Toxicology Reports 13 (2024) 101754

Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

Understanding *Strongyloides Stercoralis* infection and its relationship to chronic alcohol abuse: Understanding pathogenesis and therapeutic strategies

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ARTICLE INFO

Keywords:
Strongyloides stercoralis
Hyperinfection syndrome
Alcoholism and immunity
Antiparasitic treatment

ABSTRACT

Globally, Strongyloides stercoralis is a prevalent nematode parasite infecting over 600 million individuals, predominantly in tropical regions. Despite its widespread occurrence, it is frequently underdiagnosed and neglected, posing significant health risks, particularly to immunocompromised individuals. This parasite's life cycle includes a concerning capability for autoinfection, potentially leading to hyperinfection syndrome with high mortality rates. Alcoholism is recognized as a major risk factor for exacerbating S. stercoralis infections due to its harmful impact on the immune system. Chronic alcohol consumption impairs adaptive immunity by reducing T-cell and B-cell function, which facilitates parasitic infections. This review examines the complex relationship between alcohol abuse and strongyloidiasis, emphasizing the molecular mechanisms involved. Diagnostic challenges and treatment options, particularly the efficacy of antiparasitic drugs like ivermectin, are also discussed. Understanding these interactions is essential for developing improved diagnostic and therapeutic strategies to combat strongyloidiasis, especially among vulnerable populations, highlighting areas for future study.

1. Introduction

Strongyloides stercoralis a common parasite known to affect over 600 million people worldwide [1]. It is a roundworm species belonging to the group nematodes commonly found in tropical regions despite the wide prevalence of this parasite it is often underestimated due to lack of awareness and research. This is why the parasitic disease is often referred to as a neglected tropical disease [2]. It is an opportunistic intestinal parasite that can affect humans and domestic animals like cats and dogs, they are also capable of spreading to each other [3]. The clinical presentation of this disease can vary widely, from subtle, asymptomatic cases to severe, life-threatening complications. This parasite is mostly transmitted via the transcutaneous route meaning its larva, which can exist as a free form through this route enters the host and later matures there, it can also be transmitted via the faecal-oral route [2]. This particular parasite has a rather alarming trait; it can intensify an infection by reproducing entirely within its host causing autoinfection [4]. Known as Strongyloides hyperinfection Syndrome, this condition is especially dangerous, with studies indicating a mortality rate of over 90 % in such cases [5]. Another notable characteristic of these parasites is their ability to down-regulate the host's immune system [3]. Research suggests this parasite causes 60–85 % mortality in patients who are immunosuppressed. Due to the prevalence of this parasite, it is vital to understand and be aware of the various risk factors

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https://doi.org/10.1016/j.toxrep.2024.101754
Received 5 August 2024; Received in revised form 22 September 2024; Accepted 26 September 2024
Available online 27 September 2024

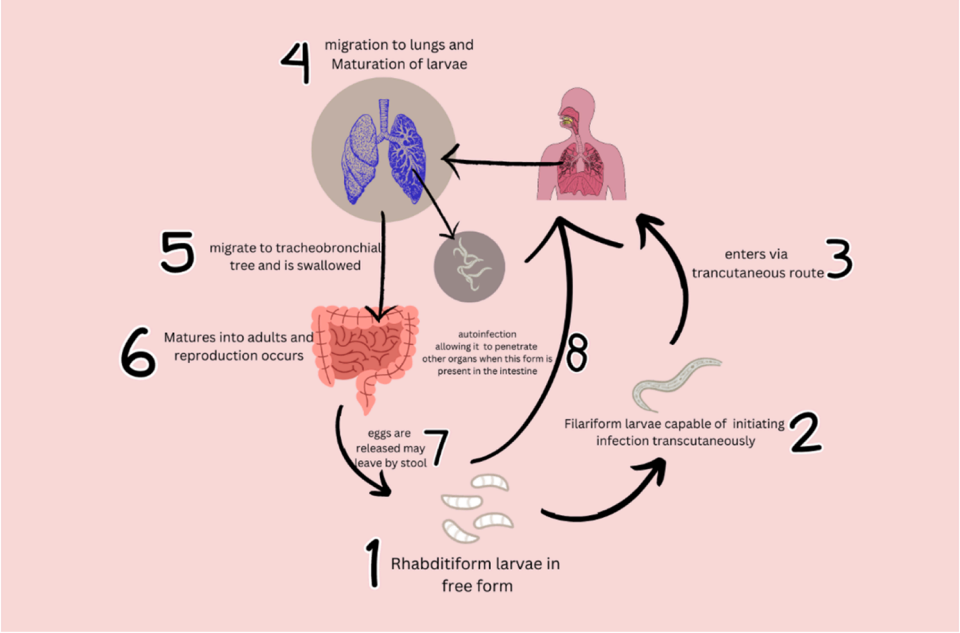

Fig. 1. This image depicts the intricate lifecycle of Strongyloides stercoralis, underscoring the challenges in managing infections due to the parasite's ability to sustain infection through both direct and autoinfective cycles. Sensitive and reliable diagnostic methods for detecting S. stercoralis include serological assays, PCR-based molecular techniques, and stool examination methods like the Baermann test and agar plate culture.

that make one vulnerable to it. Multiple research papers suggest links between HIV, alcoholism, immunosuppressive therapy, and malnutrition [1,2,6] An disadvantage is that it can be challenging to find larvae in stool samples since the parasite burden in infected persons is frequently low and the larval output is erratic. Larvae may be missed by standard stool examination methods in as much as 70 % of instances. Furthermore, the larvae could not always be found in stool samples, therefore a combination of diagnostic techniques, such as duodenal fluid analysis and serological testing, is required for a definite diagnosis. The diagnosis is made more difficult by the inadequate sensitivity of fecal-based testing. Serological procedures are thought to be more sensitive, but it isn't easy to evaluate their accuracy because there isn't a sensitive fecal-based reference standard. Consequently, while repeated sample analysis may be required, it is not always sufficient. [7,8]

Chronic heavy drinking or alcohol abuse is known to have many adverse effects such as pancreatitis, liver disease, diabetes, cardiovascular diseases, dementia, and different types of Cancer [9,10]. According to a conducted study alcohol consumption is accountable for 5.1 % of global diseases when classified based on gender, global diseases of 7.1 % for men and 2.2 % for women. It is also the predominant cause of 10 % of deaths in ages 15–49. It is also a primary cause of disabilities and premature death in newborns [11]. Apart from the systemic effects alcohol consumption can lead to depression, slower responses, and other mental side effects [11]. One of the major side effects of alcohol abuse that connects it to the increased susceptibility to Strongyloides stercoralis is its ability to disrupt humans' adaptive immune system [12]. Research shows chronic alcohol abuse decreases the peripheral T cells by affecting their activation, causing them to undergo apoptosis thereby affecting their function. It also significantly decreases the peripheral B cells. It increases liver antigen-specific antibodies leading to an increase in immunoglobulins [12]. This leads to a compromised immune and can increase the chances of infections that include parasitic infections. Alcohol worsens Strongyloides stercoralis infections by disrupting immune responses, especially by interfering with cytokine signaling, which weakens the body's ability to combat the parasite. Understanding this could lead to the development of therapies that address alcohol's harmful effects on immune function. A study was conducted in a hospital to understand if there is any variation in the frequency of Strongyloides larvae in stools with daily ethanol ingestion. The results showed that the frequency of Strongyloides was 20.5 % in alcoholics and 4.4 % in the control group which shows a significant increase in chances of infection in the alcoholic group [13]. It is vital to understand these mechanisms to prevent the spread of this parasite. Among these risk factors, this review paper aims to dive into the relationship between alcoholism and strongyloidiasis and their molecular mechanisms.

2. Lifecycle of Strongyloides stercoralis

It is vital to understand the lifecycle of Strongyloides stercoralis to understand the mechanism by which these risk factors exacerbate the condition and to find treatment methodologies. The parasite exists both in the free form as well as the parasitic form [14]. When they are in free form found in the soil, they exist as rhabditiform larvae. They are capable of surviving without a host. The larval stage is the transmission stage. The main route of transmission is by penetrating skin through a trans-cutaneous route although primary infection can occur by consuming the larvae by drinking contaminated water or eating contaminated food. When there is direct contact between skin and soil, instances when a person walks barefoot they are prone to getting infected by this parasite. It presents as a ground itch [1]. After entering the human host it migrates to the lungs where they first mature. Following this the parasite moves up the pulmonary parenchyma, it is then swallowed after being coughed up. This allows it to move to the intestine where it matures into the adult reproducing stage. As shown in Fig. 1, the method of reproduction of this parasite is asexual. Here, the mature female produces eggs which develop into the rhabdiform larvae again. These rhabdiform larvae are excreted in the faeces where they enter the free form again [1,14]. An interesting feature of these parasites is their ability to cause Autoinfection, which is when they don't leave the human host, rather they continue their lifecycle within the host. This is one of the major factors that make this parasite highly dangerous. It can penetrate through the intestinal mucosa and continue its life cycle within the host. In immune-compromised patients, it causes hyper-infection by penetrating into other organs. In many cases this is fatal. [14]

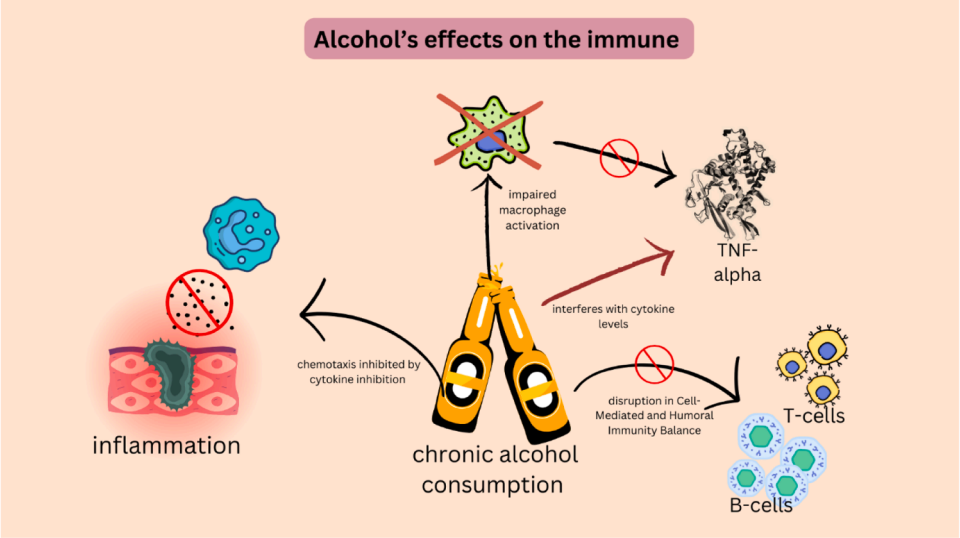

Fig. 2. The image above illustrates the various immune pathways affected by alcohol, demonstrating its impact on both innate and adaptive immunity and highlighting how alcohol intake can exacerbate multiple illnesses.

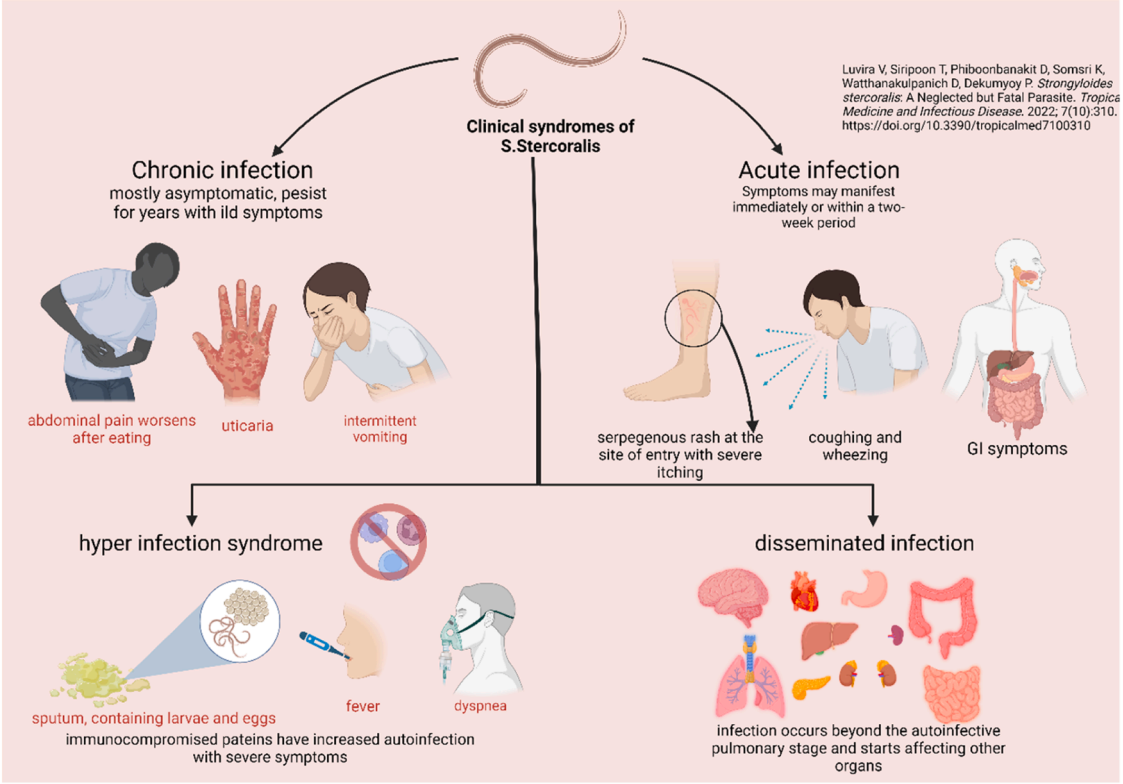

Fig. 3. The illustration shows the different clinical syndromes of Strongyloides stercoralis, including acute, chronic, disseminated, and hyperinfection syndromes.

3. Alcohol and its effects on the human immune system

The human immune system is comprised of two components innate and adaptive.[15] Innate is the non-specific component of the immune that comprises physical barriers, macrophages, neutrophils, dendritic cells, and natural killer cells. These components of the immune system are the first ones to act on an antigen. They do not exhibit any memory, so there is no variation in the effect of the primary and secondary infection [16,17,18]. Adaptive immunity is responsible for specific and targeted action on antigens. The adaptive immune consists of T cells and B cells. They have memory and therefore they provide increased protection in cases of reinfection. They are classified under cell-mediated and humoral immune response. They have various functions such as antibody production, cytokines production for recruitment of other leukocytes, and lysis of antigenic cells. [19,20,21]

The major classifications of T cells include cytotoxic T-cells and helper T cells. Cytotoxic T-cells participate in recognising surface antigens and causing lysis whereas helper T-cells secrete cytokines, promoting chemotaxis that attracts other leukocytes to the site of inflammation. B cells are majorly responsible for carrying immune

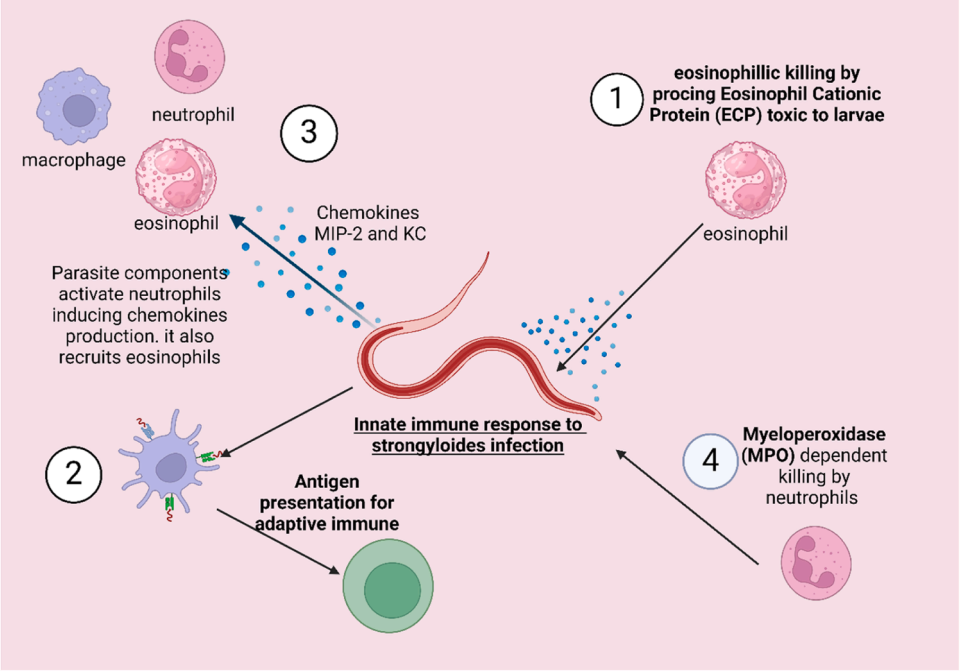

Fig. 4. The image illustrates the sophisticated strategies of the innate immune system against Strongyloides stercoralis, highlighting the roles of various immune cells and molecules in controlling the parasite and preventing its spread (macrophage-inflammatory protein-2 (MIP2), and keratinocyte-derived chemokine (KC).

proteins like immunoglobulins and antibodies. These antibodies help with opsonisation and cell lysis. They also mark the cells for T-cells and other leukocytes to recognise. They later develop into memory cells and plasma cells that assist with faster action during secondary infection [2]. The human immune system is highly vital and it is needed to prevent infection by Strongyloides stercoralis as mentioned earlier an immunocompromised patient is prone to hyperinfection [22]. Many studies suggest alcohol consumption leads to a diminished immune. That in turn suggests a chronic alcohol abuser would be a viable host for Strongyloides stercoralis (Fig. 2).

4. Strongyloides infection

Strongyloidiasis in more than 50 % of cases has been studied to be asymptomatic. Patients usually present with non-specific symptoms. The clinical presentation of the disease depends on the immune competence of the patient and the parasitic load. In immunocompetent patients, the disease is mostly asymptomatic. As shown in Fig. 3, in immunocompromised patients, it could develop into hyperinfection syndrome. That is the more complicated presentation of the disease. The disease can also present as an acute or chronic infection. [23]

Uncomplicated forms of presentation include chronic and acute infections. Acute infections are usually reported in patients travelling to high-risk regions in Southeast Asia [24]. The symptoms are acute and present within 2 weeks. It often starts with a surpentinous rash at the larval entry sight such as a ground itch, it can last for up to three weeks. The larva currens is one of the primary features of Strongyloides stercoralis infection it worsens rapidly and presents with intense itchiness as the larvae migrate. Later leads to loffer syndrome which is characterised by eosinophilic pneumonitis, wheezing and cough. The GI symptoms include vomiting, diarrhoea and epigastric pain after eating [25,26]. Contrary to acute infections Chronic infections occur more commonly as medication can only eliminate adult parasites and not the larvae therefore, multiple series of doses are required for treating it. Chronic Strongyloides Stercoralis infection in most cases is asymptomatic or presents with mild symptoms. The common symptoms include urticarial and maculopapular rashes. Non-specific GI symptoms are recorded like diarrhea, epigastric pain after meals, and constipation [1]. Lab recordings suggest peripheral eosinophilia in 75 % of the patients, they also present with cough or wheezing. Patients who have these non-specific symptoms but have been traveling to endemic areas are examined for Strongyloidiasis [27]

In immune-compromised patients, there are chances of complicated forms of the disease developing. The complicated forms of this infection are hyperinfection and disseminated infection. It occurs when autoinfection occurs, which leads to an increase in parasite load therefore worsening the symptoms [28]. The majority of the cases present with fever, GI, and respiratory symptoms. Skin manifestations include, increased purpuric rashes and larva currens predominantly found in the lower back and thighs. Diagnosis of hyperinfection can be done by testing sputum and stool, to check for an increase in larva. When larval migration occurs outside the pulmonary autoinfection cycle the larva penetrates other organs like the spleen, liver, brain, and heart. This leads to other systemic issues and chances of further infection known as disseminated infection. [23]

5. Innate immune action on strongyloides stercoralis infection

In a study conducted on the immune reaction of rats to Strongyloides infection, researchers observed increased eosinophilia at the sites with higher concentrations of parasite components suggesting an attempt by the immune against the parasite. This was during the primary infection. The innate immune response also included the attraction of neutrophils which exhibited myeloperoxidase (MPO)-dependent mechanism to assist in killing the parasite. The C3b component from complement activation helps enhance the cytotoxic capabilities of both cell types, neutrophils and eosinophils. Interestingly eosinophils play another role and act as antigen-presenting cells which help promote Th2 action thereby activating the adaptive immune and its components like the T-helper cells. This Th2 later assists with the targeted adaptive immune response by promoting B-cell proliferation and antibody production. These findings explain the complex interaction between various components of the immune during *Strongyloides* infection which will be valuable for finding therapeutic solutions. [26,27,28,29]

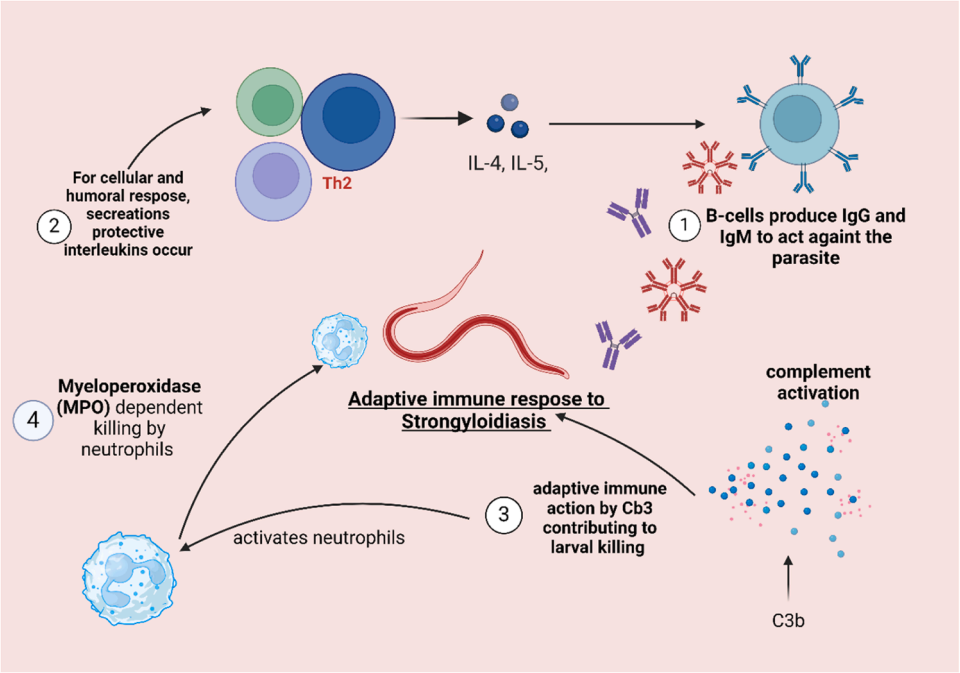

Fig. 5. This picture depicts the adaptive immune system's coordinated response to Strongyloides stercoralis infection, emphasizing the roles of various immune cells and molecules in controlling parasite growth and preventing its spread (Th, T helper cells; IFN-γ, interleukin; IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M).

6. Adaptive immune action on strongyloides stercoralis infection

The adaptive immune response to Strongyloides stercoralis is characterized by the activation of Th2 lymphocytes, which plays a vital role in the body's defence mechanism against the parasite. The main function of the Th2 cells is secretion of different cytokines, in this case, Interleukin-4 (IL-4) and Interleukin-5 (IL-5), which serve multiple functions. The main role IL-4 plays is in promoting the differentiation of naive helper T cells to Th2 cells and promoting the growth of B-cells [26]. It also helps in the neutralization and clearance of pathogens by increasing the production of immunoglobulins like IgG and IgE, which are crucial. IL-5, on the other hand, is primarily involved in the growth and differentiation of eosinophils, which as shown in Fig. 4 are the main effector cells that release cytotoxic proteins to damage the parasite.

[27] It also functions by activating B-cells and the subsequent production of IgG and IgM antibodies. These antibodies play a role in removing the parasite by binding to it and tagging it known as

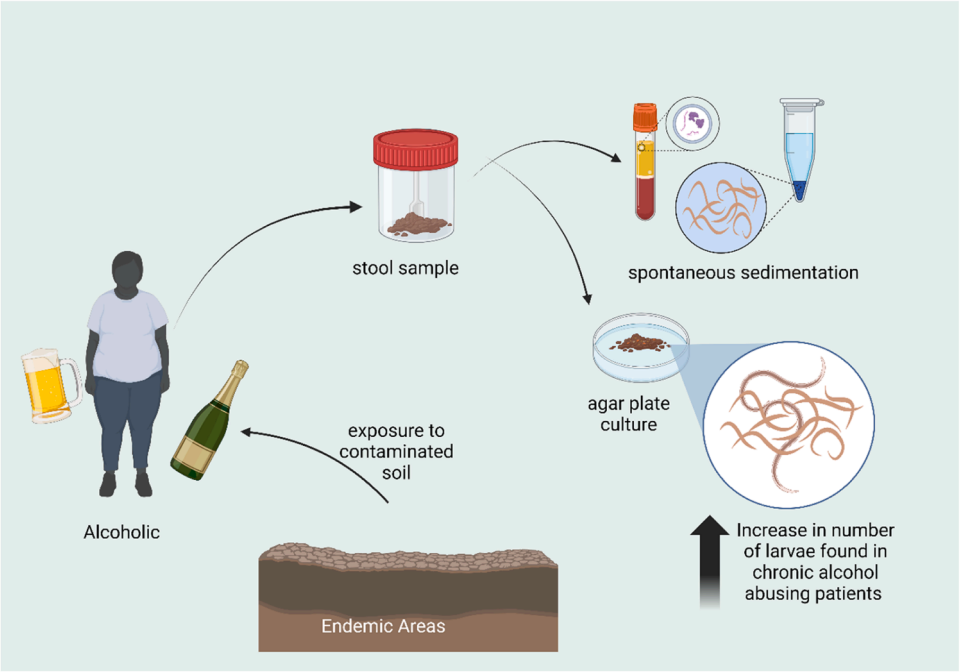

Fig. 6. Flowchart showing the diagnostic pathway for parasitic infections in chronic alcohol users in endemic areas.

Table 1
Clinical indication for parasitic infections.

Drugs for Parasitic Infections in Chronic Alcoholics	MOA	Other uses
Ivermectin	It binds to glutamate-sensitive chloride channels in the parasite, leading to the opening of these channels and affecting the central nervous system of the parasite. This leads to paralysis in the parasite.	- scabies, gnathostomiasis and myiasis [32]
Thiabendazole	Inhibits fumarate reductase, disrupting energy metabolism	-Strongyloides and other parasitic infections [33, 34]
Albendazole	It binds to the colchicine-sensitive site of tubulin, inhibiting microtubule formation which leads to a decrease in APT production and affects the parasite's intestinal cells	-cystic hydatid disease, parenchymal and neurocysticercosis [35]
-Mebendazole	-In intestinal cells of parasites, it acts by inhibiting tubulin polymerisation affecting microtubule formation	-Roundworm, Hookworm, whipworm and pinworm [36]
-Nitazoxanide	-Interferes with electron transfer reaction dependent on pyruvate:ferredoxin oxidoreductase (PFOR) enzyme	-Cryptosporidiosis and giardiasis [37]
-Levamisole	- It is a nicotinic acetylcholine receptor agonist, which causes paralysis.	- *Ascaris lumbricoides* and Rheumatoid arthritis [38,39]
-Pyrantel Pamoate	-Acts by depolarizing neuromuscular blocker, causing paralysis	-Prophylaxis against Angiostrongylus cantonensis and other hookworm, and roundworm infections [40]
-Praziquantel	It acts by increasing the cell membrane's permeability to calcium, which affects the movement of the parasite causing paralysis	- schistosomiasis [41]
-Triclabendazolenit	It acts by disrupting the outer layer of a parasite by inhibiting microtubule-based processes or by affecting adenylate cyclase activity.	- Fascioliasis [42]
- ceftriaxone	A third-generation cephalosporin antibiotic that inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs). This binding disrupts the cross-linking of peptidoglycan chains, weakening the cell wall and leading to bacterial cell lysis and death.	- Ceftriaxone is used to treat a number of serious illnesses such as bacterial meningitis (Neisseria meningitidis, Streptococcus pneumoniae), gonorrhoea (Neisseria gonorrhoeae), and community-acquired pneumonia (Haemophilus influenzae). This broad-spectrum antibiotic is also useful in treating septicaemia, acute pyelonephritis, and severe intra-abdominal infections. It works against bacteria such as Staphylococcus aureus and Escherichia coli. It is also used in surgical procedures as a prophylactic measure to avoid postoperative infections. [43]
-Piperacillin-Tazobactam	A beta-lactam antibiotic with a broad spectrum that is a member of the penicillin class is piperacillin. It functions by preventing the synthesis of bacterial cell walls. By attaching itself to penicillin-binding proteins (PBPs) found inside the bacterial cell wall, it does this. The crosslinking of peptidoglycan chains, which is necessary for the strength and stiffness of cell walls, is hampered by this binding. As a beta-lactamase inhibitor, tazobactam prevents the production of beta-lactamase enzymes by some bacteria, which renders piperacillin and other beta-lactam antibiotics ineffective.	Intra-abdominal infections (e.g., appendicitis, peritonitis), Nosocomial pneumonia (hospital-acquired pneumonia), Complicated skin and soft tissue infections, Complicated urinary tract infections [44]
Prednisolone	Prednisone reduces inflammation by reversing increased capillary permeability and inhibiting polymorphonuclear leukocyte movement. Additionally, it lowers the immune system by lowering its volume and activity.	Autoimmune conditions like rheumatoid arthritis and its used for severe alcoholic hepatitis [45, 46]
Naltrexone	It is efficient at preventing the mu-opioid receptor from being occupied by alcohol and opioids. Additionally, naltrexone is a less potent antagonist of the delta and kappa opioid receptors. By amplifying the effects of alcohol and opioids, endogenous opioids play a role in their modulation.	- Mainly used to treat alcohol addiction [47]
Disulfiram	In the stomach, disulfiram transforms into diethyldithiocarbamate, an active metabolite. It transforms into diethyldithiocarbamic acid (DDC) in the blood, which is then broken down to produce diethylamine and carbon disulphide. Phase II metabolism of DDC results in the formation of sulfoxide and sulfone metabolites. The effects of disulfiram are produced by these strong active metabolites that have undergone S-oxidation.	-alcohol and cocaine dependence [48,49,50]

opsonization. This allows other components of the immune to facilitate phagocytosis. A group of proteins that work together with antibodies against the pathogen known as the complement system is also activated by this. Neutrophils which are also activated by the complement system, contribute to the immune response through Myeloperoxidase (MPO)--dependent mechanisms, which generate reactive oxygen species to kill the parasite [26]. Another function of the complement system is to form membrane attack complexes that lyse the parasite's cells. Together, these multifaceted immune responses ensure a well-developed defence against parasitic infections [27]

7. Action of alcohol in Strongyloidiasis

Strongyloides stercoralis infection is commonly asymptomatic but severe in immunocompromised people including chronic alcohol abusers. In these cases, it can develop into a severe disease. A study was conducted in Brazil in the year 2020 under the topic 'Strongyloides stercoralis in Alcoholic Patients: Implications of Alcohol Intake in the Frequency of Infection and Parasite Load'. 1290 chronic alcoholic patients were examined by using three methods, spontaneous sedimentation, Baer-Moraes, and APC (agar plate culture). In these tests Strongyloides stercoralis was the most prominently found parasite compared to other parasites like hookeworms and Ascaris lumbricoides. The percentage frequency of Strongyloides stercoralis was 14.5 % in 129 people out of 1290.

This shows that alcohol consumption greatly affects the results in the number of larvae found. Another fact to support this is when the infected patients were further examined it was revealed that their daily consumption of alcohol was greater than those non-infected. Patients who had increased alcohol uptake of above 849.0 g/day showed more than 101 larvae per gram of faeces. It was found that Strongyloides stercoralis is the primary parasite that affects most alcoholic patients, especially in endemic areas [30]. Among the diagnostic methods mentioned (spontaneous sedimentation, Baer-Moraes, and agar plate culture) APC was the most accurate diagnostic method [31]. Research should prioritize optimizing ivermectin dosing regimens to boost efficacy and reduce both costs and side effects. This approach will help maximize the drug's benefits while minimizing adverse outcomes.

8. Treatment approach for parasitic infections

All the medications may not be used directly for strongyloides stercoralis infection, some may be used to treat symptoms, secondary infections, super infections, and some are used only during disseminated or hyperinfection. The treatments for Strongyloides stercoralis include a variety of antiparasitic medications with a wide range of mechanisms of action. For the management of chronic Strongyloides infection, the preferred drug is ivermectin which is a broad spectrum antiparasitic medication [51]. As mentioned in Table 1 it acts by paralysing the parasite. It is preferred over other drugs like Thiabendazole. The reason for this is the tolerance of ivermectin is greater and its efficacy is similar to Thiabendazole making it a more efficient option. In the USA for uncomplicated Strongyloides infection, the recommended dose is 200 micrograms per kilogram per day for 2 days. Another favourable factor of ivermectin in comparison to albendazole is that it has a greater larval clearance rate.[1] While some recommend multiple doses a study suggests that the efficacy of 1 dose of Ivermectin is similar to that of multiple doses [52–56]. A multicenter, open-label, phase 3 randomised controlled superiority trial spanning nine centres in Europe provided compelling results for the treatment of S. stercoralis infection (ClinicalTrials.gov identifier NCT01570504). In individuals with a proven S. stercoralis infection, the trial assessed the effectiveness of four doses of ivermectin 200 μg/kg vs a single dosage. Most remarkably, the single-dose group's (86 %) and the four-dose group's (85 %) 12-month clearance rates were comparable, indicating that, for patients who do not live in endemic areas, a single-dose regimen would be more cost-effective and as effective. The early conclusion of this trial for futility highlights the need for additional research to optimise treatment approaches [57–60]. Alternative and combination therapies for severe infections need further exploration and research. Additionally, further development and testing are required to integrate various diagnostic methods to improve accuracy. This approach will help ensure more reliable and precise diagnostic outcomes. Increasing public health awareness is essential for enhancing early diagnosis and treatment of S. stercoralis infections, especially in tropical areas. Educating communities about prevention and symptoms can lead to timely medical intervention and better health outcomes.

9. Conclusion

Our review study highlights Strongyloides stercoralis as a significant yet overlooked health threat, particularly in tropical regions and among immunocompromised individuals such as chronic alcohol abusers. The parasite's capacity for autoinfection and hyperinfection underscores the urgent need for increased awareness and enhanced diagnostic methods. Current diagnostic approaches often fail due to the parasite's inconsistent presence in stool samples, necessitating more sensitive serological methods despite their limitations. Future research should prioritize improving diagnostic accuracy through the development of reliable detection methods, possibly integrating multiple diagnostic strategies. Additionally, further investigations are crucial to understand how alcohol exacerbates strongyloidiasis at the molecular level, potentially informing targeted interventions to mitigate alcohol's impact on immune function. Therapeutically, optimizing treatment regimens, particularly in non-endemic areas, is vital. Evaluating the efficacy of single versus multiple doses of ivermectin extensively can establish cost-effective and efficient treatment protocols. Moreover, exploring alternative therapeutic agents and combination therapies holds promise for improving outcomes in patients with severe or complicated infections.

CRediT authorship contribution statement

K. Gowtham: Writing – original draft, Validation, Resources, Project administration, Investigation. **Satyanarayana Reddy:** Writing – review & editing, Visualization, Supervision, Resources, Formal analysis. **Vinoth Kumarasamy:** Writing – original draft, Visualization, Validation, Resources, Data curation. **Vetriselvan Subramaniyan:** Writing – original draft, Validation, Project administration, Conceptualization. **Muralikrishnan Dhanasekaran:** Writing – review & editing, Visualization, Supervision, Project administration, Data curation. **Vinibha Rajakumari Illankovan:** Writing – original draft, Validation, Project administration, Investigation, Formal analysis, Conceptualization. **Roshvin Kailashnath Pillai:** Writing – original draft, Validation, Project administration, Data curation, Conceptualization. **Rishvini Kailashnath Pillai:** Writing – review & editing, Visualization, Investigation, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors are unable or have chosen not to specify which data has been used.

Acknowledgments

We gratefully appreciate the library of MAHSA University Malaysia, Universiti Kebangsaan Malaysia, INTI International University Malaysia, JSS Academy of Higher Education and Research, India, And Sunway University Malaysia for providing literature support to complete this study.

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