

Milbemycin was first isolated in 1967, with its structure characterized in 1972, and it was subsequently used to synthesize the antihelminthic agent, milbemyicin oxime. The drug was approved in 1990 for veterinary use only [76]. Moxidectin is derived from nemadectin, a result of milbemycin fermentation, and it have proven to be an effective against cattle parasitic infections. As with the avermectins, milbemycins have efficacy against endo and ectoparasites.

Moxidectin causes paralysis of the parasite pharynx and it inhibits larval development [76]. The mechanism of action of both milbemycins and avermectins is related to high affinity binding to a chloride ion channel receptor. The milbemycins are metabolized and eliminated via efflux pump proteins, which are present on both human and parasite cells. Although the binding receptors of the two molecules are similar, binding affinity varies slightly [77] .

Moxidectin differs from ivermectin in that it is less affected by the over expression of multidrug ABC transporters (such as P-glycoprotein), which are linked to drug resistance. Therefore, resistance to moxidectin does not follow the same pattern as ivermectin resistance, and the drug might be used as a valid alternative in settings where ivermectin use is hampered by high rates of resistance. Another difference between the two molecules is the affinity for the helminth glutamate receptor, which is higher for ivermectin. Different studies on avermectin and milbemyicin resistance suggest that milbemycin resistance is a polygenic mechanism and could be acquired in different steps [78,79] . Studies of resistance *in vivo* and *in vitro*, showed that moxidectin had the lowest extent of resistance compared to avermectins in larva development assays of *H. contortus, T. colubriformis* and *O. ostertagi* [80]. As for heartworm, a few studies showed that the studied strains were resistant both to ivermectin and milbemycin oxime, but not to moxidectin extended-release products and only partially to oral-dose moxidectin [81,82].

Moxidectin is a versatile, safe and stable molecule that is widely efficacious and used in veterinary medicine in different formulations. It comes in tablets, topical use or injectable for dogs, oral drench for sheep, and oral-gel for horses [76,83]. Its lipophilicity elicits and facilitates tissue deposition and a long duration of action. In dogs, moxidectin is usually administered once every 6/12 months in the prevention of the heartworm.

In 2018, the US Food and Drug Administration approved moxidectin for the treatment of onchocerciasis in humans [84]. Currently, the drug is approved for individuals aged 12 years and older. RCT aimed at evaluating the safety of the drug in younger children are ongoing (ClinicalTrials records: NCT01035619, NCT03962062).

Researchers had already considered moxidectin as a promising alternative to ivermectin, not only for the treatment of onchocerciasis, but also against intestinal nematodes. In 2017, a trial in Laos showed good efficacy of the drug

against *S. stercoralis*, achieving a cure rate of 94% for moxidectin vs 95% for ivermectin [85]. The dose used in the trial was 8 mg in one single administration, as recommended by FDA, but different clinical and pharmacokinetic studies evaluated the safety and efficacy of different doses of the drug against *S. stercoralis* infection in humans [86,87].

Hofmann et al. [86] conducted a study based on the blood concentration of the drug and the efficacy against *S. stercoralis*, revealing that a dose of 8 mg was curative at 28 days. With a 12 mg dose, the mean cure rate was slightly lower with leveling off at higher doses, suggesting that the recommended dose was appropriate. Smit et al. [87] considered the topic from a pharmacokinetic point of view, comparing the fixed and a weight-dependent dose of moxidectin. The results showed that the fixed dose was appropriate and more use-friendly than the weight-dependent one, especially in low-income settings and in mass administration campaigns. Moreover, there was a correlation between the baseline intensity of infection and the efficacy of the drug and its different doses: with low-intensity infections, a 4 mg dose was curative, whereas with moderate-high intensity a higher dose of drug was needed to reach a good efficacy [87]. It is still to be determined whether a second dose of moxidectin after 21 days could be beneficial and increase the rate of *Strongyloides* clearance. In the meantime, an RCT comparing 8 mg moxidectin versus standard dose of 200 µg/kg ivermectin for the treatment of strongyloidiasis is underway in Cambodia (clinical trial record NCT04848688).

As a new drug for human usage, all clinical trials considered the safety of moxidectin and found the drug safe, with no major side effects registered [84–86]. Even higher doses than recommended, did not elicit any major side effects [86,87]. The reported data suggest that moxidectin is a safe and effective alternative to ivermectin for the cure of *S. stercoralis*, with the advantage of being a dose-independent formulation and less prone to drug resistance.

6. Conclusions

Currently, ivermectin is the first-line drug for the treatment of strongyloidiasis. The drug is well tolerated and has good efficacy when given as a single oral dose of 200 µg/kg. However, repeated doses should be used to treat immunosuppressed patients and in cases of hyperinfection/severe dissemination, in which case alternative routes of administration (mainly subcutaneous) might be needed. Although albendazole is also licensed for the treatment of strongyloidiasis, the demonstrated efficacy is lower than ivermectin. Thus, its use should be limited to cases where ivermectin is not recommended (i.e. younger children, women in the first trimester of pregnancy). More recently, moxidectin has been found to be a valid alternative, and could be important in case of emergence of resistance to ivermectin.

7. Expert opinion

The treatment strategies for strongyloidiasis can be regarded as population-based or individual management. Large-scale measures include mass drug administration, adequate sanitation to prevent contact with infected feces and the management of zoonotic transmission, if this was found to be significant [88–90]. Individual treatment is commonly based on the results of diagnostic tests for screening or the investigation of symptoms. However, stool tests can have reduced sensitivity in chronic infection due to low larval output and serology sensitivity is reduced in acute infection and immunocompromised states, including hyperinfection [14,91–93]. Due to these diagnostic test limitations, the excellent tolerability of ivermectin and the possible harm caused by infection, treatment may also be commenced based on epidemiological risk factors for acquisition and when i) an individual is or will be significantly immunocompromised or ii) if there are indicative symptoms or investigations, such as an eosinophilia [94,95]. Conversely, due to a lack of awareness in non-endemic areas, an infected individual may not be diagnosed until the infection is severe and life-threatening [55,74,96].

Numerous trials (Table 1) and case reports of severe infection have demonstrated the efficacy of ivermectin for the treatment of strongyloidiasis and, to date, resistance has not been reported in *S. stercoralis*. Albendazole is second-line therapy and would be chosen because of an individual contraindication or where ivermectin safety has not been definitively demonstrated, such as in pregnancy or early childhood (Table 2). However, in severe disease the therapeutic benefits of ivermectin may outweigh concerns that are based on a lack of evidence, rather than demonstrated harm. Moxidectin, is effective against strongyloidiasis, with ongoing investigations into its role in therapy [86,97]. It has a longer half-life and is less susceptible to efflux pump-mediated resistance [78,86]. It will likely represent an alternative to ivermectin in the near future, with dose-independent administration making it attractive for mass administration campaigns.

Table 3 outlines an approach to therapy that takes into account the management setting, host immune status and

Table 2. Approach to treatment in special circumstances.

Special Circumstance	Ivermectin	Albendazole	References
Pregnancy	Pregnancy Category C CDC: data is limited but doesn't indicate an increase in congenital abnormalities following accidental treatment Treatment based on risk-benefit assessment	Pregnancy Category C WHO: recommended use in 2nd and 3rd trimesters CDC: data is limited but doesn't indicate an increase in congenital abnormalities following accidental treatment Treatment based on risk-benefit assessment	[69,98]
Breastfeeding	WHO: permitted after the first week post-delivery	WHO: compatible with breastfeeding CDC: it not known whether excreted in human milk; use with caution	[41,69,99]
Children	WHO: use in children ≥ 15 kg or ≥ 90 cm tall	WHO: can be used in children ≥ 12 months of age	[98,100]

Table 3. Treatment recommendations based on management setting, immune status and disease burden.

Management Setting	Immune status	Disease Burden*	Agent	Dose per day	Route	Duration (Day number)	Monitoring after treatment	References
Population-based	Immunocompetent (assumed)	Individual diagnostics not performed	Ivermectin	200 µg/kg daily	PO	Single dose	Sub-population diagnostic survey to audit efficacy	[17]
Individual risk factors	Immunocompetent	Low level or stool not tested**	Ivermectin Albendazole§	200 µg/kg daily 400 mg 2x daily	PO	Single dose Day 1 to 7	(Re)test stool (multiple) ± serology at 6–12 months Review and retest prior to future immunosuppression	[17,32]
		High level¶	Ivermectin Albendazole§	200 µg/kg daily 400 mg 2x daily	PO	Day 1, 14 or Day 1, 2, 15, 16 Day 1 to 7		[32]
	Current or pending immunocompromise	High risk of infection with possible false-negative diagnostic tests or tests not available	Ivermectin Albendazole§	200 µg/kg daily 400 mg 2x daily	PO	Single dose or Day 1, 14 Day 1 to 7 or Day 1, 2, 3, 18, 19, 20	Monitor for symptoms, low threshold for retesting	[32]
		Low level	Ivermectin	200 µg/kg daily	PO	Day 1, 14 or Day 1, 2, 15, 16	Retest stool (multiple) ± serology at 1 month & 6 months Monitor for symptoms, low threshold for testing	[26,32,55]
		High level¶	Ivermectin	200 µg/kg daily	PO	Treat according to expert advice. e.g. Day 1 to 7, 15, 16		
	Immunocompromise hyperinfection	Very high level Larvae in other specimens (e.g. bronchial washes) Severe systemic illness	Ivermectin Consider adding Albendazole Minimize immunosuppressive therapy Antibacterial therapy to cover sepsis/supportive therapy	200 µg/kg daily 400 mg 2x daily	PO, S/C¶¶ PO	Daily until 2 weeks following clearance from stool/sputum or modify based on expert advice Monitor for toxicity	Consider therapeutic drug monitoring Test for larval clearance Consider ongoing periodic treatment/secondary prophylaxis Retest stool (multiple) ± serology at 1, 6 & 12 months following treatment Monitor for symptoms, low threshold for re-testing	[55,101,102]

PO: per oral, S/C: subcutaneous. * Disease burden is indicated by markers of the amount of larvae in the stool e.g. based on direct microscopy, Baermann concentration, culture methods and/or nucleic acid tests. Individual diagnosis may have already been made using serology. ** diagnosis based on positive serology only.

§ Alternative where ivermectin is not available or contra-indicated. ¶ no systemic illness, but evidence of high burden of larvae in stool. ¶¶ S/C: if malabsorption/paralytic ileus; until can tolerate oral therapy.

disease burden. The treatment strategy is precautionary and based on a principle that patients with a higher larval burden, or an increased risk of hyperinfection, would need a longer treatment. The amount of *Strongyloides* larvae in the stool can be indicated by direct microscopy, culture methods, Baermann concentration and nucleic acid tests. When serology is diagnostic in an immunocompetent person, prior to treatment, stool may be tested to investigate the larval burden, or treatment with a simple regimen may be used with subsequent follow-up. Due to the greater risk of severe infection immunocompromised individuals, stool testing is recommended in addition to serology.

Well-designed studies (Table 1) indicate the high efficacy (>85%) and tolerability of a single dose of ivermectin in cohorts with uncomplicated infection. In chronic strongyloidiasis, the larval output in the stool is often variable and low [14]. However, additional doses of ivermectin may be warranted, even in patients with no evident immunocompromise, if higher numbers of larvae are detected, suggesting that host immune function is unable to adequately control the larval burden [14,95].

When immunocompromise is present, multiple doses of ivermectin might be recommended, based on a possible reduced response to treatment and lack of immune response against the nematode (Table 3). Since progression toward life-threatening hyperinfection is presumably associated with a steadily increasing larval burden, an immunocompromised person with a high number of larvae in the stool would warrant a more aggressive treatment approach, even in the absence of systemic illness. Although clinical trial data to support this approach are lacking, an appropriate regimen may be treating daily with ivermectin for 1 week and further doses given on days 15 and 16 (Table 3).

Strongyloides hyperinfection is the catastrophic consequence of disease progression in the absence of an earlier diagnosis and treatment. Malabsorption, including paralytic ileus of the gut, may prevent the use of oral therapy and veterinary preparations of subcutaneous ivermectin are required [95]. Although there is a lack of evidence from RCT, the same dose as oral therapy (200 µg/kg) has been frequently used and while daily and alternate daily dosing have been tolerated, low drug levels have raised concerns about dosing adequacy [71,74]. Considering that parenteral ivermectin is usually reserved for very severe disease, daily therapy is likely warranted with a switch to the oral formulation once the patient is able to swallow tablets. In some cases combined ivermectin and albendazole therapy has been used [74,101,102]. Bacteremia is often associated with larval penetration of the intestinal wall and bacterial translocation, hence a broad-spectrum antibacterial therapy should be administered in addition to supportive management in intensive care [55]. The duration of therapy is based on evidence of larval clearance and therapeutic drug monitoring may be useful to ensure adequate levels, although this may not be available in resource-limited settings [55].

Due to reduced *Strongyloides* diagnostic test sensitivity, there is no single, reliable 'test of cure' and this may also lead to an overestimation of published treatment efficacy, depending on the testing strategy used in clinical trials [14,95] (Table 1). For individual-based management, monitoring for symptoms and consideration of repeat testing is important [103], particularly if albendazole therapy was used, which has decreased efficacy (Table 1). Where there is immunocompromise and concern regarding re-infection or incomplete clearance of the parasite, periodic repeat courses of treatment (ongoing treatment/secondary prophylaxis) may be used [55,104]. Relevant factors for consideration include the availability of diagnostic tests, the availability of treatment and patient circumstances, including the degree and duration of immunocompromise. Nonetheless, prior to the development of hyperinfection there would be an incremental increase in larval numbers, increasing the sensitivity of stool tests.

Strongyloidiasis remains a difficult diagnostic challenge and further work is required to clarify management issues. This would include RCT to investigate the safety of therapy in pregnant/breastfeeding women and children, especially considering the large population of this cohort in endemic areas. Studies to investigate optimal treatment regimens and duration for immunocompromised persons would also be valuable, with adequate monitoring to ensure parasite clearance was achieved. In addition, RCT that compare the efficacy of ivermectin and moxidectin for the purposes of mass drug administration and individual treatment would be important, including the use of repeated doses of moxidectin to treat immunocompromised persons and complicated infections.

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