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Schistosomiasis: Life Cycle, Diagnosis, and Control

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ABSTRACT

Background: Human schistosomiasis is a parasitic disease caused by blood-worms that infect multiple organs, including the liver, intestine, bladder, and urethra. This disease may be eliminated with Praziquantel, vaccines, and gene therapy.
Aims: In this review, the author describes the progress in a study of schistosomiasis that focused on the life cycle, diagnosis, and control.
Methodology: The author searched the PubMed Database at NCBI for articles on schistosomiasis published between 2014 and 2018. All articles were open access and in English.
Results: The life cycle of this parasites involve two hosts: snails and mammals. Manifestations of schistosomiasis can be acute or chronic. Clinical manifestations of acute schistosomiasis can include fever and headache. Symptoms of chronic infections can include dysuria and hyperplasia. Infection can occur in several sites including the bile ducts, intestine, and bladder. The different sites of infection and symptoms seen are related to which of the species involved. Five species can infect humans. The three most commons are *S. haematobium, S. japonicum, and S. mansoni*. Detection tools for people with schistosomiasis can include the Kato-Katz and PCR. Praziquantel is at present the only effective treatment of this disease. In the future, vaccination or gene therapy may be used.
Conclusion: Kato-Katz and PCR are tools for detecting schistosomiasis on humans. Praziquantel, diagnosis, vaccines, and gene therapy are useful methods for eliminating schistosomiasis.

Background

Schistosomiasis is caused by infection with blood flukes of the genus *Schistosoma*.[1,2] At least 5 trematode species are known to infect humans. These are *S. haematobium*, *S. intercalatum*, *S. japonicum*, *S. mansoni*, and *S. mekongi*.[3,4] Schistosomiasis infects more than 230 to 250 million people annually[3,5] and 779 million people are at risk of infection.[6] This disease causes 280,000 deaths annually,[2] and a worldwide burden of 3.3 million disability-adjusted life years.[3,7] Human schistosomiasis is among the most prevalent human parasitic infections.[3] The disease ranks second beneath malaria on the list of parasitic diseases,[3,4] and exists in 75 to 76 countries,[2,4] Schistosomes exists in many developing countries in Africa, Asia, South America,[2] and several Caribbean islands.[3] Schistosomiasis can also occur in nonendemic areas. It can be spread through water-based development projects[3] and immigration.

Two methods are available to control schistosomiasis: prevention and treatment. Eliminating snail hosts and improving sanitation are important methods to prevent schistosomiasis. To date, vaccines for schistosomiasis are unavailable. In the future, vaccines will have an important role in controlling this disease. Potential vaccines have been available, such as *Schistosoma mansoni* Chaptesin B1 (SmCB1) and *Schistosoma japonicum* insulin receptor 1 (rSjLD1). Praziquantel is a drug used to treat schistosomiasis at present. Moreover, this disease can also be prevented with snail control and vaccinations. Other drugs and genetic manipulations may also be beneficial.

In this review, the author describes the progress in a study of schistosomiasis that focused on the life cycle, diagnosis, and control. The life cycle of schistosomes includes asexual reproduction in snails and sexual reproduction in mammals, and diagnosis could include Kato-Katz and miracidium hatching test (MHT). Finally, control of schistomiasis is composed of the development of vaccines and drugs, as well as genetic manipulation techniques.

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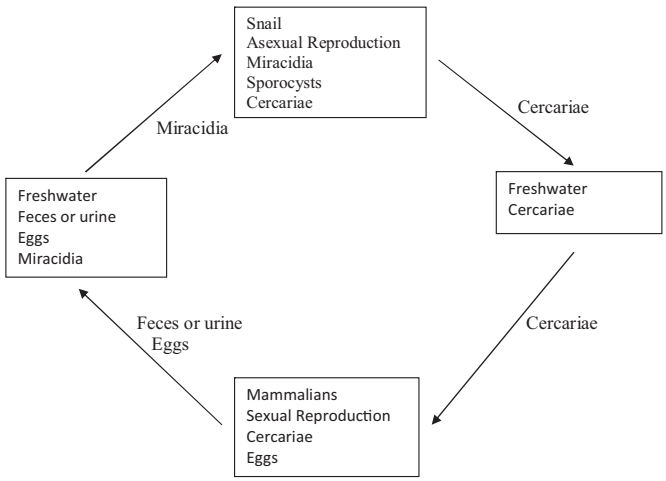

Figure 1. Schistosomiasis life cycle. Asexual reproduction in snails and sexual reproduction in mammals.

Methods

The author searched the PubMed Databases at National Center for Biotechnology Information for articles on schistosomiasis. All articles were open access and in English published between 2014 and 2018. The author also included other relevant publications in those searches.

Schistosome life cycle

The schistosome life cycle occurs in 2 hosts: snails and mammals. Either asexual or sexual reproduction occurs, depending on the type of host (Figure 1). Asexual reproduction occurs in freshwater snails. In the snail, this begins with the development of miracidia into a sporocyst. Sporocysts multiply and grow into cercariae. In the mammalian hosts, parasites grow to become mature, mate, and produce eggs.[1,8] Mammalian hosts include humans, mice, and dogs.

Snail hosts

Mammal hosts release worm eggs into the external environment through feces or urine.[9–11] In fresh water, these eggs form miracidia, which hatch and infect snails.[8,11] *S. haematobium* infects snails of the genus *Bulinus*. *S. japonicum* infects snails of the genus *Oncomelania*. *S. mekongi* infects snails of the genus *Neutricula*.[12] *S. mansoni* infects snails of the genus *Biomphalaria*.[12,13]

After infiltration, the miracidium removes the ciliated plates, develops into a mother sporocyst, and then produces daughter sporocysts.[8,13] Daughter sporocysts produce either cercaria (cercariogenous sporocysts) or more daughter sporocysts (sporocystogenous sporocysts). Daughter sporocysts can also experience a re-differentiation into new daughter sporocysts.[8] Snails can shed hundreds of cercariae daily; about 200 for *S. haematobium*, 15 to 160 for *S. japonicum*, and 250 to 600 for *S. mansoni*.[7]

Mammalian hosts

Cercariae enter human skin and shed their forked tail, forming schistosomula.[9,13] The schistosomula migrate throughout the body's tissues through blood circulation.[9] Schistosomula grow into schistosomes and adult worms.[6,13] These adult worms each have a ZZ chromosome pair in males and a ZW chromosome pair in females.[13]

Adult worms in humans exist in various locations specific to each species. *S. haematobium* exists in the bladder[9,14] and ureters, but it can also exist in the rectal venules. *S. japonicum* exists more frequently in the small intestine.[9] *S. mansoni* worms can exist in either large or small intestine[9,14] and they are able to transfer between those sites.[9] Water containing cercariae can cause human schistosomiasis.[7,9]

Clinical manifestations of schistosomiasis consist of acute (Katayama syndrome) and chronic manifestations. The incubation period of Katayama syndrome is about 14 to 84 days. Katayama syndrome's symptoms may include fever, headache, myalgia, rash, and respiratory symptoms. For *S. haematobium*, clinical manifestations of the chronic disease can cause dysuria and hematuria. It can also lead to injury of the genital tract and susceptibility to other infections. Chronic infections can cause bladder cancer. Clinical manifestations of the chronic disease are blood in the stool, constipation, and diarrhea. These clinical manifestations occur in patients with *S. japonicum* and *S. mansoni* schistosomiasis. Chronic inflammation also occurs in patients with *S. japonicum and S. mansoni* schistosomiasis. It can cause bowel wall ulceration, fibrosis, hyperplasia, polyposis, and portal hypertension.[15]

Schistosomiasis Transmission

Dam and irrigation projects are potential sites for outbreaks of schistosomiasis. Movements of populations with schistosomiasis, for example from rural to urban areas, can cause the spread of schistosomiasis. Seasonal migrations of employees can also lead to outbreaks of schistosomiasis infections, and refugees can also contribute to the outbreaks of this disease.[4]

A clean water supply, sanitation, vector control, and health education can interrupt the spread of schistosomiasis.[6] Furthermore, Braun et al[7] indicated that water treatment could help to reduce schistosomiasis. Five water treatment processes are available: storage, heating, chlorination, filtration, and ultraviolet light. Unfortunately, reliable design guidelines for water treatment to control schistosomiasis do not exist.[7] This suggests that research is still required to find an effective water treatment technique.

It is possible to use sanitation and water treatment to help control schistosomiasis. Governments in endemic areas should control schistosomiasis at provincial, district, and municipal levels. Nonendemic countries should also test and treat people from endemic countries for schistosomiasis in particular.

Diagnosis

Examination of excrement is a key method used to diagnose suspected schistosomiasis infections (Table 1). For examination purposes, several diagnostic techniques are available: the Kato-Katz, miracidium hatching test (MHT), formol-ether concentration technique (FECT), circulating cathodic antigen (CCA), point of care test (POCT), and polymerase chain reaction (PCR)-based technique. Alemu et al[3] showed that the FECT is time-consuming and requires several materials. Moreover, the sensitivity and specificity of the FECT are almost similar to the Kato-Katz technique. The Kato-Katz technique is fast, easy to perform, and requires minimal training. This technique has an 87.5% sensitivity rate and 100% specificity rate. For research purposes, Kato-Katz and FECT could be used.[3] Traditional methods cannot detect schistosomiasis in low-intensity levels.

MHT, Kato-Katz, and FECT

Many strategies are available to detect schistosomiasis. These include MHT, Kato-Katz, and FECT. MHT involves analyzing the

Table 1
Scistosomiasis, habitat, and diagnosis.

Schistosomiasis	Habitat	Diagnosis
Schistosoma haematobium	Africa, Middle East	Kato-Katz, wet-mount, FECT, POCT, PCR
Schistosoma japonicum	East Asia, Southeast Asia	Kato-Katz, MHT, wet-mount, FECT, Schistosoma japonicum thioredoxin peroxidase (SjTPx), PCR
Schistosoma mansoni	Africa, South America, Caribbean islands	Kato-Katz, Wet-mount, FECT, POCT, PCR
Schistosoma margrebowiei	Africa, Middle East	Kato-Katz, MHT, wet-mount, FECT, POCT, PCR
Schistosoma mekongi	Asia, Southeast Asia	Kato-Katz, MHT, wet-mount, FECT, SjTPx, PCR

FECT = formol-ether concentration technique; MHT = miracidium hatching test; PCR = polymerase chain reaction; POCT = point of care test; SjTPx = *Schistosoma japonicum* thioredoxin peroxidase.

concentration of eggs in stool samples. Samples come in nylon tissue bags and are suspended in distilled water in flasks. The presence of miracidia hatching from ova could be a sign of infection. Flask examination occurs at 4, 6, 8, and 24 hours. Kato-Katz stool sample examinations need 3 slides and use a light microscope.[16] The investigator takes about 42 mg stool sample and places it in a 200 μm Kato-Katz screen mesh. The stool is transferred into a 6 millimeters hole of a template on the microscopic slide. A glycerol-soaked cellophane strip covers the stool. The investigator then examines the stool for schistosome eggs. After that, eggs per gram of stool can be counted. For FECT, stool sample examinations use a centrifuge tool. The preparation contains about 500 mg stool sample. It is combined with 10 mL normal saline. Then, 2.5 mL 10% formaldehyde and 1 mL diethyl ether are added to this preparation. This preparation is placed in gauze within a funnel. The centrifugation was at 1000 g force for 3 minutes. Then, the investigator covers the supernatant with a glass cover to inspect it.[3]

Some techniques are available for detecting schistosomiasis in low-intensity levels. Nausch et al[17] suggested a rapid diagnostic test for the POCT diagnosis of *S. haematobium* and *S. mansoni*. POCTs include the CCA test and cercariae transformation fluid (SmCTF). The CCA was found to be sensitive for *S. mansoni* but less so for *S. haematobium*. A rapid diagnostic test SmCTF could detect both anti-*S. haematobium* and anti-*S. mansoni* antibodies. SmCTF was comparable to schistosome soluble egg antigens in ELISA. This technique was used for the diagnosis and treatment of schistosomiasis in travelers. It was also useful in schistosome-endemic areas.[17] Rapid diagnostic test is more sensitive than Kato-Katz[18] for the diagnosis of *S. mansoni* infections. CCA is not suitable for Asian schistosomiasis infections. To address this, MacAlanda et al[19] found the *Schistosoma japonicum* thioredoxin peroxidase 1 (SjTPx-1) as a technique to detect *S. japonicum* schistosomiasis. Although this technique is a potential method for detecting *S. japonicum* infection, the standard methods are the sole necessary tests for diagnosing *S. japonicum* schistosomiasis.

Xu et al[20] discovered the *Schistosoma japonicum* secreted protein 13 (SjSP-13) gene as a diagnostic tool for detecting schistosome infections. All the alleles of the gene were clustered into two clades (Clade A and B). *Escherichia coli* produced *Schistosoma japonicum* secreted protein 13.6 (SjSP-13.6) and *Schistosoma japonicum* secreted protein 13.25 (SjSP-13.25). SjSP-13.6 and SjSP-13.25 represented alleles of Clade A and B. SjSP-13.6 and SjSP-13.25 both had 96.7% specificity. However, they had different sensitivity. The sensitivity of SjSP-13.6 was 90.4% and SjSP-13.25 was 85.2%. Furthermore, the immunogenicity of Clade A was higher. Xu et al[20] stated that it was not necessary to combine Clade A and B for diagnostics of schistosomiasis.

PCR method

For low-intensity levels, PCR can be beneficial. PCR has sufficient sensitivity and specificity for detection of schistosome eggs in mammalians. PCR will be useful for diagnosing schistosomiasis in the future.[16]

Control of Schistosomiasis

S. haematobium exists in Africa (ie, Kenya, Nigeria, and Tanzania) and the Middle East (ie, Algeria, Egypt, and Libya). *S. japonicum* exists in East Asia (China) and Southeast Asia (Indonesia and the Philippines). *S. manconi* exists in Africa (ie, Djibouti, Eritrea, and Ethiopia), South America (ie, Brazil, Venezuela, and Suriname), and the Caribbean. *S. intercalatum* exists in Africa (ie, Cameroon, Congo, and Guinea). Japan and Tunisia have managed to control schistosomiasis. Morocco and some Caribbean islands have made significant progress in eradicating the disease. Brazil, China, and Egypt are also taking action to the eradication of schistosomiasis.[4]

Schistosomiasis infections mainly originate from *S. haematobium*, *S. japonicum*, and *S. mansoni*[4,6] (Table 1). Also, *S. bovis* and *S. margrebowiei* may infect humans.[4]

Treatment

Schistosomiasis eradication attempts commonly concentrate on controlling the infection through preventive chemotherapy. Praziquantel is cost-effective for treating schistosomiasis. The World Health Organization recommends a single dose of 40 mg/kg for all species and ages.[21] However, this recommendation has a limitation: praziquantel does not kill immature worms present in the body at the time of treatment.[22] Thus, treatment needs to be repeated after 2 to 4 weeks to increase effectiveness.[15] This disease continues to be among the most alarming diseases in humans.[4]

Snail management is helpful because it reduces the number of intermediate snail hosts. It is often achieved through molluscicide. However, with this technique, environmental destruction will occur. To avoid this, Yang et al[23] suggested linalool *Cinnamomum camphora* (L) extracts to kill *Oncomelania hupensis* snails. Linalool could also be used to treat *S. japonicum* infection. Snails treated with linalool showed gill destruction and cell degeneration. Additionally, the hepatopancreas of snails treated with linalool shrank and separated from the connective parenchyma. These snails had much smaller tubular lumen and less oval dark granules compared with snails without linalool. Hepatopancreas is the combined hepatic and pancreatic tissue. The results showed that gill damage and hepatopancreas could be the main causes of death.[23] This shows that linalool extracts are useful for treating schistosomiasis in snails. Moreover, linalool extracts do not have environmental risks.

Jatsa et al[24] showed that *Sidapilosa* Retz aqueous (SpAE) extract could treat *S. mansoni*. SpAE reduced granuloma numbers in the liver by 52% and the small intestine by 52.79%. SpAE also reduced granuloma volumes in the liver by 48.76%. The thickness of the small intestine's muscular layer was reduced by 10.52%. Thus, SpAE might be used for the development of medication against *S. mansoni* infection. Jatsa et al[24] also reported other groups had successfully reduced granuloma number and/or size on blood-worms. Those authors used *zingeber officinole* rhizome berberine and selenium nanoparticles.[24]

Sundaraneedi et al[2] discovered polypyridylruthenium (II) complexes to treat schistosomiasis in mammals. These complexes were effective against stages of schistosomes, schistosomula, and eggs.

Table 2
Schistosomiais vaccine candidates.

Vaccine candidate	Target	Reference
SmCB	*S. haematobium*	Ricciardi et al[25]
	S. mansoni	Tallima et al[26]
SmCB + CpG	*S. mansoni*	Ricciardi et al[25]
SmCB + Montanide ISA 720 VG	*S. mansoni*	Ricciardi et al[25]
SmCB1	*S. haematobium*	Ricciardi et al[25]
	S. mansoni	Tallima et al[26]
FhCl1	*S. haematobium*	Tallima et al[26]
Sh28GST	*S. haematobium*	Tebeje et al[27]
Sj97 paramyosin	*S. japonicum*	Tebeje et al[27]
Sm-14	*S. mansoni*	Tebeje et al[27]
SjAChE	*S. japonicum*	You et al[28]
rSjLD1	*S. japonicum*	You et al[29]

CpG = cytosine-guanine in the linear sequence (CpG or CG oligodeoxynucleotides); FhC11 = *Fasciola hepatica* L1; rSjLD1 = *Schistosoma japonicum* insulin receptor 1; sh28GST = *Schistosoma haematobium glutathionine* S-transferase; *Schistosoma japonicum* 97, a myofibrillar 97 kDa; SjAChE = *Schistosoma japonicum* acetylcholinesterace; Sm-14 = *Schistosoma mansoni* fatty acid binding protein; SmCB = *Schistosoma mansoni* chaptesin B; SmCB1 = *Schistosomamansoni* chaptesin B1; VG = vegetable-grade. Montanide ISA 720 VG: SEPPIC Inc., Fairfield, NJ, USA (adjuvant dedicated to human therapeutic vaccine).

The authors concluded that $Rubb_{12}$-tri and $Rubb_{7}$-tnl were able to reduce worm burdens. Both had an effect on the viability of parasite eggs *in vivo*. Sundaraneedi et al[2] stated that ruthenium compounds were able to reduce parasite eggs *in vitro*. They could also kill adult worms and praziquantel-refractory juvenile worms *in vitro*.[2] It seems therefore that ruthenium compounds have potential for treating schistosomiasis.

Vaccine Development

A schistosomiasis vaccine could create a long-term decrease in illness spectrum and transmission.[25] It could protect up to 600 to 700 million people.[26] To date, schistosomiasis vaccines are unavailable.[27] However, experiments in animals are underway (Table 2).

Tallima et al[26] found that a cysteine peptidase-based vaccination could shield against *S. haematobium* schistosomiasis. A mixture of *Schistosoma mansoni* Chaptesin B1 (SmCB1) and *Fasciola hepatica* L1 reduced worms by 70%. The mixture also reduced eggs by 60%[26] (Table 3).

You et al[28] discovered that the *S. japonicum* acetylcholinesterace (SjAChE) inhibited parasite growth and development. The authors used ribonucleic acid interference to kill parasites in vitro. You et al[28] found that immunization of mice with the recombinant SjAChE reduced male worm numbers (33%) as well as liver tumor density (41%), and decreased numbers of enteric eggs (73%). In addition, You et al[29] suggested a vaccination with rSjLD1 and 2. The authors stated that rSjLD1 and 2 would be safe for immunizing bovines and humans.[29] The rSjLD1 vaccine reduced the number of female worms (30%–44%), fecal eggs (61%–68%), liver eggs (44%–56%), intestinal eggs (46%-48%), and mature intestinal eggs (58%-63%).[29] These studies confirm the potential of SjAChE and rSjLD1 as vaccine/drug candidates.

Moreover, to control *S. Mansoni* schistosomiasis, Ricciardi et al[25] discovered *Schistosoma mansoni* Chaptesin B (SmCB) as a vaccine candidate. The authors performed in vitro killing assays in schistosomula stage parasites targets for lung-derived leukocytes and serum obtained from mice vaccinated with SmCB adjuvant with either Montanide ISA 720 VG (SEPPIC Inc., Fairfield, NJ, USA) or cytosine-guanine in the linear sequence (CpG or CG oligodeoxynucleotides) (CpG) and from mice not vaccinated. The SmCB + Montanide 720 VG (SEPPIC Inc., Fairfield, NJ, USA) resulted in the highest death rate (63%). The SmCB + CpG vaccinated animals experienced a significant death rate (53%). Also, the Sm-cathepsin alone had a substantial success rate (41%).[25] It seems that SmCB can help to reduce schistosomiasis for *S. haematobium* and *S. mansoni.*

Table 3
Vaccine development for schistosomiasis.

Agent	Description	Stage	Reference
SmCB + Montanide ISA 720 VG	Reduce parasites 63%	Schistosomula	Tallima et al[26]
SmCB + CpG	Reduce parasites 53%	Schistosomula	Tallima et al[26]
SmCB1	Reduce worms burden 70%	Schistosomula	Tallima et al[26]
SjAChE	Reduce female worms 30%–44% Reduce fecal eggs 61%–68% Reduce liver eggs 44%–56% Reduce intestinal eggs 46%–48% Reduce mature intestinal eggs 56%–63%	Eggs and adults	You et al[28]
rSjLD1	Reduce male worms 33% Reduce liver granuloma density 41% Reduce mature intestinal eggs 73%	Adults	You et al[29]

CpG = cytosine-guanine in the linear sequence (CpG or CG oligodeoxynucleotides); rSjLD1 = *Schistosoma japonicum* insulin receptor 1; SjAChE = *Schistosoma japonicum* acetylcholinesterace; SmCB + Montonide 720 VG = *Schistosoma mansoni* chaptesin B + Montanide ISA 720 VG (SEPPIC Inc., Fairfield, NJ, USA); SmCB1 = *Schistosoma mansoni* chaptesin B1; VG = vegetable-grade.

Genetic Manipulation

Genetic manipulation techniques can be beneficial to control schistosomiasis. These techniques include the adeno-associated virus (AAV), clustered regularly interspaced short palindromic repeats (CRISPR/Cas9) system, and end-joining homology techniques (EJHTs). EJHTs can include homology-mediated end joining (HMEJ) and homology-independent targeted integration (HITI).[30]

For example, He et al[31] suggested that rAAV8-mediated miR-203-3p could become a drug for human diseases. The authors showed that rAAV8-mediated miR-203-3p protected mice from schistosome infection and alleviated hepatic pathology. He et al[31] showed that rAAV8-mediated miR-203-3p managed the enlargement of hepatic lymphoid cells. It also reduced the production of hepatic lymphoid cells throughout infection.[31] This study shows that rAAV8-mediated miR-203-3p is a potential method for treatment of schistosomiasis.

CRISPR/Cas9 system and EJHTs can edit incorrect genes. Thus, these techniques are potential tools for eliminating schistosomiasis. However, there are currently no studies analyzing the utility of these 2 tools for schistosomiasis treatment. Thus, CRISPR/Cas9 system, HMEJ, and HITI could become new treatment methods for schistosomiasis.

Conclusions

Schistosomiasis is a blood-worm disease that exists in either the intestine or urethra in humans. Three main species can infect humans. These are *S. haematobium*, *S. japonicum*, and *S. mansoni*. The schistosomiasis life cycle has 2 hosts: snails and mammals. Asexual reproduction occurs in snails and sexual reproduction occurs in mammals. To control schistosomiasis, diagnosis has an important role. Diagnosis techniques include MHT, Kato-Katz, FECT, POC-CCA, SmCFT, and PCR. Currently, praziquantel is the only drug treatment available for schistosomiasis. Several drug

candidates have been studied, including linalool, SpAE, $Rubb_7$-tn1, and $Rubb_{12}$-tri. No vaccines are available for this disease at present. However, vaccine candidates, such as SmCB1, SjAChE, and SmCB, have been studied. Furthermore, genetic manipulation techniques are potential tools to control schistosomiasis in the future. These tools may include rAAV8-mediated miR-203-3p, CHRISPR/Cas9 system, and the EJHTs HMEJ and HITI.

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Conflicts of Interest

The author has indicated that he has no conflicts of interest regarding the content of this article.

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