



EAU Guidelines

EAU Guidelines for the Management of Urogenital Schistosomiasis

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Abstract

More than 100 million people worldwide are affected by bilharziasis, caused by *Schistosoma haematobium*. For travellers precaution is most important. For the population in endemic areas, an integrated approach including health education is necessary. Effective pharmacologic treatment is available.

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1. Introduction

More than 100 million people in the world, especially in rural and agricultural areas, are affected by bilharziasis of the urogenital tract, a parasitic disease caused by *Schistosoma haematobium* [1,2]. European urologists may see heavily infected migrants from endemic zones or tourists and development aid workers returning home with early stages of this disease.

2. Parasitic life cycle

S. haematobium is a parasitic trematode (flatworm). Humans are the main hosts for this parasite and both male and female worms reside in the pelvic venules. Fertilized eggs pass through the walls of the blood vessels into the tissues and the lumen of the rectum and sigmoid colon. They also pass into the urinary bladder, from which they are shed into the environment beginning a new life cycle. The fertilized eggs hatch in fresh water lakes, ponds, or rivers before developing into miracidia.

Miracidia migrate into a specific, intermediate host—the small snails of the genus *Bulinus*. The disease cannot spread beyond its natural habitat. The miracidia develop into sporocysts and after approximately 4 wk produce cercariae (by asexual multiplication), which infect the human host by penetrating unbroken skin during bathing, fishing, agricultural activities, or washing.

Once the skin is penetrated, the larvae migrate around the body via the circulatory system, reaching sexual maturity in about 6 wk. The adult worms may live for several decades in the venous plexuses around the pelvic organs, bladder, rectum, pelvic ureters, and deep genital organs. The worms lay eggs that migrate into these organs causing micro-mucosal perforation. Repeated micro-mucosal urothelial perforation causes haematuria. The eggs that are not secreted remain in the submucosa of the pelvic organs where they are encapsulated in fibrous granulomas.

The chronic lesions of schistomiasis depend on the extent of infection [3]. The disease is caused by the presence of the eggs rather than the worms themselves; the worms living in the veins are tolerated and do not lead to thrombosis.

3. Epidemiology

Schistosomiasis occurs in certain oases in southern Algeria, Morocco, and Tunisia, and in tropical Africa, between the latitudes of 35° North and 25° South, in the Savana and Sahel zones, while sparing the Sahara

and the peri-equatorial forest belt. It occurs in Madagascar, Mauritius, all of the Nile valley, certain Middle Eastern countries, Yemen, Saudi Arabia, Iraq, and Iran. It has been eradicated in Lebanon and Israel. In the Far East, Australia, and South and Central America, bilharzial infections are mostly intestinal and caused by *S. mansoni*, *S. japonicum*, or *S. mekongi* according to the region [1,2,4].

The prevalence of the disease is closely linked to the educational and economic level of the population, the absence of adequate sanitation, and unprotected contact with contaminated fresh water. Bathing, swimming, and fishing are the main activities leading to infection. Frequency of contact is more important than duration of exposure.

4. Clinical features

Following cutaneous penetration by the cercariae, a localized itching may occur, or a rash may develop accompanied by fever. These early signs are quite often not noticed or entirely absent. Symptomatic disease begins months after the initial infection. Initial symptoms are dysuria, frequency, and haematuria. The migration of the parasite can cause mild fever, headache, dyspnea, and itchy rashes.

The chronic active phase of the disease is characterized by a massive increase in eggs in the urothelium, causing haematuria. Urinary tract obstruction (eg, due to vesical sclerosis or ureteral stenosis), renal insufficiency, and genital lesions are seen at a later stage of the infection. Typical symptoms in the later ulcerative stage are urethralgia, frequency, suprapubic pain, and haematuria [5,6].

Genital lesions such as epididymitis, salpingitis, endometritis, and cervicitis may cause sterility [7,8]. Vesical lesions will lead to inflammation, sclerosis, calcifications, loss of bladder capacity, bladder-neck stenosis, and later bladder cancer. Ureteral fibrosis and stenosis may lead to progressive deterioration in renal function, which may, ultimately, be totally lost [6].

Nephrotic syndrome develops sometimes in patients with *S. haematobium* infection. Severe renal changes are seen in up to 25% of patients with bilharzial infections [9]. Clinical symptoms are proteinuria and oedema. Renal biopsy specimens demonstrate mostly proliferative glomerular lesions.

Ectopic locations may be seen due to aberrant worm migration into the appendix, the spleen, and the spinal cord. In endemic areas, due to permanent reinfection, it is common to see lesions of different stages in the same patient [10]. Persistent haema-

turia in children may cause asthenia, protein loss, and growth retardation in a population already affected by other unfavourable factors [11]. An association between schistosomiasis and bladder cancer has been noticed; this occurs most commonly in Egypt, the Nile valley, and the Middle East [1,6,12], but is significantly less common in Africa for unknown reasons.

5. Investigations

5.1. Diagnosis

Diagnosis is based on the detection of *S. haematobium* eggs in the urine [1,13].

5.1.1. Urine collection

Urine should be collected between 11 AM and 2 PM (peak output). The sediment should be sampled after the urine has been allowed to stand for 30 min. Several specimens taken on consecutive days should be examined.

Urinalysis includes looking for microhaematuria and proteinuria. An egg count is also done to estimate the severity of infection.

Egg count: According to the number of eggs per 10 ml of urine [1,9]:

- <100 = light infection
- 100–400 = moderate infection
- >400 = severe infection.

Viability of eggs (egg hatch procedure): Congo Red stain has been used to test the viability of eggs obtained from urine sedimentation. The eggs are first incubated with warm water (30–40 °C) for 1 h. Moving miracidia can be seen [1,9].

Urine cytology should reveal bladder cancer associated with schistosomiasis [1,14,15].

5.1.2. Diagnostic markers

Serologic tests are not useful in screening because they cannot discriminate between light infection and severe infection. Cross-reaction may sometimes occur with other parasitic diseases [9].

It remains to be seen whether new diagnostic markers, such as eosinophil cationic protein (ECP), will be used in future screening studies. ECP is currently discussed as an indicator of the egg-induced granulomatous inflammation due to *S. haematobium* infection. Eosinophil granulocytes release ECP from eosinophil granules. The protein can be measured in the urine of infected persons by enzyme-linked immunoabsorbent assay [7,16–18].

5.1.3. Genitourinary schistosomiasis

Genitourinary schistosomiasis due to *S. haematobium* infection is common in endemic areas [7,19], and should be considered a risk factor for the spread of sexually transmitted disease, especially HIV [7,8].

Haemospermia is a symptom of male genital schistosomiasis, usually seen in the early stages of disease. Sperm analysis is a diagnostic tool of male genitourinary schistosomiasis [7,19]. However, Feldmaier et al. believe that haemospermia usually occurs unnoticed and can only be diagnosed by a specific medical examination [7,19].

Gynaecologic examination: Because female genitourinary schistosomiasis of the lower reproductive tract frequently occurs without egg excretion in urine, gynaecologic examination is needed [7,8].

5.2. Evaluation of the consequences of urogenital tract lesions

Cystoscopic findings are very characteristic. Cystoscopy is generally followed by transurethral resection of the bladder lesions and histologic examination of the resected tissue. The diagnosis is confirmed by finding terminally spurred eggs surrounded by granuloma. Any signs of bladder cancer will also be detected during this procedure [1]. All the lesions described below can coexist depending on when the first infection occurred and on the extent and intensity of reinfections.

In the early stages of disease, there are defined haemorrhagic alterations; later on in the disease, nodules (with ova) and ulcers are seen; and finally “sandy” patches (fibrotic areas) develop [1,9]. The microgranuloma-like, “sandy” patches may be seen around the bladder neck and ureteral orifices. Macrogranulomas show up like cooked rice grains. Inflammatory polypoid erythematous lesions are mostly found on the dome and lateral walls of the bladder.

Typical symptoms and signs that may occur in the late stages of disease include hypertrophy of the bladder wall, frequent micturition, retention, calcification, and stones [1,20,21]. Squamous cell carcinoma of the bladder is the latest complication to develop and may occur up to 10–20 yr after infection [1,20,21].

The diagnosis of bladder cancer requires evidence from cytology and cystoscopy with biopsy. The detection of p53 autoantibodies may be a useful screening test for detecting patients at high risk for bilharzial bladder cancer [1].

Cystoscopy may also be used to evaluate bladder-neck stenosis, bladder calcification, and ureteral orifices stenosis.

5.3. Other diagnostic (screening) tests for urinary tract sequelae

Ultrasonography may be helpful in screening for ureteral obstruction when urography is not available [22,23]. It may also be used to detect hydronephrosis.

Urography may be used to evaluate bladder morphology, especially calcifications on plain film, and ureteral stenosis (usually predominant in the pelvic ureters). Renal function and morphology may be evaluated after an intravenous injection of contrast medium.

Computed tomography (CT) scanning is useful in suspected cases of kidney tumour.

Retrograde cystography may be used to assess vesicoureteral reflux related to ureteral orifices stenosis. Urodynamic retrograde cystography is helpful in cases of high-pressure contracted bladder and bladder outlet obstruction (mainly due to bladder-neck stenosis). Extensive ureteral stenotic lesions may lead to the loss of renal function. Renal parenchymal lesions are the consequences of obstructive uropathy, with the exception of rare immune glomerulonephritis.

6. Prevention

For an individual traveller, this entails strictly avoiding contact between bare skin and contaminated fresh water in rivers, lakes, or ponds in endemic areas. This means no swimming, no washing, and no barefoot river crossing, that is, absolutely no exposure of any bare skin to contaminated water. However, in the case of accidental exposure, the skin should be briskly dried and rubbed with alcohol to prevent the penetration of cercariae.

In addition, the parasite can be destroyed by boiling contaminated water; special filters can also be used to filter out the parasite. It is important to know which areas are endemic prior to travelling.

Prevention on a larger scale is more difficult for cultural and economic reasons and should be approached in the context of the general health system. This can be achieved only through health education, improvement in general living conditions, management of the environment (ie, adequate sanitation for the proper disposal of urine and faeces), and use of protective clothes.

The quantity of excreted eggs can be reduced by mass eradication with antischistosomal drugs. However, chemical eradication of *Bulinus* snails is not feasible because of environmental consequences, although biocontrol agents, such as predatory snails, are being introduced. Research is ongoing into the production of a vaccine [24–28].

7. Medical treatment

Two drugs active against *S. haematobium* are readily available: praziquantel and metrifonate (not registered in all countries). The drug, oxamniquine (not registered in all countries), is available for intestinal infestations, especially hepatic schistosomiasis (*S. mansoni* and *S. japonicum*).

These drugs are known to reduce and sometimes inhibit the in situ worm's activity. However, the drugs cannot prevent recontamination nor do they affect the nonreversible, fibrotic lesions. Nevertheless, both praziquantel and metrifonate are effective in treating both incidental infections and infections in endemic areas, because they reduce prevalence and parasitic burden [22].

7.1. Praziquantel

Mechanism: praziquantel disturbs the ionic exchange through the worm's membrane resulting in tetanic paralysis and reduced glucose absorption.

Administration: oral; adverse effects are limited.

Contraindication: pregnancy.

Dosage: treatment is given either as 40 mg/kg, administered in one dose, or two administrations of 20 mg/kg, 4 hr apart. Because one tablet contains 600 mg, the average dose is four tablets for a 60-kg adult. A single course of treatment should suffice [29]. For *S. japonicum* a 1-d regimen of 60 mg/kg divided in three doses is recommended [30].

For the treatment of *S. mansoni*, oxamniquin is an alternative [30].

7.2. Metrifonate

Mechanism: an organophosphate that paralyzes the worm by blocking the worm's cholinesterase enzyme.

Administration: oral.

Dosage: 5 mg/kg, administered in three doses at 2-wk intervals for the treatment of *S. haematobium*. The need for three, biweekly administrations makes metrifonate a less suitable drug than praziquantel in endemic areas because the population is often mobile and hard to reach [27].

Contraindications: pregnancy and in cases of occupational exposure to organophosphate pesticides.

7.3. Oxamniquine

Oxamniquine is useful for treating infection with *S. mansoni* (schistosomiasis of the intestinal tract). The drug causes an irreversible inhibition of nucleic acid

synthesis in sensitive schistosomes. In some areas, *S. mansoni* and *S. haematobium* are both endemic. Praziquantel is more effective to treat the double infection.

Dosage: Single dosage of 15–20 mg/kg should be sufficient.

7.4. Glycosaminoglycans for uroprotection

For uroprotection (especially of the bladder), it is useful to give glycosaminoglycans (GAGs) to patients with chronic cystitis, either by bladder instillation or orally [1,31–33], because the surface coat of the urothelium contains GAGs. The authors prescribe glycosaminesulphate (GAS).

Dosage: GAG is administered in three doses of 250–500 mg/d over a period of 3 mo.

8. Surgical treatments

8.1. Endoscopic endovesical procedures

These include the following:

- Endovesical proliferative inflammatory lesions must be resected to provide histologic samples for examination, to reduce bladder irritative symptoms, and to reduce haematuria.
- Sandy patches may only be biopsied.
- Ulcers should be multibiopsied and coagulated or resected.
- Tumours should be deeply resected for further staging, taking care not to perforate the bladder in case a cystectomy should prove necessary.
- Bladder-neck stenosis often requires incision or a transurethral resection, particularly if an uretero-ileoplasty (augmentation) has to be done, to avoid high-pressure vesicoureteral reflux [34].

8.2. Reconstructive surgery

Ureteral stenotic lesions are the main problem because they may cause renal failure [35]. Repairing these lesions involves a complete range of ureteral reconstructive surgery [36]. However, due to the pathologic characteristics of schistosomiasis, which include mucosal lesions, granulomas, submucosa fibrosis, calcifications, and perivesical and periureteral sclerosis, certain types of surgery should be avoided:

- Minimal invasive ureteral surgery involving balloon dilatation or ureteral endoscopic incisions; these generally fail, except in rare cases of minimal lesions.

- Ureterocystoneostomies of any kind have a high failure rate because generally the ureter has to be replaced higher than the pelvic level. Because the bladder is infiltrated and ischaemic due to calcified sclerosis, bladder tissue cannot be safely used for either a psoas hitch or a Boari-type flap, except in the case of limited lesions [37].

Ileal ureteral replacement is the recommended procedure. It allows the surgeon to go as high as necessary to meet a healthy ureter to ensure revascularization and also ensures that the transplant is free from parasitic colonization [38].

Enterocystoplasty alone for a small contracted bladder is rarely indicated. Despite calcifications, the bladder capacity is generally preserved for a long time.

8.3. Ablative surgery

Ablative surgery is indicated in schistosomiasis-related bladder cancer, which is treated like any other bladder cancer depending on staging, with the particularity of a 60% rate of squamous cell differentiation. If the bladder cannot be removed, radiotherapy is indicated. An effective chemotherapy is unknown.

9. Conclusion

1. For travellers, development aid workers, and others visiting an endemic area, taking appropriate precautions is the best approach to avoid getting infected.
2. For the population in endemic areas, an integrated approach is necessary, with health education being the first step.
3. Effective pharmacologic treatment is available. However, none of these drugs prevents reinfection nor can they reverse the damage done by the infection. Controls are necessary (urinalysis). Uroprotection should be considered.
4. Vaccines are under investigation.

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