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Praziquantel as the preferred treatment for schistosomiasis

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ABSTRACT

Schistosomiasis, caused by Schistosoma trematode worms, represents a significant global health challenge. This review offers a thorough examination of the disease's epidemiology, transmission dynamics, diagnostic modalities, and treatment options. Diagnostic techniques encompass direct parasitological methods, immunological assays, DNA/RNA detection, and biomarker utilization, each with distinct advantages and limitations. There is an urgent need for improved diagnostic tools with enhanced sensitivity and specificity. Praziquantel remains the cornerstone of treatment, exhibiting efficacy against all Schistosoma species, while the potential of artemisin derivatives in combination therapy is also explored. In this review, we focus on the importance of praziquantel administration as the central aspect of schistosomiasis treatment, highlighting ongoing efforts to optimize its utilization for improved patient outcomes.

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Keywords: schistosomiasis, schistosome, praziquantel

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].

Infection with schistosomiasis occurs upon contact with water containing cercariae, which are released by intermediate host snails such as Biomphalaria (for *S. mansoni*), Oncomelania (for S. *japonicum*), or Bulinus (for *S. haematobium*). Although cercariae can persist in water for up to 1 to 3 days, their infectivity diminishes rapidly within hours [3]. Poor sanitation and hygiene practices elevate the risk of infection across all age groups, including children, adolescents, and adults, as the parasites can be transmitted through contact with contaminated water. Engaging in activities like utilizing open freshwater for domestic purposes, recreational bathing in rivers and lakes, or occupations involving water exposure can amplify the likelihood of cercariae exposure [2, 4].

Manage schistomiasis by administering praziquantel to affected populations on a large scale and providing regular treatment to all groups at risk [4]. Currently, there is a lack of straightforward, affordable, and precise diagnostic methods for schistosomiasis, which hinders the collective endeavours 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 in order to attain superior outcomes [5]. In this review, we specifically focus on the treatment of schistosomiasis through praziquantel administration.

DIAGNOSIS OF SCHISTOSOMIASIS

In recent decades, a range of diagnostic methods have

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been created to identify schistosomiasis, including basic microscopic detection and advanced molecular techniques [6]. The current diagnostic approaches can be classified into four main groups, as outlined in Table 1: direct parasitological diagnosis, immunological diagnosis, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) detection, and the utilization of cytokines, metabolites, and other schistosome molecules as biomarkers. Table 2 presents the diagnosis and assessment of diseases associated with the intestine, liver, genitourinary system, and neuroschistosomiasis [7].

The initial diagnostic procedures employed parasitologic techniques, such as identifying eggs in faecal samples to detect intestinal schistosomiasis or in urine to detect urinary schistosomiasis [29]. 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 [4].

Intradermal tests, which are immunologic diagnostic procedures, are characterized by their simplicity and affordability, making them a popular choice for conducting early prevalence studies [7]. The COPT test exhibits a high level of sensitivity and specificity, making it a valuable tool for diagnosing *S. japonicum* infection, particularly in China. The CHR test yields a positive result when the patient's serum is combined with live cercariae [4]. The IHT method de-

Table 1. Various diagnostic approaches for Schistosomiasis

Diagnostic strategy	Description	References
Direct parasitological diagnosis	The Kato-Katz (KK) thick faecal 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 cystosomiasis and quantitatively assessing the severity of infection.	[8, 9]
	The primary parasitologic methods employed for diagnosing urinary cystosomiasis involve urine filtration and concentration of *S. haematobium* eggs, followed by microscopic examination.	[3, 10]
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.	[6, 11]
	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).	[11–19]
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).	[20–22]
	Loop-mediated isothermal amplification (LAMP) is a recently developed method that is both cost-effective and practical for detecting schistosome DNA in faecal and serum samples. It is considered an alternative to conventional PCR.	[23, 24]
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 tumour 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.	[25]
	From day 41 after infection, significant alterations in the metabolite composition of urine, faeces, 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.	[26]
	Components of *S. 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.	[27]
	The utilization of recombinant SjLAP (rSjLAP) and recombinant SjFBPA (rSjFBPA) in ELISA proved to be effective for the detection of *S. japonicum* in humans.	[28]

PCR — polymerase chain reaction

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 parasitologic methods, involved detecting eggs in faecal samples to diagnose cases of intestinal schistosomiasis. The diagnosis is established through the detection of schistosome eggs in faeces, rectal scrapings, or rectal incisions.	[29]
	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.	[4]
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.	[7, 30]
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, 7]
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 oedema.	[31, 32]

tects the interaction between antibodies found in the serum of infected individuals and red blood cells that are covered with schistosome antigens [33]. 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 [17]. 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 [34].

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) [20]. Biomarkers for the diagnosis of schistosomiasis have been assessed, including host cytokines and different metabolites produced by schistosome. Biomarkers related to metabolism and cytokine levels lack specificity in diagnosing *Schistosoma* infection and have limited diagnostic utility [25].

There have been thorough examinations of the existing diagnostic techniques and the difficulties they present. It is crucial to increase efforts in order to create novel diagnostic tools that are more affordable, highly sensitive, and specific [5]. 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 [35].

In cases of intestinal cystosomiasis, 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, the formation of open sores, and the creation of pus-filled pockets. These symptoms are primarily observed as abdominal discomfort, persistent loose stools, and bleeding from the rectum [2, 4]. 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 [7]. The genitourinary system is primarily affected by *S. haematobium* through the induction of granulomatous inflammation caused by the deposition of eggs in the genitourinary tract. These conditions may arise as a consequence: polyposis, bladder carcinoma, bladder calcification, ulceration, and ureteral stricture [1, 7]. 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 dys-

function, whereas myeloradiculopathy arises from spinal cord dysfunction [31].

MANAGEMENT OF SCHISTOSOMIASIS

Praziquantel (PZQ) is the preferred medication for the treatment of cystosomiasis. 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 [36]. Praziquantel exhibits efficacy against mature schistosome worms, while its impact on juvenile schistosome larvae is limited [1]. The widely accepted effective treatment for *S. haematobium* and *S. 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 *S. japonicum* and *S. mekongi* is 60 mg/kg of body weight [1, 37]. This drug demonstrates a 63-85% effectiveness against *S. haematobium*, *S. japonicum*, and *S. mansoni*, and has the ability to decrease the number of eggs by over 90% following 6 months of treatment [7]. 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 [38]. Praziquantel 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 have the ability to eliminate the early larval stages of schistosome development. Meta-analyses have demonstrated that the combination therapy of praziquantel and artemisinin has a cure rate that is twice as high as that of praziquantel monotherapy. 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 [39, 40].

Praziquantel 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 [41, 42].

Artemisin derivatives, such as artemeter and artesunate, were initially created as drugs to treat malaria. However, they also have the ability to eliminate the early larval stages of the developing schistosome. In regions with ongoing transmission, the administration of artemisin derivatives in conjunction with praziquantel can enhance the overall rates of successful treatment and control of infection [38, 43].

SUMMARY

The management of schistosomiasis revolves around the administration of praziquantel, which remains the cornerstone of treatment due to its efficacy against all species of schistosomes. Despite its effectiveness, there are challenges associated with praziquantel administration, including its limited impact on juvenile schistosome larvae and the occurrence of side effects such as abdominal pain, headache, and dizziness. To address these challenges, it is crucial to optimize the dosage and administration of praziquantel, particularly in regions with varying species prevalence and infection intensities. Additionally, research into combination therapies, such as pairing praziquantel with artemisin derivatives, holds promise for enhancing treatment outcomes, although further investigation is warranted to establish standardized protocols and assess potential drug interactions. Ultimately, ongoing efforts to refine praziquantel administration and explore alternative treatment strategies are essential for improving patient outcomes and advancing the global fight against schistosomiasis.

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