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REVIEW

THE IMPACT OF DIAGNOSING AND TREATING SCHISTOSOMIASIS

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Abstract

Schistosomiasis, a parasitic disease caused by Schistosoma trematode worms, poses a substantial global health threat, affecting over 800 million individuals across 76 endemic countries. Predominantly caused by *Schistosoma haematobium, Schistosoma japonicum*, and *Schistosoma mansoni*, the disease thrives in regions with inadequate sanitation and hygiene practices. Despite its significant impact, current diagnostic methods lack affordability, precision, and straightforwardness, hindering effective disease control.

This manuscript extensively reviews various diagnostic approaches, encompassing parasitological, immunological, and molecular techniques. The need for novel, cost-effective, and highly sensitive diagnostic tools, especially in low-transmission regions, is emphasized. The manuscript also delves into the complexities of managing schistosomiasis, primarily reliant on the administration of praziquantel. While effective, challenges such as side effects and potential resistance necessitate ongoing research. The combination of artemisin derivatives with praziquantel presents a promising avenue for enhanced treatment outcomes. In conclusion, the manuscript underscores the urgency of advancing diagnostics and therapeutics, alongside

Résumé

L'impact du diagnostic et du traitement de la schistosomiase

La schistosomiase, une maladie parasitaire causée par les vers trématodes Schistosoma, représente une menace considérable pour la santé mondiale, affectant plus de 800 millions de personnes dans 76 pays endémiques. Principalement causée par Schistosoma haematobium, Schistosoma japonicum et Schistosoma mansoni, la maladie se développe dans les régions où l'assainissement et les pratiques d'hygiène sont inadéquats. Malgré son impact significatif, les méthodes de diagnostic actuelles manquent d'accessibilité financière, de précision et de clarté, ce qui entrave l'efficacité de la lutte contre la maladie. Ce manuscrit passe en revue les différentes approches diagnostiques, y compris les techniques parasitologiques, immunologiques et moléculaires. Il souligne la nécessité de disposer d'outils de diagnostic nouveaux, rentables et très sensibles, en particulier dans les régions à faible transmission. Le manuscrit se penche également sur la complexité de la gestion de la schistosomiase, qui repose principalement sur l'administration de praziquantel. Bien qu'il soit efficace, des défis tels que les effets secondaires

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strategic interventions for interrupting disease transmission, to comprehensively address the global impact of schistosomiasis.

Keywords: Schistosomiasis, praziquantel, parasitic disease, trematode worms, schistosomes.

List of abbreviations:
DNA – Deoxyribonucleic Acid
RNA – Ribonucleic Acid
PCR – Polymerase Chain Reaction
PZQ – Praziquantel

et la résistance potentielle nécessitent une recherche continue. La combinaison des dérivés de l'artémisine avec le praziquantel constitue une voie prometteuse pour améliorer les résultats du traitement. En conclusion, le manuscrit souligne l'urgence de faire progresser les diagnostics et les thérapies, ainsi que les interventions stratégiques visant à interrompre la transmission de la maladie, afin de s'attaquer à l'impact mondial de la schistosomiase.

Mots-clés: Schistosomiase, praziquantel, maladie parasitaire, vers trématodes, schistosomes.

Introduction

Schistosomiasis, or bilharziasis, is a parasitic disease caused by trematode worms of the genus *Schistosoma* that infect humans.[1] The main species accountable for schistosomiasis are *Schistosoma haematobium*, *Schistosoma japonicum*, and *Schistosoma mansoni*, while *Schistosoma intercalatum*, *Schistosoma guineensis*, and *Schistosoma mekongi* have a relatively lower occurrence globally.[2]

Schistosomiasis is the second most significant tropical disease in terms of its impact on public health, following malaria. Schistosomiasis poses a risk to over 800 million individuals residing in 76 countries where the disease is prevalent. There is a global prevalence of approximately 207 million cases of schistosomiasis. *Schistosoma haematobium* is responsible for over 50% of all cases of schistosomiasis worldwide, amounting to approximately 112 million infections. The parasites *Schistosoma haematobium* and *Schistosoma mansoni* are responsible for causing approximately 280,000 deaths each year.[3]

Infection arises when an individual encounters water that contains cercariae discharged by an intermediate host snail, which can belong to the genus *Biomphalaria* (for *Schistosoma mansoni*), *Oncomelania* (for *Schistosoma japonicum*), or *Bulinus* (for *Schistosoma haematobium*). While cercariae can remain viable in water for a period of 1 to 3 days, their capacity to cause infection decreases rapidly within a few hours after being released.[4] Inadequate sanitation and hygiene practices can put individuals of all age groups, including children, teenagers, and adults, at risk of infection, as it can be transmitted through contact with water contaminated by cercariae. Contamination primarily affects socioeconomically disadvantaged regions and developing nations, where the disease's prevalence is elevated. Engaging in other water-related activities, such as using open freshwater for domestic purposes like washing clothes and dishes, participating in recreational activities like bathing in rivers and lakes, or having an occupation that involves contact with water, can increase the likelihood of being exposed to cercariae.[2,5]

Currently, there is a lack of straightforward, affordable, and precise diagnostic methods for schistosomiasis, which hinders the collective endeavors to fully control the disease. In the pursuit of discovering novel diagnostic techniques and indicators, it is crucial to enhance the efficacy of current diagnostic methods to attain superior outcomes.[6] The management of schistosomiasis consists in administering praziquantel to affected populations on a large scale and providing regular treatment to all groups at risk. Priority should be given to interrupting the transmission of this disease in countries with low transmission rates.[5]

Diagnosis of Schistosomiasis

In recent decades, a range of diagnostic methods have been created to identify schistosomiasis, including basic microscopic detection and advanced molecular techniques.[7] The existing diagnostic approaches can be categorized into four main groups: direct parasitological diagnosis, immunological diagnosis, DNA and RNA detection, and the utilization of cytokines, metabolites, and other schistosoma molecules as biomarkers (Table 1). Table 2 shows the diagnosis and evaluation of diseases related to the intestine, liver, genitourinary system and neuroschistosomiasis.[8]

The initial diagnostic procedures employed parasitological techniques, such as identifying eggs in fecal samples to detect intestinal schistosomiasis or in urine to detect urinary schistosomiasis.[30] The Kato-Katz (KK) thick stool smear and urine egg concentration detection techniques are particularly well-suited for regions with intense schistosome transmission owing to their straightforwardness and cost-efficiency. Moreover, these tests require only basic training and are appropriate for use in large-scale population surveys.[5]

Table 1. Various diagnostic approaches for schistosomiasis

Diagnostic Strategy	Description	References
Direct Parasitological Diagnosis	The Kato-Katz (KK) thick fecal smear technique, which was developed in 1972 and relies on microscopy, remains widely utilized and is considered the standard method recommended by the World Health Organization (WHO) for diagnosing intestinal schistosomiasis and quantitatively assessing the severity of infection.	9,10
	The primary parasitological methods employed for diagnosing urinary schistosomiasis involve urine filtration and concentration of *Schistosoma haematobium* eggs, followed by microscopic examination.	4,11
Immunologic Diagnosis	Immunologic diagnosis involves conducting tests to identify the presence of antibodies against the parasite schistosome or the presence of the parasite's antigens in plasma, serum, urine, or sputum.	7,12
	The following diagnostic tests are used to detect antibodies and antigens related to parasitic infections: intradermal test, circumoval precipitin test (COPT), cercarien hüllen reaction (CHR), indirect hemagglutination test (IHT), enzyme-linked immunosorbent assay (ELISA). The antigens that are tested for include soluble egg antigen (SEA), larval and adult worm antigens (AWA), circulating cathodic antigen (CCA), and circulating anodic antigen (CAA).	12-20
Identification of DNA and RNA	The use of conventional or more sophisticated PCR-based methods, such as real-time quantitative PCR (qPCR) or multiplex PCR, shows promise as a diagnostic test for accurately detecting schistosome DNA or RNA. This test can be used to diagnose schistosomiasis with high precision. Notable progress has been made in identifying egg DNA, circulating cell-free parasite DNA (CFPD), and circulating microRNA (miRNA).	21-23
	Loop-mediated isothermal amplification (LAMP) is a recently developed method that is both cost-effective and practical for detecting schistosome DNA in fecal and serum samples. It is considered an alternative to conventional PCR.	24,25
Utilization of cytokines, metabolites, and other molecules from Schistosome as biomarkers	Typically, in the initial acute stage of infection, when the parasite is mainly in its juvenile form, a Th1 cell-mediated response occurs. This response involves the release of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interleukin-1 (IL-1), and IL-2. Subsequently, when schistosome eggs are deposited in tissues, there is a transition to a Th2-mediated immune response, which is characterized by the generation of IL-4, IL-5, IL-10, and IL-13, in addition to IgE antibodies.	26
	From day 41 after infection, significant alterations in the metabolite composition of urine, feces, and plasma were observed. Notably, urinary changes were particularly prominent, with hippurate, phenylacetylglycine (PAG), and 2-oxoadipate serving as important urinary markers. Conversely, D-3-hydroxybutyrate and glycerophosphorylcholine consistently acted as markers in plasma.	27
	Components of *Schistosoma japonicum* expressed during various stages of its life cycle, such as specific tegument proteins (SjTs4) and eggshell proteins (MF3), have the potential to be useful as targets for diagnostic purposes..	28
	The utilization of recombinant SjLAP (rSjLAP) and recombinant SjFBPA (rSjFBPA) in ELISA proved to be effective for the detection of S. japonicum in humans.	29

Intradermal tests, which are immunologic diagnostic procedures, are characterized by their simplicity and affordability, making them a popular choice for conducting early prevalence studies.[8] Antibody detection has demonstrated efficacy in diagnosing the three main types of human schistosome and is essential for identifying infections in regions with low prevalence, where patients show low levels of egg production.[11] The COPT test exhibits a high level of sensitivity and specificity, making it a valuable tool for diagnosing *Schistosoma japonicum* infection, particularly in China. The CHR test yields a positive result when the patient's serum is combined with live cercariae.[5] The IHT method detects the interaction between antibodies found in the serum of infected individuals and red blood cells that are covered with schistosome antigens.[34] The ELISA method can be employed to evaluate the interaction between antibodies in the patient's serum and antigens derived from different phases of the schistosome life cycle.[18] The identification of schistosome antigens (derived from schistosomules, adult worms, or eggs) in blood, urine, or sputum has been established as a reliable and highly efficient diagnostic method.[35]

Notable progress has been made in the identification of schistosome DNA or RNA, such as egg DNA, LAMP, circulating cell-free parasite DNA (CFPD), and circulating microRNA (miRNA).[21] Biomarkers for the diagnosis of schistosomiasis have been assessed, including host cytokines and different metabolites produced by schistosoma. Biomarkers related to metabolism and cytokine levels lack specificity in

Table 2. Diagnosis and assessment of gastrointestinal, hepatic, genitourinary, and central nervous system disorders resulting from Schistosome infection.

Diagnosis and Assessment	Description	References
Intestinal disease caused by schistosomes	The earliest diagnostic procedures, known as parasitological methods, involved detecting eggs in fecal samples to diagnose cases of intestinal schistosomiasis. The diagnosis is established through the detection of schistosome eggs in feces, rectal scrapings, or rectal incisions.	30
	Proctocolonoscopy is a diagnostic procedure that aids in determining the diagnosis, ruling out similar lesions such as ulcerative colitis and amoebic colitis, and classifying the histopathologic pattern.	5
Liver disease caused by schistosomes	The identification of structural and biochemical alterations is beneficial for diagnosing and assessing liver diseases induced by schistosomes. The primary techniques employed for disease evaluation include liver biopsy, liver imaging, and biomarker detection. The invasive nature, low patient and clinician acceptance, resulting complications such as bleeding, and potential sampling errors have restricted the routine use of liver biopsy with histology in clinical practice, despite its ability to provide significant direct evidence of localized liver damage.	8,31
Urogenital disorders caused by schistosomes	Direct visualization through cystoscopy, microscopic analysis via biopsy, and utilization of imaging techniques enable the detection and assessment of structural alterations in the genitourinary tract. Imaging modalities encompass x-ray, computed tomography (CT) scan, magnetic resonance imaging (MRI), and ultrasound. Ultrasound imaging, a non-invasive and convenient technique, is frequently employed for the detection and evaluation of pathological lesions in the urinary tract.	1,8
Neuroschistosomiasis	Direct detection of parasite eggs and pathological changes by biopsy is considered the definitive method for diagnosing neuroschistosomiasis. Nevertheless, this procedure is extremely invasive and perilous. Neuroimaging techniques like CT and MRI can be used to identify central nervous system (CNS) involvement. These techniques are effective in detecting signs of lesions, such as masses and tissue edema.	32,33

diagnosing schistosoma infection and have limited diagnostic utility.[26]

There have been thorough examinations of the existing diagnostic techniques and the difficulties they present. It is crucial to increase efforts to create novel diagnostic tools that are more affordable, highly sensitive, and specific. These tools should enable precise determination of infection status in regions with low rates of transmission.[6] While the eradication of schistosomiasis necessitates the creation of novel diagnostic tools that possess both high sensitivity and specificity, the issue of test validity poses an additional challenge for diagnostic techniques.[36]

In cases of intestinal schistosomiasis, the eggs are primarily deposited in the liver and intestinal wall, resulting in the development of multiple granulomas and tissue lesions in these organs. Consequently, there is an occurrence of excessive growth of the intestinal lining, the development of multiple abnormal growths, formation of open sores, and creation of pus-filled pockets. These are primarily manifested as abdominal discomfort, persistent loose stools, and bleeding from the rectum.[2,5] The primary cause of liver damage induced by schistosome is the formation of granulomas and fibrosis around the eggs of schistosome that are lodged in the presinusoidal portal vein. This immunological response is responsible for the occurrence of severe complications associated with chronic schistosomiasis.[8] The genitourinary system is primarily affected by *Schistosoma haematobium* through the induction of granulomatous inflammation caused by the deposition of eggs in the genitourinary tract. These conditions may arise consequently: polyposis, bladder carcinoma, bladder calcification, ulceration, and ureteral stricture.[1,8] Neuroschistosomiasis is a condition that arises from the severe complications of an infection with schistosome eggs, which then spreads to the central nervous system. The condition causes the formation of granulomas in the nervous tissue, resulting in cerebral and spinal schistosomiasis. Seizures commonly arise from brain dysfunction, whereas myeloradiculopathy arises from spinal cord dysfunction.[32]

Management of Schistosomiasis

Praziquantel (PZQ) is the preferred medication for the treatment of schistosomiasis. It exhibits efficacy against all species of schistosoma, although its mode of action remains incompletely elucidated. An efficient host antibody response is necessary for the drug to exert its effectiveness.[37] PZQ exhibits efficacy against mature schistosome worms, while its impact on juvenile schistosome larvae is limited.[1] The widely accepted effective treatment for *Schistosoma*

haematobium and *Schistosoma mansoni* infections is a recommended dosage of 40 mg/kg body weight. Moreover, it is deemed safe for administration during pregnancy, starting from the second trimester. The optimal dosage for *Schistosoma japonicum* and *Schistosoma mekongi* is 60 mg/kg of body weight.[1,38] This drug demonstrates a 63-85% effectiveness against *Schistosoma haematobium*, *Schistosoma japonicum*, and *Schistosoma mansoni*, and has the ability to decrease the number of eggs by over 90% following 6 months of treatment.[8] To achieve a complete cure of the parasite, higher doses of medication, up to a maximum of 80 mg/kg given in multiple doses, are necessary.[39] PZQ commonly causes abdominal pain, headache, and dizziness as side effects. Severe infections are associated with a significant likelihood of experiencing side effects, which reach their maximum intensity approximately 2-4 hours after the administration of the medication.[1]

Artemisin derivatives, such as artemether and artesunate, were originally created as drugs to treat malaria. However, they also can eliminate the early larval stages of *Schistosoma* development. Meta-analyses have demonstrated that the combination therapy of PZQ and artemisinin has a cure rate twice as high as that of monotherapy with PZQ. Prior to standardizing combination treatment, further research is required on dosage, formulation, and drug interactions. Additionally, it is important to take into account the possibility of malaria parasites developing resistance to artemisin before implementing the combination in regions where malaria is prevalent.[40,41]

PZQ is the preferred medication for the treatment of schistosomiasis. It exhibits efficacy against all species of schistosomes. It is postulated that PZQ interferes with the balance of calcium levels in mature worms by interacting with and regulating calcium ion channels, thus causing harm to the outer covering of adult worms. Following the administration of PZQ, there was a notable increase in the differentiation of type 1 regulatory T cells (Tr1) and a decrease in inflammation. This indicates that PZQ improves immune regulation.[42-44]

Conclusions

Schistosomiasis remains a global health concern, affecting millions of people in endemic regions. There is a need for affordable, precise, and sensitive tools to enhance disease control. Addressing the limitations of existing diagnostics, particularly in low-transmission settings, is imperative for accurate disease detection.

The management of schistosomiasis relies heavily on PZQ, yet challenges such as side effects and potential resistance underscore the importance of ongoing research into alternative or combined treatments. Artemisin derivatives in conjunction with PZQ may be used, offering a higher cure rate and necessitating further investigation. Strategic interventions for interrupting disease transmission, especially in regions with low prevalence, should be prioritized. In conclusion, a comprehensive approach that integrates advanced diagnostics, therapeutic innovations, and targeted transmission control is essential for effectively combating the global impact of schistosomiasis.

Authors Contribution:

All the authors have made equal contributions.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study"

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