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ORIGINAL PAPER

The diagnosis and treatment of urogenital schistosomiasis in Italy in a retrospective cohort of immigrants from Sub-Saharan Africa

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Abstract

Objectives To evaluate ultrasound and praziquantel to, respectively, assess and reduce urogenital schistosomiasis (UGS)-associated morbidity in migrants from Sub-Saharan Africa (SSA).

Methods Migrants from SSA with UGS attending three Italian centres for tropical diseases during 2011–2016 were retrospectively enrolled. Data on clinical symptoms, routine laboratory, parasitological tests, and ultrasound reported as per the WHO–Niamey protocol were collected at baseline and at available follow-up visits after treatment with praziquantel 40 mg/kg/day for 3 days.

Results One hundred and seventy patients with UGS were enrolled and treated with praziquantel. Baseline ultrasonography showed urinary tract abnormalities in 115/169 patients (68%); the mean global *Schistosoma haematobium* score was 2.29 (SD 2.84, IQR 0–2), the mean urinary bladder intermediate score 1.75 (SD 1.73, IQR 0–2), and the mean upper urinary tract intermediate score 0.54 (SD 2.37, IQR 1–10). Abnormalities were more common among the 111 (65%) who were symptomatic ($p < 0.02$; OR 2.53; 95% CI 1.19–5.35). Symptoms started in 94/111 (85%) before arriving (median 63 months, IQR 12–119). At follow-up, we observed a significant reduction in the prevalence of UGS-related symptoms, blood, urine, and ultrasound abnormalities.

Conclusions Our study results support the use of ultrasound and praziquantel for assessing and reducing UGS-associated morbidity in migrants. Health-seeking behaviour, diagnostic, and treatment delays contribute to the advanced pathology and qualified treatment success. To ensure earlier treatment, based on our findings, clinical experience, and available literature, we propose an algorithm for the diagnosis and clinical management of UGS. Multicentre studies are needed to improve the management of subjects with UGS in non-endemic countries.

Keywords Schistosoma · Schistosomiasis · Migrant · Praziquantel · Ultrasonography · Ultrasound

Introduction

Urogenital schistosomiasis (UGS) is caused by *Schistosoma haematobium*. Adult worms dwell in the venous plexum of the bladder, where they can live for years producing eggs, which penetrate the bladder wall and are released in the urine [1]. UGS is caused by the inflammatory and fibrotic reaction to the release of enzymes from the passage and trapping of eggs in urogenital tissues [1]. It is characterised by urinary tract damage, which may lead to severe and irreversible complications such as hydronephrosis, renal impairment, and bladder cancer, and is associated with an increased risk of HIV transmission [2–5].

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Schistosoma haematobium is currently reported in 43 countries in tropical and sub-tropical areas of the globe [6], and is increasingly being seen in Europe in international travellers and displaced populations [7–9]. Sub-Saharan Africa (SSA) is the area that bears the heaviest burden of UGS with approximately 112 million of affected individuals [10]; about 20% of migrants from SSA arriving in Italy are affected by UGS [11]. Despite its growing importance in Europe, including local transmission [12–14] and possible implication in transplant medicine [15], awareness of UGS is low among European health professionals, leading to disease progression caused by diagnostic and treatment delays. This happens despite guidelines such as the 2006 guidelines of the European Association of Urology (EAU) [16].

The diagnosis of UGS should be suspected in patients with compatible symptoms (such as haematuria), and/or history of exposure in endemic countries, and should be confirmed by serological, parasitological, radiological and/or histopathological exams [16]. Ultrasonography is a well-established tool to assess advanced schistosomiasis-related morbidity [17–19].

The treatment of choice for schistosomiasis is praziquantel (PZQ). In non-endemic areas, PZQ is often administered in multiple doses—generally 40 mg/kg/day per 2–3 days [20, 21] aiming to eradicate the infection based on the finding that in endemic areas, the parasitological eradication rate of a single PZQ dose is about 80% [22].

The present study aims to evaluate the burden of UGS and UGS-associated urinary tract pathology, and the effects thereupon of PZQ in immigrants from SSA to Italy.

Methods

A retrospective cohort study of cases of UGS among immigrants from SSA into Italy.

Settings

The study was conducted in three Italian centres for tropical diseases: the Tuscany Reference Centre for Tropical Diseases, Florence; the Centre for Tropical Diseases, IRCCS S. Cuore-Don Calabria Hospital, Negrar (Verona); and the University Department of Infectious and Tropical Diseases, University of Brescia and Spedali Civili General Hospital, Brescia. All the study sites are specialised in the diagnosis and treatment of tropical diseases, and are referral centres for their respective region. Patients were referred to the inpatient or outpatient departments of the three centres by the emergency department of the hospital, a general practitioner, a specialist or a public health service.

Study population and inclusion criteria

All immigrants from SSA with UGS aged > 18 years by the time of the retrospective enrolment who presented to one of the three participating centres in the period 2011–2016 were enrolled in the study.

To identify patients with UGS, we first reviewed all migrant patients from SSA with at least one positive "schistosoma-specific" test, namely:

- (a) *Schistosoma* serology and/or
- (b) direct *Schistosoma* spp. egg identification by parasitological analysis of urine or stool, or in histopathologic samples and/or
- (c) immunochromatographic (ICT) test for Circulating Cathodic Antigen (CCA) on urine.

Among these patients (migrant from SSA with at least one test positive), we identified those with UGS if they satisfied at least one of the following criteria:

- (a) *Schistosoma haematobium* eggs identified in urine or in urogenital histopathologic samples; and/or
- (b) presence of lesions compatible with UGS detected by ultrasonography.

Collected data

Data collected included demographics, presence and type of UGS-related symptoms, date of onset of schistosomiasis-related symptoms, date of first medical consultation for schistosomiasis-related symptoms, date of diagnosis of schistosomiasis, results of *Schistosoma* serology, urine parasitological examination for *Schistosoma* eggs, routine blood and urine test (haemoglobin level; white blood cell total count; eosinophil count; creatinine; complete standard urine analysis; HBsAg, HCV-Ab, HIV 1–2 Ab/Ag), presence and type of urinary abnormalities compatible with UGS. We also collected the results of parasitological tests, routine blood and urine tests as well as results of post-treatment abdominal ultrasound for those patients who returned for one or more follow-up visits.

The results of abdominal ultrasonography were reported according to the WHO-Niamey protocol for *S. haematobium*-associated ultrasound findings [19], whereby the assessment of burden of *S. haematobium*-related pathology is given by the sum of two scores: the urinary bladder intermediate score, which measures bladder irregularity, thickening, masses/polyps and shape of the bladder, and the upper urinary tract intermediate score, which evaluates abnormalities of ureters and renal pelvises. A global

score of 0 means normal findings, while higher score indicates presence and degrees of pathology (Supplementary Table 1 and Supplementary Figs. 1 and 2). The scores were retrospectively calculated using ultrasonography images and radiological reports.

Standard case management

All patients received PZQ 40 mg/kg/day in two divided doses 4–8 h apart with a meal for three consecutive days with followed-up visits scheduled at 1–2 months and then every 3–6 months for at least 1 year.

Statistical analysis

Statistical analyses were performed using Epi Info7™. Descriptive statistics were used to present the frequency of variables at baseline. The clinical, laboratory, and UGS-specific features were compared (1) at baseline between subjects with at least one post-treatment follow-up visit and those without and (2) in the subjects with at least one follow-up visit before and after treatment. To compare categorical dichotomous variables, we used the Fisher test and Chi-square test (for independent variables) or McNemar test (for paired data), and for continuous variable the Student's *t* test (for independent variables) or the Wilcoxon test (for paired data). p value < 0.05 was considered significant.

Ethics

The study protocol was submitted to the ethics committee of the coordinating centre (Comitato Etico Regione Toscana AREA VASTA CENTRO, Florence, Italy) and was approved on 30th January 2018.

Results

Of the total 443 migrants from SSA with schistosomiasis (with at least one "schistosoma-specific test positive) seen at our facilities, all the 170 cases of UGS (38%) were enrolled in this study. The majority of UGS patients (165, 97%) were male, with mean age 24.9 years (range 12–76 years). Seven subjects, seen in the early period of study (2011/2012), were < 18 years by the time of first presentation at the centre, but all were > 18 years at the time of retrospective enrolment. With few exceptions, patients were from West Africa (see Fig. 1).

The majority of patients (120, 71%) reached Europe in 2014–2016; 58% of cases ($n = 98$) was diagnosed during 2015–2016 (Fig. 2).

The diagnosis of UGS was based on: presence of (1) *Schistosoma* eggs only in 55 (32%) cases, namely in urine

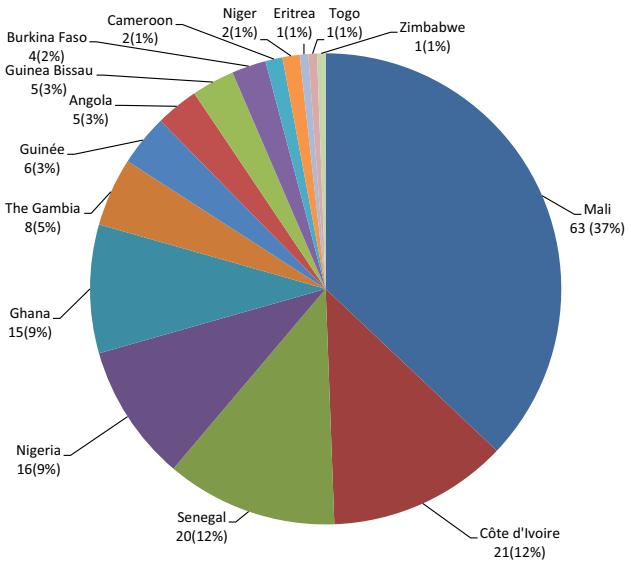

Fig. 1 Country of origin of migrants form Sub-Saharan Africa with urogenital schistosomiasis

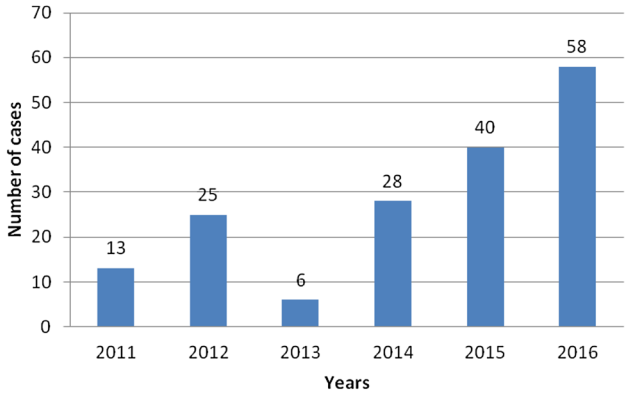

Fig. 2 Number of cases of urogenital schistosomiasis per year of diagnosis

($n = 52$) or in urogenital histopathological tissue samples ($n = 2$), or both ($n = 1$) as the only UGS-defining condition; (2) both ultrasound abnormalities and eggs in urine or tissues in 73 (43%), namely, 55 cases with eggs in urine only, 10 in histopathological tissues only, 8 in both; and (3) ultrasound abnormalities compatible with UGS in 42 (25%) as the only UGS-defining condition. In the latter group, research of eggs in urine was negative for all patients except two, in which the research was not performed. In this group, the diagnosis of schistosomiasis was established because of positive serology (namely, 23 patients with positive ELISA only, 6 with IFAT only, 4 with WB only and 5 with both WB and ELISA) or positive CCA (4 patients). Fourteen patients with UGS had a *S. mansoni* co-infection (presence of *S. mansoni* eggs in stools).

Serology was available in all but three patients (for whom diagnosis was based on a positive direct test only). Of the 167 patients with UGS and a serology result, 150 (90%) were positive on at least one serological test and 17 (10%) were negative. The combined serological tests sensitivity was 90%. The individual test sensitivity was 83% for ELISA (99/120), 85% (57/67) for Western Blot (WB), and 100% (27/27) for IFAT. Details follow. Of the 150 cases with a positive serology, 105 (70%) were diagnosed on a single test (61 ELISA, 27 IFAT, and 17 WB) and 45 on one or both two tests (33 both WB and ELISA positive, 7 WB positive and ELISA negative, and 5 ELISA positive and WB negative).

Of the 17 cases with negative serology, two were negative on both WB and ELISA, three had a negative WB (ELISA not performed), and 12 a negative ELISA (WB not performed). Among them, 13 were addressed to our centres because of compatible symptoms, while in 4, the diagnosis was suspected due to incidental findings, a pathological ultrasonography (2) or altered urine exams (2). Two patients with baseline WB negative serology were retested one month after treatment and seroconverted with the same test. These 17 patients all were diagnosed as UGS with at least one direct positive test: one case had eggs in urine, CCA positive, histopathology positive; seven cases had eggs in urine, CCA negative, histopathology not performed; one had eggs in urine, CCA not performed, histopathology not performed; two had a positive histopathology, no eggs in urine, CCA not performed; one had positive histopathology, eggs in urine not performed, CCA not performed; and five had CCA positive, no eggs in urine, histopathology not performed.

Ninety-nine patients were tested with both parasitological examination of urine and urine CCA (results reported in Table 1). Test concordance was low (Cohen's Kappa was 0.056). Baseline findings are shown in Table 2. At diagnosis, 133 patients (78%) presented with at least one UGS-related symptom, most commonly macroscopic haematuria and lower back pain.

Among the 111 symptomatic patients for whom the date of symptoms onset was available, 94 (85%) reported that the symptoms started before arriving in Italy (median 63 months before arriving in Italy, IQR 12–119) and 17 (15%) after arriving in Italy (median 12 months after arriving in Italy, IQR 4–20). The median time from arrival in Italy or symptoms onset (whichever last) and diagnosis was 151 days (IQR 48.5–281). The median time from diagnosis and treatment was 11 days (IQR 3–30). For 37 asymptomatic subjects, the median delay between the arrival in Italy and diagnosis was 61.5 days (IQR 10.5–242.2) and the median delay between diagnosis and treatment was 17 days (IQR 3–39.5).

Table 1 Analysis of concordance in 99 cases with both circulating cathodic antigen and research of eggs in urine performed

		Eggs in urine	
		Present	Absent
CCA	Positive	31	9
	Negative	42	17

CAA cathodic circulating antigen

Among the 169 patients with baseline ultrasonography, urinary tract abnormalities were found in 115 (68%). At diagnosis, UGS-related symptoms were more common among patients with ultrasound abnormalities (83%, 96/115) than those without abnormalities (67%, 36/54) ($p < 0.02$; OR 2.53; 95% CI 1.19–5.35). Concerning ultrasonography findings, the mean global *S. haematobium* score at baseline was 2.29 (SD 2.84, IQR 0–2), the mean urinary bladder intermediate score was 1.75 (SD 1.73, IQR 0–2), and the mean upper urinary tract intermediate score was 0.54 (SD 2.37, IQR 0–0).

Twenty-one patients (12%) underwent a surgical procedure, which was a bladder biopsy for suspected bladder cancer in 15, either before treatment, because schistosomiasis was not suspected ($n = 8$), or after PZQ treatment due to incomplete resolution of lesions ($n = 7$). In all cases, the histopathological examination showed the presence of *S. haematobium* eggs and was negative for neoplasm. One patient underwent nephrectomy because of end-stage monolateral renal disease secondary to hydroureteronephrosis (the diagnosis was confirmed by the histopathological examination of the removed kidney and ureter which showed extensive ureter fibrosis with embedded *S. haematobium* eggs). Five patients underwent bioptic procedures of other organs (two rectums, two lungs, and one kidney). In all cases but one lung biopsy, histology showed *S. haematobium* eggs in the samples examined.

Testing for HBsAg was positive in 20% of patients (30 out of 153 with known serologic status) and for HIV in 2% (3 out of 165 with known serologic status), while none of the 104 tested for HCV resulted positive.

Findings after praziquantel treatment

Table 2 reports the baseline clinical, laboratory, and ultrasonographic findings of all patients and compares the findings of those with at least one follow-up value available to those with none. Patients with at least one follow-up visit were more likely to have one or more alterations at baseline than those who did not—specifically if they had had any symptom (OR 7.26, 95% CI 1.66–31.68), macroscopic haematuria (OR 2.80, 95% CI 1.32–5.93), microhaematuria (OR 2.63 95% CI 1.18–5.86), leukocyturia (OR 2.08, 95% CI 0.99–4.36), presence of schistosoma eggs in urine (OR 12.36, 95% CI 2.85–53.58), presence of at least one

Table 2 Symptoms, blood, and urine tests alterations in patients with urogenital schistosomiasis at baseline evaluation

	All patients *n*/*N* (%)	Patients with at least one follow-up visit	Patients without any follow-up visit	*p*	Odds ratio
Symptoms					
Any symptom	133/170 (78%)	39/41 (95%)	94/129 (73%)	**0.0026**	7.2606 (1.6643–31.6753)
Macroscopic haematuria	79/162 (49%)	27/40 (68%)	52/122 (43%)	**0.0063**	2.7959 (1.3171–5.9348)
Lower back pain	75/162 (46%)	16/41 (39%)	59/121 (49%)	0.2799	0.6725 (0.3268–1.3840)
Dysuria	26/163 (16%)	9/40 (23%)	17/123 (14%)	0.1928	1.8102 (0.7348–4.4599)
Painful urination	20/163 (12%)	6/40 (15%)	14/123 (11%)	0.5446	1.3739 (0.4900–3.8523)
Pollakiuria	8/162 (5%)	1/40 (2.5%)	7/122 (6%)	0.4121	0.4212 (0.0502–3.5326)
Haemospermia	1/160 (0.6%)	0/39 (0%)	1/121 (0.8%)	0.5690	na
Blood and urine tests					
Haemoglobin < 13 g/dL	13/165 (8%)	6/87 (7%)	7/78 (9%)	0.6208	0.7513 (0.2412–2.3399)
White Blood Cells (WBC) $< 4 \times 10^9$/L	19/164 (12%)	8/87 (9%)	11/78 (14%)	0.3241	0.6168 (0.2345–1.6225)
White Blood Cells $> 10 \times 10^9$/L	4/164 (2%)	2/87 (2%)	2/78 (2.5%)	0.9119	0.8941 (0.12229–6.5036)
Eosinophils $> 0.5 \times 10^9$/L	86/166 (52%)	49/88 (56%)	37/78 (47%)	0.2886	1.3922 (0.7550–2.5672)
Creatinine > 1.14 mg/dL	11/164 (7%)	5/77 (6.5%)	6/76 (7.9%)	1	0.8225 (0.2408–2.8096)
Microhaematuria	93/164 (57%)	28/38 (74%)	65/126 (52%)	**0.0159**	2.6277 (1.1782–5.8606)
Leukocyturia	76/163 (47%)	23/38 (61%)	53/125 (42%)	**0.0490**	2.0830 (0.9929–4.3699)
Haemoglobin in urine	48/163 (29%)	15/38 (39%)	33/125 (26%)	0.1215	1.8182 (0.8482–3.8972)
Proteinuria > 20 mg/dL	28/161 (17%)	10/38 (26%)	18/123 (15%)	0.0960	2.0833 (0.8656–5.0141)
Presence of eggs in urine	116/165 (70%)	40/42 (95%)	76/123 (62%)	**< 0.001**	12.3684 (2.8552–53.5778)
Presence of CCA in urine	40/99 (40%)	17/35 (49%)	23/64 (36%)	0.2206	1.6836 (0.7292–3.8871)
				p	*T* test
Mean haemoglobin g/dL	14.58	14.66	14.50	0.4748	0.71624
Mean white blood cells $\times 10^9$/L	5797	5953	5621	0.2766	1.09166
Mean eosinophils $\times 10^9$/L	628	655	599	0.5204	0.6441
Ultrasound-detectable alterations*				*p*	Odds ratio
At least one urinary alteration	115/169 (68%)	40/46 (87%)	75/123 (61%)	**0.001**	4.2667 (1.6810–10.8294)
Urinary bladder shape alteration	2/169 (1%)	1/46 (2%)	1/123 (0.8%)	0.4665	2.7111 (0.1660–44.2660)
Bladder wall irregularities	45/169 (27%)	12/46 (26%)	33/123 (27%)	0.9225	0.9626 (0.44595–2.0780)
Bladder wall thickening	50/169 (30%)	19/46 (41%)	31/123 (25%)	**0.041**	2.0884 (1.0224–4.2659)
Bladder wall mass	23/169 (14%)	11/46 (24%)	12/123 (10%)	**0.0168**	2.9071 (1.1795–7.1653)
Pseudopolyps	15/169 (9%)	7/46 (15%)	8/123 (7%)	0.0762	2.5801 (0.8784–7.5783)
Ureter dilatation	7/169 (4%)	0/46 (0%)	7/123 (6%)	0.098	Undefined
Renal pelvis hydronephrosis or moderate damage	10/169 (6%)	3/46 (7%)	7/123 (6%)	0.8385	1.1561 (0.2859–4.6747)
				p	*T* test
Mean *S. haematobium* global score	2.29	2.91	2.04	**0.0049**	2.61295
Mean urinary bladder intermediate score	1.75	2.48	1.48	**0.0003**	3.45085
Mean urinary upper intermediate score	0.54	0.43	0.58	0.3644	0.34718

n number of patients with a symptom or alteration, *N* number of patients with available information concerning a symptom or alteration

*Each patient could present one or more lesions

urinary tract alteration (OR 4.27, 95% CI 1.68–10.83), bladder thickening (OR 2.09, 95% CI 1.02–4.27), bladder mass (OR 2.91, 95% CI 1.18–7.16), higher mean *S. haematobium* global score ($p = 0.005$), and higher mean urinary bladder intermediate score ($p = 0.0003$).

Table 3 presents changes from baseline for patients with at least one follow-up value available (for patients with more than one follow-up visit, the last follow-up value is considered). There was a significant trend towards improved clinical signs/symptoms, laboratory values and ultrasonographic findings after PZQ treatment. Nine patients had persisting eggs in urine and/or positive ICT CCA in the urine after treatment: six of them were seen 1 month post-treatment (four with CCA positive and eggs not determined, two with

Table 3 Baseline and follow-up clinical, laboratory, and ultrasound findings among patients with available baseline data and at least one follow-up available (for patients with more than one follow-up data available, the last follow-up visit was considered)

	Features at baseline	Features at follow-up	*p*	Odds ratio
Symptom				
Any symptom	39/41 (95%)	9/41 (22%)	**< 0.0001**	61 (3.7300–997.6078)
Macroscopic haematuria	27/40 (68%)	3/40 (8%)	**< 0.0001**	49 (2.9797–805.7877)
Lower back pain	16/41 (39%)	5/41 (12%)	**0.0114**	23 (1.3553–390.3210)
Dysuria	9/40 (23%)	0/40 (0%)	**0.0044**	19 (1.1058–326.4595)
Painful urination	6/40 (15%)	0/40 (0%)	**0.0233**	13 (0.7323–230.7749)
Pollakiuria	1/40 (2.5%)	1/40 (2.5%)	1	1 (0.0198–50.4004)
Haemospermia	0/39 (0%)	0/39 (0%)	1	1 (0.0198–50.4004)
Blood and urine tests				
Haemoglobin < 13 g/dL	6/87 (7%)	4/87 (5%)	0.2482	50 (0.24–104.1526)
White blood cells $< 4 \times 10^9$/L	8/87 (9%)	12/87 (14%)	0.2059	0.4286 (0.1108–1.6574)
White blood cells $> 10 \times 10^9$/L	2/87 (2%)	2/87 (2%)	0.3417	1 (0.1409–7.0993)
Eosinophils $> 0.5 \times 10^9$/L	49/88 (56%)	31/88 (35%)	**0.0010**	4 (1.6351–9.7856)
Microhaematuria	28/38 (74%)	4/38 (11%)	**< 0.0001**	25 (3.3874–183.5078)
Leukocyturia	23/38 (61%)	9/38 (24%)	**0.0017**	5.6667 (1.6606–19.3366)
Haemoglobin in urine	15/38 (39%)	2/38 (5%)	**0.0005**	27 (1.6050–454.2099)
Proteinuria > 20 mg/dL	10/38 (26%)	4/38 (10%)	0.0832	3 (0.8122–11.0815)
Presence of eggs in urine	40/42 (95%)	4/42 (9.5%)	**< 0.0001**	73 (4.4803–1189.4411)
Presence of CCA in urine	17/35 (49%)	5/35 (14%)	**0.0008**	25 (1.4801–422.2629)
			p	*Z* value
Mean haemoglobin g/dL	14.66	14.86	0.3173	− 1.0012
Mean white blood cells $\times 10^9$/L	5953	5565	0.1187	− 1.5618
Mean eosinophils $\times 10^9$/L	655	467	**0.0061**	− 2.7361
Ultrasound-detectable abnormalities[a]				
Presence of at least one urinary alteration lesion	40/46 (87%)	27/46 (59%)	**0.0005**	27 (1.6050–454.2099)
Urinary bladder shape alteration	1/46 (2%)	1/46 (2%)	1	1 (0.0198–50.4004)
Bladder wall irregularities	12/46 (26%)	11/46 (24%)	0.7388	1.25 (0.3357–3.6550)
Bladder wall thickening	19/46 (41%)	12/46 (26%)	**0.0133**	15 (0.8567–262.6477)
Bladder wall mass	11/46 (24%)	5/46 (11%)	**0.0233**	13 (0.7323–230.7749)
Pseudopolyps	7/46 (15%)	4/46 (9%)	0.1797	4 (0.4471–35.7890)
Ureter dilatation	0/46 (0%)	0/46 (0%)	na	na
Renal pelvis hydronephrosis or moderate damage	3/46 (7%)	0/46 (0%)	0.1336	7 (0.3616–135.5244)
			p	*Z* value
Mean *S. haematobium* global score	2.91	1.56	**0.0013**	− 3.2141[#]
Mean urinary bladder intermediate score	2.48	1.43	**0.0003**	− 3.6213[+]
Mean urinary upper intermediate score	0.43	0.13	Not applicable[¥]	Not applicable[¥]

n number of patients with a symptom or abnormality, *N* number of patients with available information concerning a symptom or abnormality; * each patient could present one or more lesions; [#]the *W* value is 27.5, the critical value of *W* for $N = 22$ at $p \leq 0.05$ is 65, therefore, the result is significant at $p \leq 0.05$, [+] the *W* value is 8, the critical value of *W* for $N = 20$ at $p \leq 0.05$ is 52, therefore, the result is significant at $p \leq 0.05$; [¥] it was not possible to perform the test on upper urinary tract scores, since there were not enough paired scores

persistent eggs and CCA negative), one after 2 months (with persistent eggs and CCA negative), and two after 3 months (one with CCA positive and eggs not determined and one with persistent eggs and CCA negative). All these patients were then lost to follow-up.

Both the mean global score and urinary bladder intermediate score decreased significantly after treatment with PZQ. A follow-up ultrasound was systematically planned for all patients, either with or without pathological findings at baseline examination, but the majority did not come to the visit (Fig. 4a, b). Considering the last available finding of the 46 patients with at least one ultrasonography examination at follow-up (performed, on average, 4 months after treatment, IQR 2.7–5.2 ; range 1–24 months), 6 (13%) presented no alterations at both baseline and follow-up; 20 (44%) with baseline alterations improved post-treatment (in 11 the score

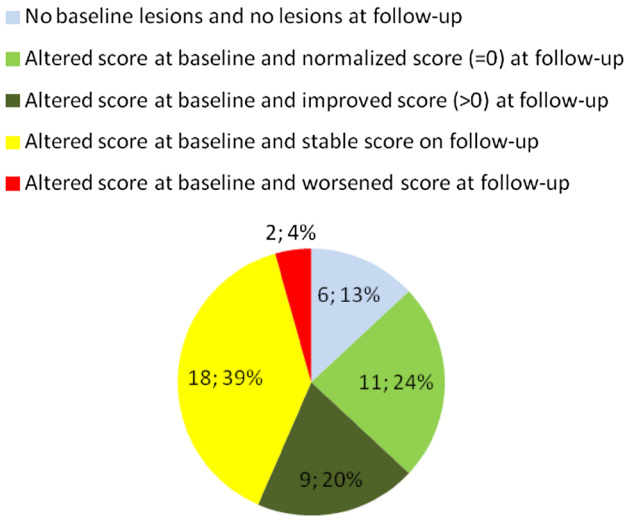

Fig. 3 Variation of the global score after treatment with praziquantel in patients with at least one follow-up visit

became 0, in 9 the score decreased but was still > 0); and in 18 (39%), the score did not change, and in 2 (5%), it worsened (Fig. 3).

As for safety, after PZQ treatment, 6 out of 150 for which the information was available (4%) reported mild self-resolving adverse events, specifically nausea, dizziness, and itching.

Figure 4 reports a flowchart illustrating the patient's rate of loss to follow-up according to the presence of symptoms and the presence of ultrasonographic alterations at baseline.

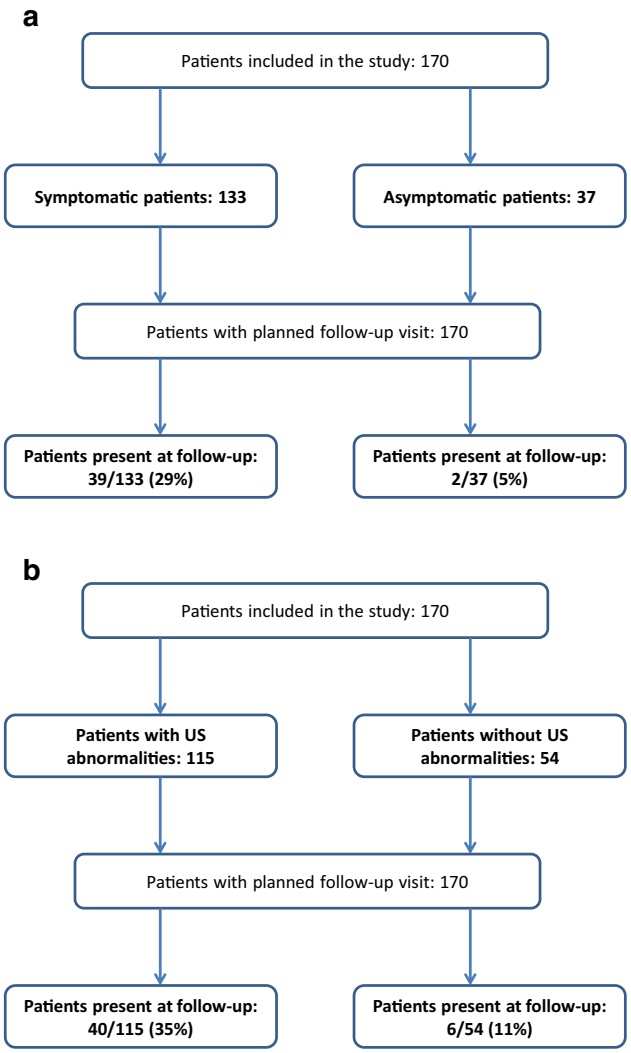

Fig. 4 Flowchart reporting the patient's rate of loss to follow-up according to the presence of symptoms at baseline and the presence of ultrasonographic alteration at follow-up

Discussion

Consistent with trends across Europe [7], Italy as well is experiencing an increase in the number of cases of schistosomiasis, related to the migratory influx from SSA [23]. However, awareness of the disease among health professionals remains limited, leading to diagnostic and treatment delays.

In our cohort of migrants from SSA to Italy diagnosed with schistosomiasis, more than one-third of the cases were UGS, a higher proportion than the 22% found in a large multicentre case series of imported schistosomiasis in Europe [7]. The difference might be related to different geographical origins (95% vs. 67% of cases being migrants from West Africa in our study vs. the European series).

Diagnostic delays

Our data show that in the Italian context, much remains to be done to diagnose and treat UGS at earlier stages. The diagnosis was reached among symptomatic patients, on average 5 months after their arrival in Italy or symptom onset (whatever the last) and the majority of patients had suffered for UGS-related symptom for years (5 years in median) before arriving in Italy. This meant that on presentation, over two-thirds of patients had one or more urinary tract lesions detected by ultrasonography. This delay is mainly due to difficult access to care, lack of appreciation of the significance of symptom, and misdiagnosis due to lack of awareness of the disease by Italian physicians.

About four-fifth of the patients had symptoms on presentation at our facilities: macroscopic haematuria and lower back pain accounted for the majority of symptoms, while dysuria and painful urination were less frequent. More than half of the cases presented with laboratory findings such as microhaematuria, eosinophilia, and leukocyturia and less frequently haemoglobin in urine and proteinuria.

One-fifth were asymptomatic and they were referred to our centres for unrelated clinical problems; in these subjects, schistosomiasis was suspected because of haematological or urinary subclinical alterations (eosinophilia or proteinuria or microhaematuria) or just because they originated from an endemic country. In half of these, ultrasonography detected urinary alterations, demonstrating that even asymptomatic subjects may have relevant schistosomiasis-associated urinary tract morbidity.

Case identification and management

Recent national Italian guidelines [24] are aligned with other guidelines [25–27], and recommend screening for schistosomiasis by serological tests of all migrants from endemic countries, but this has not become practice yet. If implemented systematically, this policy would allow to shorten the diagnostic delay, avoid inappropriate diagnostic procedures (such as biopsy for suspected bladder cancer), and identify subjects with asymptomatic infections—who, as we pointed out, could already have subclinical urinary tract pathologies. Some of us participated in a recent independent evaluation of several diagnostic tools for schistosomiasis, which found that a rapid commercial serological ICT test with 96% sensitivity would have the potential for being used as a single screening test for migrants from SSA [28].

The next question is which ones should be the right procedures to follow once subjects have been found positive. All the above-mentioned guidelines say little about how to manage seropositive subjects whether asymptomatic or with symptoms suggestive of urinary or intestinal schistosomiasis.

Australian guidelines recommend a urinary and faecal parasitological test in subjects with positive *Schistosoma* serology, followed by ultrasonography only in the presence of eggs in excreta [26]. Our results show that one-quarter of the patients with UGS has urological lesions detected by ultrasonography with negative parasitological tests, suggesting that an ultrasound should be performed in all patients with positive serology.

The 2006 guidelines of the EAU [16] contain an overview of the clinical presentations, and the diagnostic and treatment approaches for UGS, but provide no details about baseline assessment and follow-up.

The suggested diagnostic algorithm based on our own findings, clinical experience, and information from the literature is reported in Fig. 5. In brief, we recommend screening with a serological test for all subjects, whether symptomatic or asymptomatic, with history of exposure in endemic countries, such as migrants or long-term expatriates living in SSA, or travellers reporting having bathed in fresh water in an endemic area. The serological test may be falsely negative in case of recent exposure (< 3–6 months) [29, 30]. Patients with suggestive symptoms and/or laboratory alterations should also be tested with direct microbiological test (urine CCA and parasitological examination of urine) to increase the probability of identify the few (17, 10% in our case series) seronegative affected subjects. Subjects with at least one positive serological or direct test should undergo a full assessment which includes abdominal ultrasound to assess the presence of urinary tract alterations and should be treated with PZQ. Of note, as we did in our patients, we suggest treating seropositive patients even in case of negative results of both parasitological tests and CCA in urine, since the rate of false negative of these tests may be very high [28]. In particular, the CCA test investigates the presence of *S. mansoni* antigen and the sensitivity towards *S. haematobium* is lower [31–34].

Patients with baseline alterations should repeat ultrasound and the others altered test (excluding the serological tests, because the persistence of antibodies does not indicate treatment failure) 2 months after treatment with PZQ. In the event, baseline alterations do not improve or worsen, the managing clinician should consider a second-level diagnostic procedure, a strict ultrasound, laboratory and clinical follow-up and PZQ re-treatment in selected cases. Re-treatment would attempt to clear persistent eggs in bladder tissues, as there are indications of a partial yet measurable effect of PZQ on schistosome eggs lodged in tissues [21, 37, 38]. In our study, seven patients with bladder lesions persisting after a 3-day PZQ course underwent bladder biopsy which showed persistent eggs in the bladder wall. In most cases, subjects with UGS and ultrasound-detectable urinary trait alterations at baseline do not need to undergo any bioptic procedure and may be strictly followed-up with ultrasound after PZQ treatment to assess the improvement of the alterations. In case of worsening or not satisfying improvement of bladder lesions 6 months after antihelmintic treatment, an invasive diagnostic procedure such as a biopsy is advisable to exclude the presence of *S. haematobium*-associated bladder cancer, as suggested by other authors [18].

Treatment effects

Our study has confirmed the efficacy of PZQ in inducing symptoms remission, parasitological cure, and reduction of ultrasound-detectable urinary alterations in adult migrants from SSA. Concerning the ultrasonographic evaluation of PZQ effects, we observed a significant decrease in mean global and urinary bladder intermediate scores after treatment. Studies carried out in schistosomiasis-endemic countries on the effects of PZQ in resolving urinary tract lesions in adults have shown variable levels of efficacy [39, 40], and only few studies on resolution of lesions were conducted on adults living in endemic areas. Magak et al. found, 1–2 years after treatment with a single dose of PZQ 40 mg/

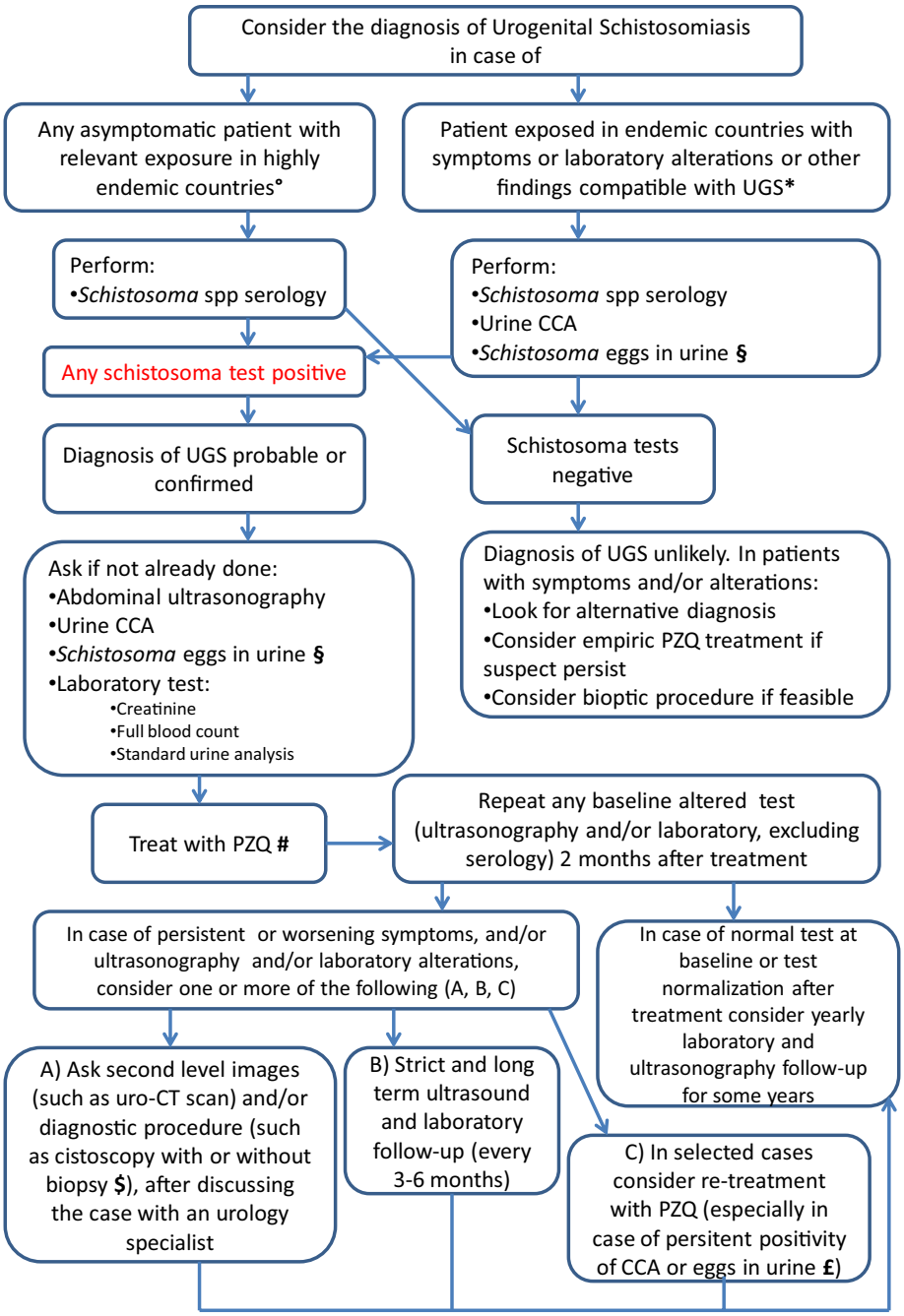

Fig. 5 Suggested algorithm for diagnosis, treatment, and follow-up of urogenital schistosomiasis in non-endemic countries. *UGS* urogenital schistosomiasis, ° referred especially to migrants and long-term expatriate who have lived in Sub-Saharan Africa for years, or travellers reporting having bathed in fresh water in an endemic area. The serological test may be false negative in case of recent at risk exposure (< 3–6 months), * includes haematuria, dysuria, microhaematuria, haemospermia, infertility, eosinophilia, proteinuria, leukocyturia, urogenital tract lesions (such as bladder pseudopolyps), § collect fresh samples of terminal urine after physical exercise (such as 20–30 squatting exercise) between 10 and 14 h for 1–3 consecutive days [16, 35], # consider to use 40 mg/kg/day in two divided doses 4–6 h apart with fatty meal for three consecutive days; consider a second PZQ treatment course some weeks apart from the first cycle at in subjects who have been diagnosed within few months after their arrival in Italy to eliminate possible persisting worms once they are fully matured. Before prescribing PZQ assess for possible cysticerocosis (ask for history of severe headache, epilepsy and look for subcutaneous nodules and prescribe brain MRI or TC scan in case of any relevant symptoms) [36], $ biopsy is highly recommended in case urinary bladder lesions persisting more than 6 months after antihelmintic treatment to exclude the presence of *S. haematobium*-associated bladder cancer, £ if locally feasible look for miracidia vitality in to the eggs or perform miracidia hatching test (which suggests presence of persistent viable adults worms)

kg, an improvement of global score in 92% of 77 Kenyan aged > 17 years with abnormal baseline findings, with an improvement of bladder wall lesions in 81% of cases and of urinary tract lesions in 22% [41]. Similarly, Wagatsuma et al. reported that a single dose of 40 mg/kg in Ghanaians aged > 14 years produced an overall pathology clearance rate in 89.2% of cases [42]. Ramarakoto et al. in Madagascar found a decrease in the prevalence of lesions from 57 to 11% in 44 women and from 74 to 27% in 86 men aged ≥ 16 years 6 months after treatment with a single 40 mg/kg PZQ dose [43].

The lower efficacy of PZQ in reducing urinary tract morbidity in our cases might be due to a selection bias, as subjects with persisting symptoms would be more likely to return for follow-up visits; availability high-performance ultrasound devices could also have contributed to the finding of more subtle anomalies.

On the other hand, the partial efficacy of PZQ in reversing alterations is not surprising when considering that the drug is mainly active against mature adult parasites, while juvenile schistosomula and eggs (especially immature eggs) are relatively resistant to PZQ [37, 44]. Urinary tract lesions are the result of inflammation and fibrosis caused by enzymes released by viable *Schistosoma* eggs; thus, the persistence of these lesions could be due to the persistence of fibrotic tissues which are unaffected by treatment [37, 45]. Finally, some patients (especially those recently arrived in Italy) could have harboured immature schistosomes that were not killed by PZQ and matured and subsequently deposited eggs, resulting in the reappearance or worsening of urinary lesions [44]. Centers of Disease Control (CDC) recommend treating travellers for schistosomiasis 6–8 weeks after the last exposure to potentially contaminated freshwater [21]. In a cohort like this, the mean diagnostic delay was long probably resulting in irreversible fibrosis in at least some of our patients.

Considering these facts, it can be reasonable to consider a second PZQ treatment course some weeks apart from the first cycle at least in subjects who have been diagnosed within few months after their arrival in Italy to eliminate persisting worms once they are fully matured. However, at least in our experience, the majority of migrant patients from SSA were evaluated at least some months after exposure, so the probability that they would harbour immature schistosomula is quite low. In accordance with the available literature data demonstrating that the parasitological eradication rate of a single 40 mg/kg PZQ dose is about 80% [22] and considering that the drug is well tolerated, the CDC suggest the possibility of administering a second PZQ dose 2–4 weeks after the first to increase the effectiveness of treatment [21]. However, we think that spacing the additional PZQ doses by several weeks could increase the risk of losing the patient to follow-up before completing the planned treatment schedule. Some patients could not return at the clinic to collect the additional PZQ dose or in case the drug is directly delivered to the patient by the time of initial evaluation, they could forget to take the second dose weeks later. For these reasons, we opted for a 3 consecutive days treatment course.

Considering that *S. haematobium* is a class 1 carcinogen [2], that eggs embedded in the urogenital tissues can persist for long time after a successful treatment, and that ultrasound is a non-invasive harmless and not expensive test, in high-income countries a long-term ultrasound follow-up should be offer to patients with UGS and persistent ultrasound-detectable alterations.

Conclusions

This study has some inherent limitations, due to its retrospective design. There is a substantial amount of data losses due to the high drop-out rate during follow-up which has been mostly related to the precarious life conditions of migrants, often being moved within and out of Italy. The calculation of the ultrasonography score was done in a retrospective way using available images and radiological reports. Moreover, the current study may not be representative of the entire burden of schistosomiasis in migrants from SSA to Italy, as it is a cohort of patients seen at three referral hospital only. Procedures across the sites were coordinated but not completely standardised.

Despite these limitations, we believe that this study provides important elements to the management of UGS in migrants. We have been observing UGS cases increasing in immigrants from SSA. Diagnostic delays are significant and may result in advanced pathology and, consequently, difficulty in treatment. Increased awareness of the condition, systematic screening by serological tests, and use of standardised diagnostic algorithms including ultrasonography can improve case management and reduce pathology. This should include serology-positive asymptomatic subjects, as subclinical pathology can be seen by ultrasonography. Three doses of PZQ reduce the number of lesions and the severity of pathology detected by ultrasonography, but damages caused by long-term inflammation are difficult to correct. The diagnostic algorithm and prolonged follow-up proposed, along with measures to enhance awareness of schistosomiasis among healthcare professionals, could help to improve case management and reduce morbidity and sequelae.

Many questions remain without a clear answer such as the ideal dose and treatment scheme of PZQ in imported schistosoma infection and the length of the necessary follow-up after a standard treatment course. There is a need for multicentre studies in non-endemic, high-income countries, to identify adequate standards for diagnosis, treatment, and follow-up of subjects with UGS.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Colley DG, et al. Human schistosomiasis. Lancet. 2014;383:2253–64. **(ISSN 0140–6736)**.
2. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Biological agents. Volume 100 B. A review of human carcinogens. IARC Monogr Eval Carcinog Risks Hum. 2012;100:1–441.
3. Khalaf I, Shokeir A, Shalaby M. Urologic complications of genitourinary schistosomiasis. World J Urol. 2012;30:31–8. **(ISSN 0724–4983)**.
4. Van der Werf MJ, et al. Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa. Acta Trop. 2003;86:125–39. **(ISSN 0001-706X (Print) 0001-706x)**.
5. El-Sebaie M, et al. Squamous cell carcinoma of the bilharzial and non-bilharzial urinary bladder: a review of etiological features, natural history, and management. Int J Clin Oncol. 2005;10:20–5. **(ISSN 1341–9625 (Print) 1341–9625)**.
6. IAMAT. World schistosomiasis risk chart. 2015. Available online: https://www.iamat.org/elibrary/view/id/2969#. Accessed 6 Jan 2019.
7. Lingscheid T, et al. Schistosomiasis in European travelers and migrants: analysis of 14 years TropNet surveillance data. Am J Trop Med Hyg. 2017;97:567–74. **(ISSN 0002–9637)**.
8. Zammarchi L, et al. Spectrum and burden of neglected tropical diseases observed in an infectious and tropical diseases unit in Florence, Italy (2000–2015). Intern Emerg Med. 2017;12:467–77. **(ISSN 1828–0447)**.
9. Martelli G, et al. Seroprevalence of five neglected parasitic diseases among immigrants accessing five infectious and tropical diseases units in Italy: a cross-sectional study. Clin Microbiol Infect. 2017;23:335. **(ISSN 1198-743x)**.
10. World Health Organization. Schistosomiasis—current estimated total number of individuals with morbidity and mortality due to *Schistosomiasis haematobium* and *S. mansoni* infection in Sub-Saharan Africa. 2018. http://www.who.int/schistosomiasis/epidemiology/table/en/. Accessed: 26 July 2018.
11. Buonfrate D, Gobbi F, Marchese V, et al. Extended screening for infectious diseases among newly-arrived asylum seekers from Africa and Asia, Verona province, Italy, April 2014 to June 2015. Euro Surveill. 2018;23:17-00527. https://doi.org/10.2807/1560-7917.ES.2018.23.16.17-00527.
12. Holtfreter MC, et al. *Schistosoma haematobium* infections acquired in Corsica, France, August 2013. Eurosurveillance. 2014;19:20821. **(ISSN 1025-496x)**.
13. Beltrame A, et al. Schistosomiasis screening of travelers from Italy with possible exposure in Corsica, France. Emerg Infect Dis. 2015;21:1887–9. **(ISSN 1080–6040)**.
14. Beltrame A, et al. Schistosomiasis screening of travelers to Corsica, France. Emerg Infect Dis. 2016;22:159–60. **(ISSN 1080–6040)**.
15. Carrai P, Zammarchi L, Pollina LE, Giordani L, Mangano V, Iapoce R, Rinaldi F, Bartoloni A, Filipponi F, De Simone P, Bruschi F. Post-transplant liver graft schistosomiasis in a migrant from Sub-Saharan Africa. Transpl Infect Dis. 2018;20:e12950.
16. Bichler KH, et al. EAU guidelines for the management of urogenital schistosomiasis. Eur Urol. 2006;49:998–1003. **(ISSN 0302–2838 (Print) 0302–2838 (Linking))**.
17. Akpata R, et al. The WHO ultrasonography protocol for assessing morbidity due to *Schistosoma haematobium*. Acceptance and evolution over 14 years. Systematic review. Parasitol Res. 2015;114:1279–89. **(ISSN 0932–0113)**.
18. Richter J, et al. Ultrasound assessment of schistosomiasis. Z Gastroenterol. 2016;54:653–60. **(ISSN 1439–7803 (Electronic) 0044-2771 (Linking))**.
19. Niamey Working Group, et al. Ultrasound in schistosomiasis. A practical guide to the standardized use of ultrasonography for the assessment of schistosomiasis-related morbidity. Geneva:World Health Organization;2000.
20. Yong MK, et al. Long-term follow-up of schistosomiasis serology post-treatment in Australian travelers and immigrants. 2010;J Travel Med. 17:89–93. **(ISSN 1195–1982)**.
21. Centers for Disease Control and Prevention. Schistosomiasis. Resources for Health Professionals. 2012. https://www.cdc.gov/parasites/schistosomiasis/health_professionals/index.html. Accessed 26 July.
22. Zwang J, Olliaro PL. Clinical efficacy and tolerability of praziquantel for intestinal and urinary schistosomiasis-a meta-analysis of comparative and non-comparative clinical trials. PLoS Negl Trop Dis. 2014;8:e3286. **(ISSN 1935–2727)**.
23. Ministero Dell'interno. I numeri dell'asilo. 2017. http://www.interno.gov.it/it/sala-stampa/dati-e-statistiche/i-numeri-della silo. Accessed 26 July.
24. ISTITUTO NAZIONALE PER LA PROMOZIONE DELLA SALUTE DELLE POPOLAZIONI MIGRANTI E PER IL CONTRASTO DELLE MALATTIE DELLA POVERTÀ. I controlli alla frontiera. La frontiera dei controlli. Controlli sanitari all'arrivo e percorsi di tutela per i migranti ospiti nei centri di accoglienza. 2017. http://www.inmp.it/lg/LG_Migranti-web.pdf. Accessed 6 Jan 2019.
25. U.S. Department of Health and Human Services, et al. Intestinal parasite guidelines for domestic medical examination for newly arrived refugees. 2013.
26. Chaves NJ, et al. The Australasian Society for Infectious Diseases and Refugee Health Network of Australia recommendations for health assessment for people from refugee-like backgrounds: an abridged outline. Med J Aust. 2017;206:310–315. **(ISSN 1326–5377 (Electronic) 0025-729X (Linking))**.
27. Pottie K, et al. Evidence-based clinical guidelines for immigrants and refugees. Cmaj. 2011;183:E824–925. **(ISSN 1488–2329 (Electronic) 0820–3946 (Linking))**.
28. Beltrame A, et al. Accuracy of parasitological and immunological tests for the screening of human schistosomiasis in immigrants and refugees from African countries: an approach with Latent Class Analysis. PLoS Negl Trop Dis. 2017;11:e0005593. **(ISSN 1935–2727)**.
29. Soentjens P, et al. Late seroconversion of acute schistosomiasis. J Travel Med. 2014;21:219–20. **(ISSN 1708–8305 (Electronic) 1195–1982 (Linking))**.
30. Jones ME, Mitchell RG, Leen CL. Long seronegative window in schistosoma infection. Lancet.1992;340:1549–50. **(ISSN 0140–6736 (Print) 0140–6736 (Linking))**.
31. Ashton RA, et al. Accuracy of circulating cathodic antigen tests for rapid mapping of *Schistosoma mansoni* and *S. haematobium* infections in Southern Sudan. Trop Med Int Health. 2011;16:1099–103. **(ISSN 1360–2276)**.
32. Sanneh B, et al. Field evaluation of a schistosome circulating cathodic antigen rapid test kit at point-of-care for mapping of schistosomiasis endemic districts in the Gambia. PLoS One. 2017;12:e0182003. **(ISSN 1932–6203)**.

33. Midzi N, et al. Use of circulating cathodic antigen strips for the diagnosis of urinary schistosomiasis. Trans R Soc Trop Med Hyg. 2009;103:45–51. **(ISSN 0035–9203)**.
34. De Dood CJ, et al. Refining diagnosis of *Schistosoma haematobium* infections: antigen and antibody detection in urine. Front Immunol. 2018;9:2635. **(ISSN 1664–3224)**.
35. Checkley AM, et al. Eosinophilia in returning travellers and migrants from the tropics: UK recommendations for investigation and initial management. J Infect. 2010;60:1–20. **(ISSN 1532–2742 (Electronic)0163–4453 (Linking)**).
36. Zammarchi L, et al. Screening, diagnosis and management of human cysticercosis and Taenia solium taeniasis: technical recommendations by the COHEMI project study group. Trop Med Int Health. 2017;22:881–94. **(ISSN 1365–3156 (Electronic)1360–2276 (Linking))**.
37. Giboda M, Smith JM. *Schistosoma mansoni* eggs as a target for praziquantel: efficacy of oral application in mice. J Trop Med Hyg. 1994;97:98–102. **(ISSN 0022–5304 (Print) 0022–5304)**.
38. Richards F. JR. et al. Effect of praziquantel on the eggs of *Schistosoma mansoni*, with a note on the implications for managing central nervous system schistosomiasis. Ann Trop Med Parasitol. 1989;83:465–72. **(ISSN 0003–4983 (Print) 0003–4983 (Linking))**.
39. Richter J. Evolution of schistosomiasis-induced pathology after therapy and interruption of exposure to schistosomes: a review of ultrasonographic studies. Acta Trop. 2000;77:111–31. **(ISSN 0001-706X (Print) 0001-706x)**.
40. Richter J. The impact of chemotherapy on morbidity due to schistosomiasis. Acta Trop. 2003;86:161–83. **(ISSN 0001-706X (Print) 0001-706x)**.
41. Magak P, et al. Case–control study of posttreatment regression of urinary tract morbidity among adults in *Schistosoma haematobium*-endemic communities in Kwale County, Kenya. Am J Trop Med Hyg. 2015;93:371–6. **(ISSN 0002–9637)**.
42. Wagatsuma Y, et al. Resolution and resurgence of *Schistosoma haematobium*-induced pathology after community-based chemotherapy in ghana, as detected by ultrasound. J Infect Dis. 1999;179:1515–22. **(ISSN 0022–1899 (Print) 0022–1899)**.
43. Ramarakoto CE, et al. Ultrasonographical findings in the urogenital organs in women and men infected with *Schistosoma haematobium* in northern Madagascar. Trans R Soc Trop Med Hyg. 2008;102:767–73. **(ISSN 0035-9203 (Print) 0035–9203)**.
44. Cioli D, Pica-Mattoccia L. Praziquantel. Parasitol Res. 2003;90:S3–9. **(ISSN 0932–0113 (Print) 0932–0113)**.
45. Richter J, et al. Acute anuria after a family vacation to Corsica/France. Parasitol Res. 2016;115:1733–5. **(ISSN 1432–1955 (Electronic) 0932–0113 (Linking))**.

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