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EDUCATIONAL REVIEW

Urinary schistosomiasis

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Abstract Schistosomiasis is the second most common socio-economically devastating parasitic disease after malaria, affecting about 240 million residents of developing countries. In Africa, it predominantly manifests as urogenital disease, and the main infective agent is *Schistosoma hematobium.* Endemicity is propagated by poor socio-economic status and environmental degradation due to rapid urbanization. Recreational swimming is a potent medium for the spread of disease in children and adolescents. Most affected individuals are asymptomatic. The male and female worms are equipped with an extraordinary capacity for immune evasion and are able to co-habit for several decades within the pelvic venous plexus. Eggs deposited in the bladder wall resist elimination by type 1 T lymphocytes. Instead, they are sustained by pro-fibrogenic encapsulation (as modulated by type 2 helper cells). Progressive bladder disease results in obstructive uropathy and predisposes to (mostly) squamous cell carcinoma. Schistosomal glomerulopathy manifests as a clinical spectrum of asymptomatic proteinuria, nephrosis and/or nephritic syndrome. Findings on renal biopsy may be influenced by co-morbidity with *Salmonella* bacteria, amyloidosis and hepatitis C infection. Potentially fatal Katayama fever and spinal radiculopathy may ensue in tourists visiting an endemic zone. Early detection by urine microscopy is hampered by low urinary excretion rates of the parasite eggs. Although useful in travelers with newly acquired disease, the results of the serological antibody assay may be false positive in residents of an endemic zone. Cystoscopy, however, may be invaluable. Due to its safety, effectiveness and once-daily dosing, praziquantel is the drug of choice. An integrated approach that includes mass chemotherapy, environmental health programs and public health education is the most cost-effective preventive strategy.

Keywords Urinary schistosomiasis · Schistosomal glomerulopathy · Pediatric tropical disease

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Urinary schistosomiasis

Epidemiology

After malaria, schistosomiasis is the second most common socio-economically devastating tropical parasitic disease. Parasite infestation has been documented in 78 countries of Africa, Asia, the Middle East and South America [1]. Despite the availability of effective drugs, the annual death rate is around 200,000 in sub-Sahara Africa alone, making the group of parasites which cause schistosomiasis the most lethal worms in the world. The majority of human disease is mediated by *Schistosoma hematobium*, *S. mansoni* and *S. japonicum* [2]. Each of these species has a tropism for different body organs, with *S. hematobium* being the main cause of urogenital disease [2, 3]. Poor access to economic opportunity accounts for the uneven distribution of infection in endemic regions. Subsistence farming, inadequate water supply, poor public sanitation, rapid urbanization and dam construction are common predisposing factors [3]. Although parasite infection has been reported in early infancy, peak incidence occurs in early adolescence as a result of frequent bathing in contaminated pools of water [4]. Apart from lower exposure in adults, the capacity to resist new infection by eosinophil secretion of antigen-specific immunoglobulin E (IgE) is age dependent [5]. Children younger than 13 years have a higher serum level of IgM, IgG2 and IgG4 isotypes which block the protective effect of IgE [6].

Biological life cycle

Schistosoma hematobium is a digenean trematode that uses humans as the definitive host and molluscs (genus *Bulinus*) as the intermediate host (Fig. 1). Its life cycle begins with urinary excretion of eggs of the trematode into freshwater populated by susceptible snails. The eggs are then hatched to release motile, non-feeding, ciliated miracidiae that survive for only 7 days. After penetrating the water snail, the larvae replicate to form sporocysts which produce thousands of free swimming cercariae [2] which are able to penetrate the skin of a human within a few seconds of contact. Once in the human body, they are transformed into schistosomula which enter the circulatory system and migrate through the lungs to the liver where they mature into adult male or female worms. Bound by the male gynecophoric groove, both types of worms move to the pelvic venous plexus for 3–5 years of reproductive co-habitation [7].

Immunopathology

The migrating larva avoids destruction by the membrane attack complex (C5–C9) by rapidly shedding its glycocalyx outer covering [8]. During migration, the schistosomule adopts a host-derived outer membrane to prevent elimination by type 1 helper cells. Of the eggs produced, 50 % are not excreted but trapped in the bladder wall where they activate resident inflammatory cells to secrete tumor necrosis factor (TNF-α) and eotaxin (potently attracts eosinophils) [9]. Ultimately, there is encapsulation of the egg by granuloma formulation (Fig. 2a). An attempt to eliminate the sequestered eggs may be halted by a shift from the type 1 immune response (secretion of interferon-γ) to a pro-fibrogenic Th2 cell activity which produces interleukin (IL)-4, IL-10 and IL-13 [10]. There is concurrent transformation of classically activated macrophages (induction of nitric oxide synthase) to the alternatively activated variants (expression of arginase-1, Ym-1 and Fizz1). Over time, IL-10 and regulatory T cells downregulate the progression of chronic bladder fibrosis. This modulatory effect may be suppressed in individuals with polymorphism in the promoter gene for ficolin-2 [11].

Clinical manifestations

Transient pruritic dermatitis or swimmer's itch (Fig. 2b) may occur in response to cercarial skin penetration [12, 13]. However, newly infected patients are often asymptomatic [7]. Common symptoms are urinary frequency, urgency, dysuria and end-stream hematuria. Of these symptoms, terminal hematuria may be the most feasible and is often the basis for epidemiologic diagnosis. Iron deficiency anemia may be exacerbated by co-morbidity with other endemic tropical

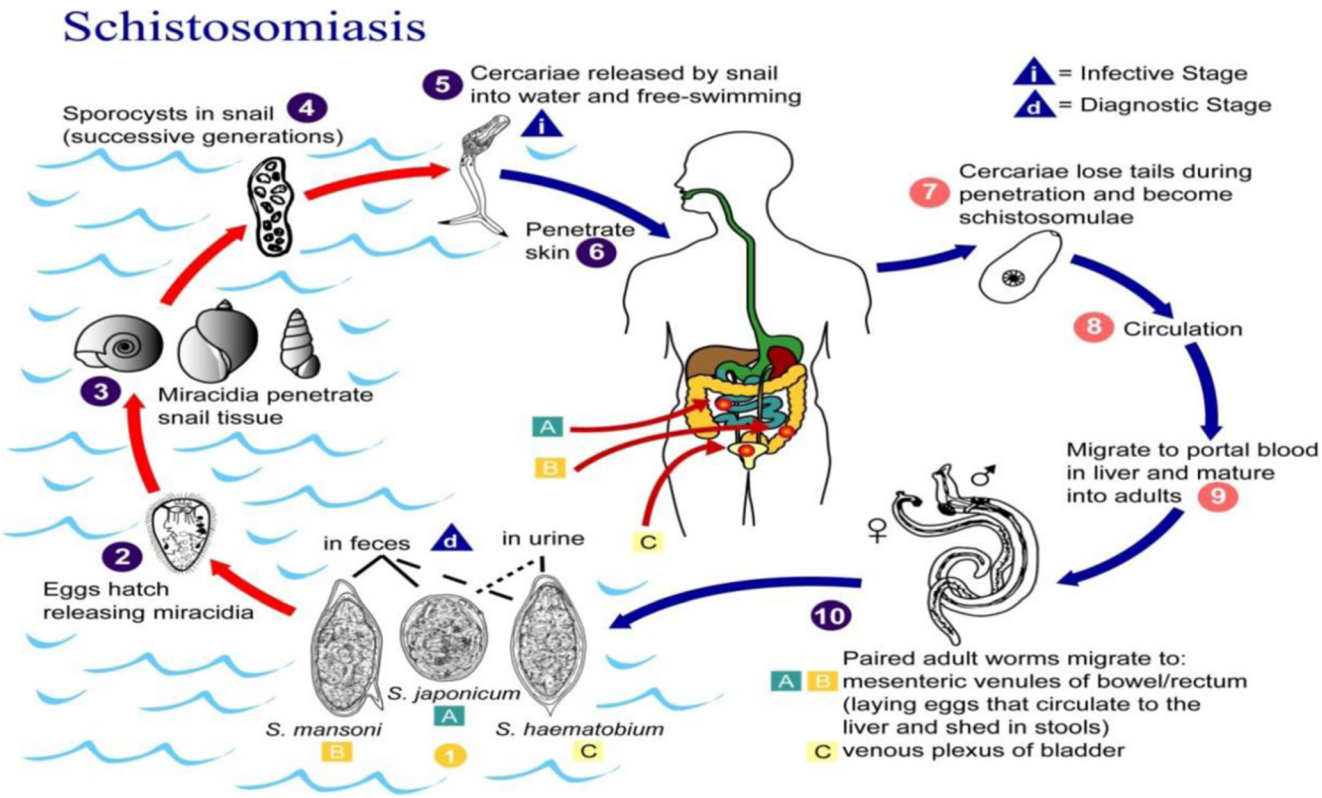

Fig. 1 Illustrative diagram of the biological life cycle of *Schistosoma hematobium*, *S. mansoni* and *S. japonicum*. Source: U.S. Centers for Disease Control and Prevention (CDC), Atlanta, Georgia

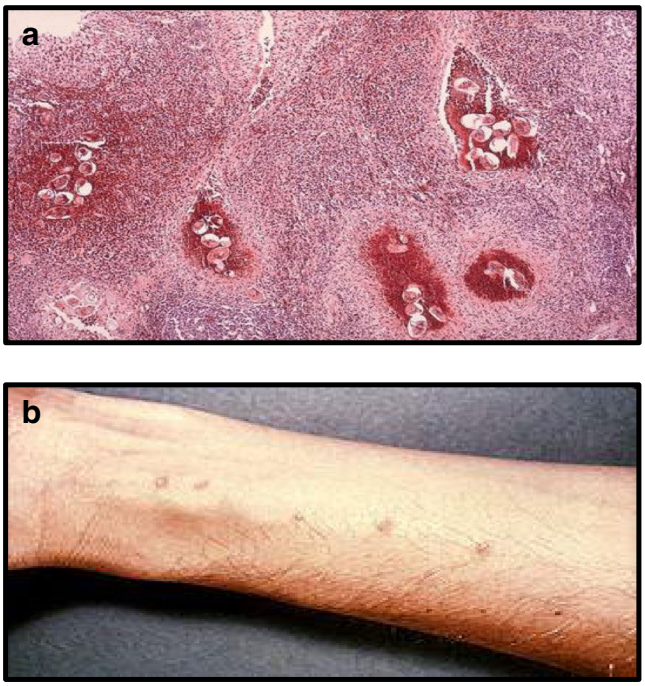

Fig. 2 **a** Granulomatous encapsulation of *Schistosoma* eggs, **b** forearm dermatitis from cercaria skin penetration. Source: Centers for Disease Control (CDC) Atlanta, Georgia

diseases, such as malaria and heminthiasis. A substantial amount of iron is sequestered by vitelline cells for the formation of the parasite eggshell [14]. In addition, host iron recycling is disrupted by a pro-inflammatory synthesis of hepcidin, an acute phase reactant [15]. Although structural deficits are sometimes reversible by medical treatment, obstructive uropathy may invariably result from progressive bladder fibrosis, ureteral dilatation and hydronephrosis, particularly in older patients [16]. Ulcerations of bladder mucosa, focal bladder wall calcification and renal stone formation may result. Urological surgery is seldom required for rehabilitation. Genital disease may cause sexual dysfunction, facilitates human immunodeficiency virus transmission and promotes infertility in adolescents and young adults [17].

The ease of access to wider geographical regions for tourism has increased the infection rate among travelers [12]. Such individuals lack any acquired immunity and within 6 weeks after infection they may experience a severe hypersensitivity reaction in response to the first bout of egg antigen release by adult worms. Katayama fever is characterized by hyperpyrexia, myalgia, headache, cough, emesis and diarrhea [18]. In addition, paraplegia from transverse myelitis may result from paravertebral migration of parasite eggs. Nevertheless complete neurological recovery is feasible with early medical intervention [19].

Urinary tract infection Due to disruption of the mucosal barrier, there is a high rate of bacterial superinfection, ranging from 30 to 80 % in endemic communities [20, 21]. Isolates are mostly regular uropathogens, but *Salmonella* infection is not uncommon [21]. *Salmonella* evades the host immune response by attaching itself to the adult worm's surface receptors [22]. Urinary carriers may serve as a source of epidemic typhoid fever. Urine isolation of *Salmonella* bacteria in endemic regions should arouse suspicion for a co-morbid schistosomiasis [21, 22].

Bladder carcinoma There is a 30-fold higher risk of developing bladder cancer, mostly squamous cell carcinoma (SCC) variant in regions of Egypt with endemic schistosomiasis [23]. A fall in the prevalence rate of schistosomiasis from 1980 to 2005 due to a public health intervention was followed by a six-fold lower rate of SCC, clearly suggesting a cause and effect relationship [24].

Schistosomal glomerulopathy Schistosomal glomerulopathy (SGN) occurs in response to infection with both *S. hematobium* and *S. mansoni*. Apparently due to the greater occurrence of subclinical disease in patients with *S. hematobium*, a higher prevalence of glomerular disease is often reported in those infected with *S. mansoni* (Tables 1, 2) [25–27]. SGN manifests as a clinical, spectrum of asymptomatic, proteinuria, nephrosis and/or nephritic syndrome. Based on experimental and clinicopathologic data, in 1992 the African Association of Nephrology (AFRAN) recognized six categories of SGN. The most common category is Class I SGN and it is characterized by mesangial proliferative histology. Infected individuals are often asymptomatic (60 %) [26]. Class II SGN is an exudative proliferative lesion that occurs in response to *Salmonella* bacteria superinfection. Class III SGN has a membrano-proliferative glomerular pattern, Class IV has focal segmental glomerulosclerosis, Class V is due to secondary amyloidosis and Class VI is a mixed pathology of proliferative, focal sclerosis, amyloidosis and thrombotic cryoglobulin from a co-morbid hepatitis C infection. Except for the clinical recovery observed in patients with Class I and II SGN, patients with the other categories often progress to end-stage kidney disease by adulthood. Data in the 2008 Egyptian Renal Registry showed that SGN may account for 2.8 % of the 483 adult patients with end stage kidney disease per million of population [www.esnonline.net]. Immune complex deposits (IgM, C3, and C1q) containing adult worm antigens (gut-associated proteoglycan) in the glomerulus are the early pathological features [27]. There may be late deposits of IgG and IgA. Membrano-proliferative response to a direct localization of egg granuloma in kidney tissue is a rare event [25]. Because most immune complexes are non-nephritogenic, there is no correlation between overt kidney disease and low level of serum C3 [28].

Diagnosis

Detection of parasite eggs and motile miracidium by urine microscopy is simple, inexpensive and is considered to be the gold standard for diagnosis (Fig. 3) [29]. The result may be a false

Table 1 Clinical aspects of schistosomal glomerulopathy as classified by the African Association of Nephrology

AFRAN classification	Etiology	Clinical syndrome	Treatment
I: Mesangio-proliferative	SH, SM	>50 % asymptomatic; mild proteinuria	PZQ, metrifonate
II: Proliferative exudative	SH, SM, Salmonella sp.	Rapid onset nephrotic/nephritic syndrome; *Salmonella* sepsis	PZQ, metrifonate, antibiotics
III: Membrano-proliferative	SH, SM	Non-Black patient; hepatic cirrhosis; High serum IgA; NS, CGN, ESKD	None effective
IV: Focal segmental glomerulosclerosis	SM	Mostly in Blacks; hepatic cirrhosis; NS, CGN, ESKD	None effective
V: Amyloidosis	SH/ SM	Systemic amyloidosis; NS, CGN, ESKD	None effective
VI: Cryoglobulinemia	SM, HCV	Purpura, arthralgia, myalgia; low C3, very low serum C4, NS, CGN, ESKD	IFN-α, ribavirin, immunosuppressive agent, plasmapheresis

AFRAN, African Association of Nephrology; C3, complement 3, C4, complement 4; CGN, chronic glomerulonephritis; ESKD, end stage kidney disease; FSGS, focal segmental glomerulosclerosis; HCV, hepatitis C virus; IFN-α, interferon-alpha; NS, nephrotic syndrome; PZQ, praziquantel; SH, *Schistosoma hematobium*; SM, *Schistosoma mansoni*.

negative in the first 6 weeks prior to full maturity of the worm and due to a lower rate of egg excretion. Collection of three daily filtered urine samples after a mid-day session of physical exercise, the peak period for egg output, increases the detection rate [2]. Field surveys of end-stream hematuria, urine evaluation for blood and protein and bladder ultrasonography (assesses morbidity) are useful screening tools [2, 30, 31]. In addition, the excretion of eosinophil cationic protein in the urine (as detected by enzyme-linked immunosorbent assay) may be a biomarker of inflammatory bladder injury [30]. In cases of diagnostic challenges, cystoscopy may show a typical hemorrhagic mucosa, submucosal nodules and sandy patches (micro-granuloma). Late findings of cystoscopy are a "cooked rice grain" appearance (macro-granuloma) and erythematous fibrous polyps [31]. Bladder biopsy may show granuloma-encased eggs but may fail to demonstrate the viability of the eggs (Fig. 2a). Direct detection of miracidium-containing eggs using cystoscopy-aided confocal laser scanning microscopy produces stronger evidence of disease activity [32].

Due to a light parasite burden, serological assays for detection of IgG, IgM or IgE antibody response to antigen derivatives of parasite are often required for the diagnosis of infected travelers to endemic zones [33]. It is less useful diagnostic tool in an endemic community as it fails to discriminate current from previous infection, and the parasite antigen may cross-react with those of other tropical helminths. Due to late seroconversion, these tests may not be positive until a minimum of 6 weeks after the primary infection [2]. Although less robust, circulating cathodic antigens may be detected in the urine or serum samples using labeled monoclonal antibodies [34]. The PCR of parasite DNA in a urine sample (sensitivity 84 %, specificity 97 %) may prove useful in post-chemotherapy surveillance [35].

Treatment

In the last four decades, safer and more effective drugs have replaced the toxic older generation of anti-infective agents [36]. According to the World Health Organization, only 11.5 % of the 243 million people in 52 countries who required treatment received pharmacological intervention in 2011 [1]. Praziquantel (PZQ), an acylated quinoline–pyrazine compound, is regarded as the gold standard of therapy. It is

Table 2 Pathological features of schistosomal glomerulopathy based on the classification of the African Association of Nephrology

AFRAN classification	Histology: light microscopy	Immunofluorescence/electron microscopy
I: Mesangio-proliferative	Mesangial cell proliferation; matrix expansion	Mesangial IgM, C3, GASP deposits
II: Proliferative/ exudative	Mesangial neutrophil, monocyte & eosinophil; epithelial/ endothelial/ mesangial cell proliferation	Sub-endothelial/ mesangial C3, IgG, IgM deposits
III: Membrano-proliferative	Mesangial/ endothelial cell proliferation, glomerular basement membrane thickening	Sub-epithelial & sub-endothelial IgG, IgA, C3, GASP deposits
IV: Focal segmental glomerulosclerosis	Focal segmental proliferative or sclerosing lesion	Sub-endothelial IgG, IgM, IgA, GASP deposits
V: Amyloidosis	Glomerular amyloid; arterial wall involved; interstitial fibrosis, tubular atrophy	Amyloid A deposits in kidney, liver, subcutaneous fat; GASP
VI: Cryoglobulinemia	Mesangial/ endothelial cell proliferation, hyaline thrombi; fibrinoid necrosis; fibro-cellular crescents	Mesangial and sub-endothelial IgG, C3, cryoglobulin, fibrin, amyloid A, HCV-RNA deposits

HCV-RNA, HCV ribonuclear acid particles; GASP, gut-associated schistosomal proteoglycan; GN, glomerulonephritis; Ig, immunoglobulin

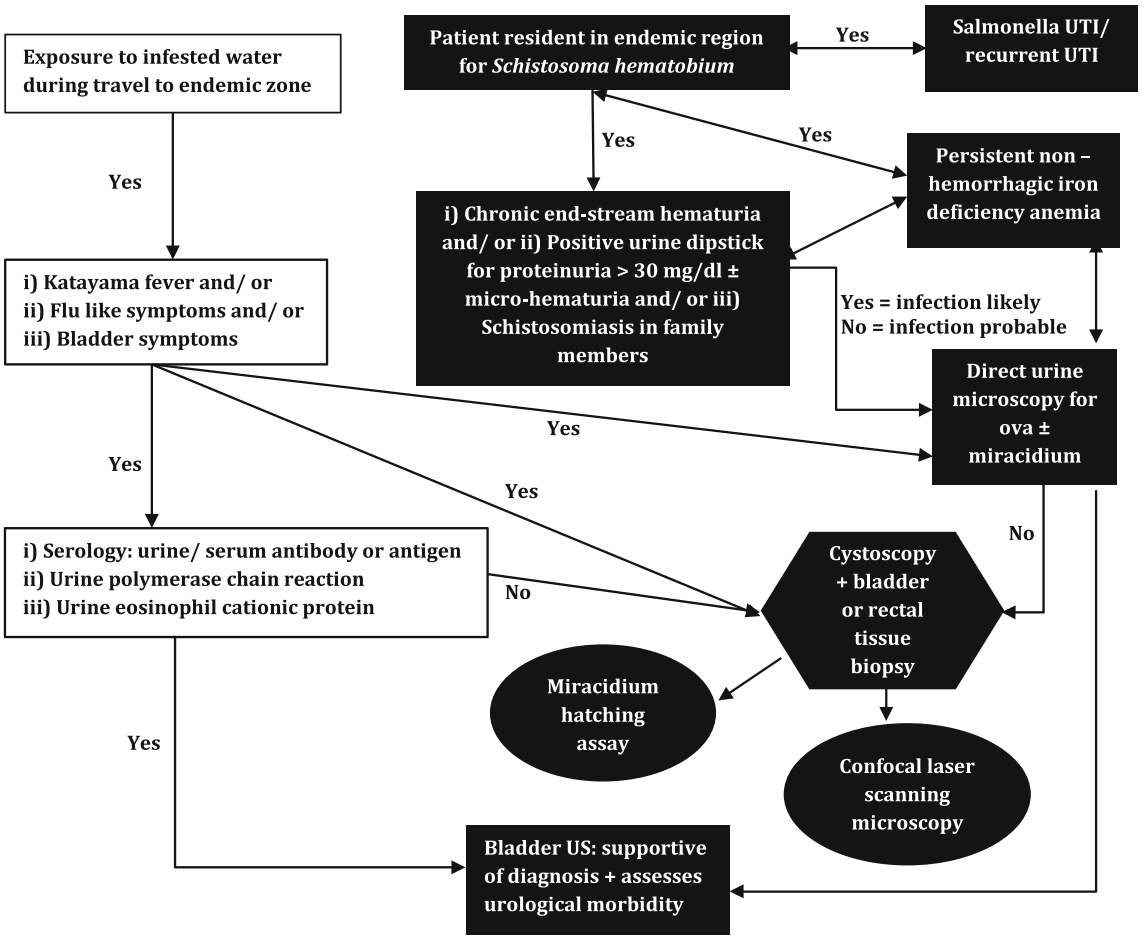

Fig. 3 Approach to a difficult diagnosis of urogenital schistosomiasis. Due to an only intermittent excretion of the parasite in the urine, diagnosis of schistosomiasis can be challenging. Early diagnosis may prevent a fatal outcome, particularly in patients with Katayama fever (*white boxes*). A high index of suspicion is crucial, and a multi-diagnostic approach may improve accuracy. Due to the light parasite burden, serological diagnosis based on antibody detection of antigen derivatives of ova, adult worms and cercaria is of practical importance in infested travelers to an endemic zone. The test may be falsely negative due to late seroconversion (>6 weeks). Direct antigen detection with monoclonal antibody may improve yield. New diagnostic tools are the PCR for detection of parasite DNA in urine sample and the enzyme linked immunoabsorbent assay for detecting urine eosinophilic cationic protein (suggests active bladder infection). Direct urine microscopy is the main diagnostic tool among residents of endemic zone (*black boxes*). Cystoscopy may be required if non-invasive tools are unhelpful. Rectal biopsy may improve isolation of *S. hematobium* ova. Eggs containing miracidium indicate active bladder infection. Detection of miracidium can be facilitated by the miracidium hatching assay and a more recent development, confocal laser scanning microscopy. *UTI* Urinary tract infection

effective against the three principal schistosomal species. With a single oral dose of 40 mg/kg body weight, it is the drug of choice for mass treatment programs [2, 37]. In the clinic setting, children are treated with two doses of 20 mg/kg PZQ at intervals ranging from 1 day to 4 weeks. Although pharmacokinetic studies are lacking, a suspension formulation or crushed tablets have been successfully used in the treatment of younger children [37, 38]. Side effects may include nausea, emesis, diarrhea, dizziness, headache and pyrexia, but these are less likely to occur with the two-daily dosing regimen than with the single-dose treatment [38]. Because first pass metabolism is mediated by the cytochrome P450 (CYP) system (e.g. CYP3A4), PZQ may interfere with the hepatic clearance of tacrolimus, cyclosporine and sirolimus [39]. Furthermore, the anti-parasitic effect may be impaired by the concurrent use of intestinal P-glycoprotein inhibitor (e.g. chloroquine) and CYP inducers (e.g. rifampin) [39, 40]. Serum level may be increased by cytochrome P450 inhibitors, such as ketoconazole and grapefruit juice [39]. To avoid worsening of the hypersensitivity reaction from the release of egg antigens by the killing of the adult worm, treatment with PZQ should be delayed in patients with Katayama fever. Instead, the initial wave of immune-related symptoms are relieved by the administration of intravenous hydrocortisone [18, 19].

Prevention

With the introduction of PZQ, mass treatment programs of high-risk populations have had a profound short-term benefit on morbidity [41, 42]. Prevention of parasite re-infection may

require many years of regular annual chemotherapy. An integrated approach that includes provision of basic sanitation, clean water supply and public health education holds the greatest prospect for a more durable outcome. These measures are generally cost effective and are able to curtail other neglected tropical diseases. Development of an effective vaccine has the potential for making a considerable impact. A chimeric vaccine fusion of the antigens for both hookworm and *Schistosoma* parasites (Sm-TSP-2 and Na-APR-1) was recently used successfully in an experimental murine challenge study [43]. This vaccine is particularly suitable for use in areas with endemicity for both diseases. Other candidate vaccines awaiting phase I human trials are the derivatives of Sm-p80 (calpain) and Sm-14 antigens [44].

Questions (answers are provided following the Reference list)

1. The following contributes to the epidemiological pattern of schistosomiasis except:

   a. Extreme poverty
   b. Dam construction
   c. Type of molluscs
   d. Tourism
   e. Cold climate

2. All are reasons for greater incidence of urogenital schistosomiasis in children except:

   a. Recreational activity
   b. Poor education
   c. Higher serum level of IgM
   d. Urinary tract infection

3. Urogenital schistosomiasis is a potent mediator of transitional cell carcinoma of the bladder:

   a. True
   b. False

4. Katayama fever is due to one of the following:

   a. Cercaria skin penetration
   b. Schistosomule migration
   c. Miracidium in the bladder wall
   d. Hypersensitivity to egg antigen

5. One of the following is a fairly reliable means of detecting active bladder infection:

   a. Urine microscopy
   b. Confocal laser scanning microscopy
   c. Ultrasonography
   d. Cystoscopy

6. An effective preventive strategy for endemic urinary schistosomiasis should include:

   a. Adequate treatment of bacterial cystitis
   b. Mass chemotherapy
   c. Health education
   d. Water supply
   e. Relocation from endemic zone

   I. a and c
   ii. a and b
   iii. b, c and d
   iv. a and e

7. A true statement about schistosomal glomerulopathy:

   a. The most common pathogen is *S. hematobium*
   b. Histological type III is due to *Salmonella* superinfection
   c. Granulomatous egg deposit in renal tissue is common
   d. Not seen in the absence of bladder infestation
   e. Low serum C3 is common

   I. a and b
   ii. a and e
   iii. c only
   iv. None of the above

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Answers:

1. e
2. d
3. b
4. d
5. b
6. iii
7. iv