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MAJOR ARTICLE

Urogenital *Schistosoma haematobium* Cases at the Hospital for Tropical Diseases, London (1998-2018), and Suggested Pragmatic Follow-up Pathway for Non-endemic Settings

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Background. Characteristics of confirmed urogenital *Schistosoma haematobium* infections and outcomes in non-endemic regions are scarce in the literature and there is a minimal evidence base for appropriate management in this setting. Specific schistosomal urinary and urological complications include risk of hydronephrosis, renal impairment, and malignant transformation. Therefore, approach to follow-up should be robust and systematic.

Methods. This is a retrospective case-note review of all patients with confirmed *S haematobium* infection (defined as visible ova in terminal urine and/or histopathological diagnosis on biopsy) at the Hospital for Tropical Diseases (HTD), London, between 1998 and 2018. Outcomes of follow-up were reviewed and formulated into a pragmatic guideline for follow-up of these patients in this setting.

Results. A majority of the 186 patients with confirmed *S haematobium* infection presented before 2012. Young, male migrants were at highest risk of complications from chronic infection and were most prone to being lost to follow-up. One patient was referred with squamous cell carcinoma of the bladder found on biopsy with *S haematobium* infection.

Conclusions. We put forward a pragmatic pathway for *S haematobium* investigation and follow-up for patients presenting to nonendemic settings with the current resource capabilities of the United Kingdom.

Keywords. imported infection; *Schistosoma haematobium*; schistosomiasis; urogenital; non-endemic.

BACKGROUND

Schistosomiasis is a Neglected Tropical Disease and is a recognized significant public health challenge in endemic settings. Globally, an estimated 800 million people are at risk of infection; 230 million are thought to be infected [1]. In Europe, imported schistosomiasis is increasingly regarded as "a hidden epidemic." Nearly 700,000 migrants from endemic countries sought asylum in Italy, Germany, or Spain between 2010 and 2020 with a 5.7% reported prevalence of urogenital schistosomiasis [2, 3]. The Hospital for Tropical Diseases laboratory in London diagnosed 769 cases of schistosomiasis serologically in 2023, of which 114 were managed locally.

The *Schistosoma haematobium* adult worms mainly reside as mating pairs in the pelvic venous plexus, with the female laying 500–3000 eggs per day in the venules of the pelvic organs [4]. At least one third of eggs do not successfully migrate through the bladder wall and become entrapped in tissue, causing persistent inflammation, which if left untreated may cause irreversible damage to the genitourinary tract [5, 6]. Disease-related mortality is low, but complications include; hydronephrosis, renal insufficiency, and squamous cell carcinoma [7]. The International Agency for Research on Cancer classifies *S haematobium* as a biological carcinogen, and infection should be robustly investigated and managed to minimize complications (including litigious) [8, 9]. Genital tract complications of *S haematobium* can present with a broad spectrum of symptoms, are strongly correlated with concurrent HIV infection, and are likely underrecognized by clinicians [10]. Observations of patients presenting with female genital schistosomiasis in this cohort will be written up separately. Adequate monitoring is required to ensure that permanent urogenital tract damage, specifically malignant transformation, is avoided in high-risk *S haematobium*–infected patients.

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Existing guidance is predominately centered on paediatric populations in high-endemicity settings, fraught with the challenges of ongoing reexposure to the pathogen [11, 12]. Literature relating to appropriate investigation and follow-up of *S haematobium* infection in nonendemic settings is limited [13, 14].

Challenges for clinicians in nonendemic settings include evaluation of schistosomal diagnostics, and risk of complications in the individual patient under review. Significant exposures (e.g., diving instructors in lakes with well-established endemicity, migrants who have lived in endemic areas for a prolonged period) are easily identified. However, travelers who have unknowingly encountered a high-level exposure to schistosomiasis may face delays in diagnosis in non-endemic settings through physicians' lack of familiarity with the diagnosis or assumed low risk of complications.

Current diagnostic tests such as urine microscopy, widely used in non-endemic areas, have low sensitivity in this heterogeneous population with variable exposures and pretest probabilities. The level of antibody positivity is not representative of an individual's burden of disease, but rather a measure of exposure to infection. The antibody test can remain positive for many years, despite treatment [15]. The presence of viable ova is indicative of active infection, and transition to nonviable/undetectable ova is of some reassurance, but there can also be periodic variation in the excretion of ova in urine, leading to false reassurance from a negative test [16]. Histopathological diagnosis from cystoscopic biopsies is valuable, but if the tissue targeted does not contain ova, the condition may remain undiagnosed. Circulating anodic antigen detection is also of value, but not yet widely available [17]. Hence, risk assessment, diagnosis, treatment and follow-up is multifactorial and physician- and resource-dependent.

This review of confirmed *S haematobium* cases diagnosed at the Hospital for Tropical Diseases, London, over 20 years aimed to describe the characteristics, management, and outcomes of this patient cohort, and to devise a pragmatic pathway to approach future testing.

METHODS

A retrospective case-note review of patients with confirmed *S haematobium* infection presenting to the Hospital for Tropical Diseases, London, between February 1998 and August 2018 was performed. Patients with viable or nonviable ova in their terminal urine (current "gold standard" diagnostic method) or cystoscopic biopsies were included. Serum antibody enzyme-linked immunosorbent assay testing (in-house immunoglobulin G enzyme-linked immunosorbent assay using *S mansoni* soluble egg antigen (SEA) [18] was in operation from 1984 to 2015, when *S haematobium* SEA antigen was added as the second antigen) results were also documented. Paper and electronic notes were then interrogated to obtain demographic, geographical, clinical, hematological, biochemical, radiological, pharmaceutical, and urological information at presentation and over the course of their follow-up.

Migrants were defined as patients who had moved to the United Kingdom having grown up abroad. Holiday makers were those who identified recreation as their reason for traveling to a schistosomiasis-endemic area (regardless of duration). Business travelers were those whose reason for traveling to endemic countries was for work purposes. Visiting friends and relatives was a self-selecting group whose reason for travel to endemic areas fitted this definition.

Radiological review of imaging of all accessible scans on the current computer database was performed by a consultant radiologist with expertise in parasitological urinary tract imaging and reviewed in accordance with the World Health Organization ultrasound classification for schistosomiasis [19]. Descriptive analysis of these variables and (if captured) outcome of the patient was performed using STATA version 13 and Microsoft Excel 16.16.27.

RESULTS

In total, 186 patients with *S haematobium* (viable or nonviable) ova in their urine (98%, 184/186) and/or histopathological evidence of infection on biopsy (22%, 40/186) were diagnosed at the Hospital for Tropical Diseases, London, between 1998 and 2018. Figure 1 shows that the number of cases has reduced during that period. Figure 2 demonstrates countries of travel in 185 patients presenting with confirmed *S haematobium* infection on return from Africa. Lake Malawi exposure was reported in 50% of patients, of whom 96% were tourists.

Table 1 shows a majority were young (median age, 25 years), male (67%) patients who had traveled to schistosomiasis endemic regions for holidays (50%); migrants from endemic areas accounted for 31% of cases. The median minimum time since last exposure in a schistosomiasis endemic setting was 8 months overall, 22 months in migrants, and 5 months in holiday makers. At diagnosis, 23% (42/186) were asymptomatic. The most common symptoms described were hematuria (62%, 114/186), lethargy (19%), and abdominal pain (15%). The median duration from symptom onset to diagnosis was 6 months (range, 0.07–270 months).

Diagnostics

Ova (149 viable, 32 nonviable, 3 no comment made on viability) were seen in urine of 184 patients. Among those with viable ova 85% (128/149) were seropositive, 42% (63/149) urine dip blood positive, and 20% histopathology specimens were positive. This demonstrates there is no value in using urine dip positivity as a tool for determining whether to request terminal urine microscopy. Two patients were positive on bladder biopsy, but negative for ova on terminal urine.

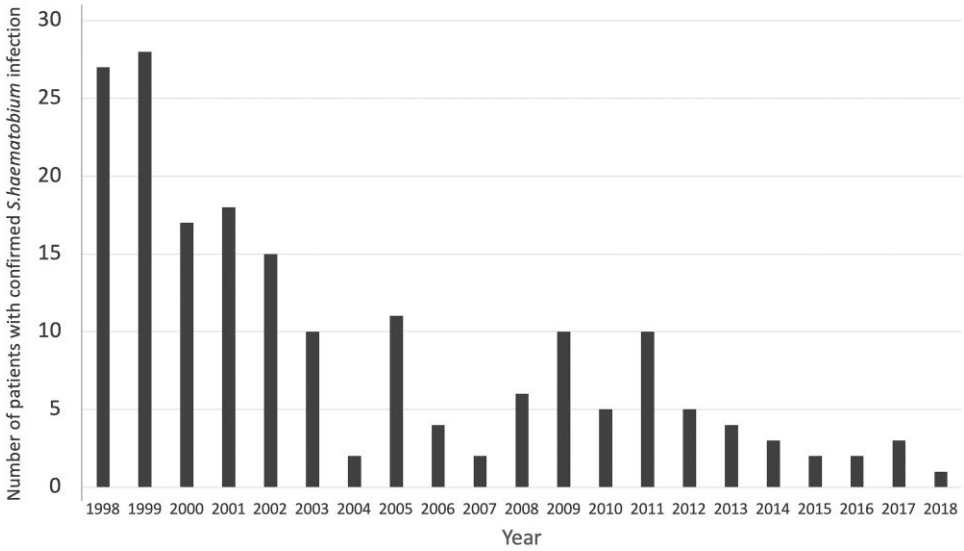

Figure 1. Number of patients seen each year at the Hospital for Tropical Diseases with confirmed *Schistosoma haematobium* 1998–2018 (n = 186).

Table 1 outlines the investigations performed in patients with confirmed *S haematobium* infection.

Eosinophilia (defined as eosinophils $\geq 0.5 \times 10^9$/L) was present in 46% of cases (n = 171). HIV testing was undertaken in only 14% of patients, with 1 positive, which is reflective of diminished acceptability of HIV testing in the 1990s. One third of patients had ultrasound imaging 66/186 (35%). A majority of the ultrasound findings were "abnormal bladder wall thickening" or "evidence of obstruction"; 82% of abnormal scans were attributed to schistosomiasis related changes. Ultrasound scans were planned in a further 8 patients (mainly the migrant group) but were not performed because of loss to follow-up. Follow-up ultrasounds were undertaken in 3 patients, 2 of whom remained abnormal on repeat.

A majority of the cystoscopies done (43/186) were abnormal in the migrant group (21/43, 54%). Eleven patients went on to have repeat cystoscopies, all of which remained abnormal, within the next year (7 of whom were in the migrant group). Gynecological findings will be written up separately.

Outcomes

Table 1 demonstrates the clinical complications identified in each of the patient groups. Overall, 53/186 patients were lost to follow-up. The highest burden of complications, 25/57 (44%), was seen in the migrant group, many of whom had significant exposure. No patients met criteria for treatment failure (viable ova in urine 3 months or more after treatment). In 3 patients with presumed high worm burden infection (based on cystoscopy findings including sandy patches and bladder masses), nonviable ova persisted in the last urine samples tested before discharge.

Neoplastic Complications

One patient, a migrant from Angola who had daily exposure to fresh water in an endemic area, presented to his local hospital in the United Kingdom with a 4-month history of base of penis pain and hematuria. After initial treatment for bacterial urinary tract infection failed, he was referred for investigation and was found to have a muscle-invasive G3 PT2a squamous cell carcinoma with viable *S haematobium* ova seen on histopathological specimens and in terminal urine. Serology was borderline negative. His last exposure was between 5 to 10 years before onset of his presenting symptoms. The diagnosis had been made at an external urology unit and referred to our specialist center for advice on treatment. No patient diagnosed and investigated in our center was found to develop neoplastic complications.

Nonneoplastic Complications

Six patients reported erectile dysfunction, their average time to presentation was 59 months, and in the 4 in which cystoscopy was performed there were numerous lesions seen in the bladder. Eight patients reported infertility issues, which may be attributable to male genital schistosomiasis, but this was not confirmed.

Referrals

A majority of referrals to tropical medicine physicians were from general practice (69%, 128/186). Overall, 31% (58/186) were seen by a urology team, either before or after review by the infectious diseases team. Among those referred directly from urologists (25%, 28/186), 27 had cystoscopy which revealed findings prompting Hospital for Tropical Diseases

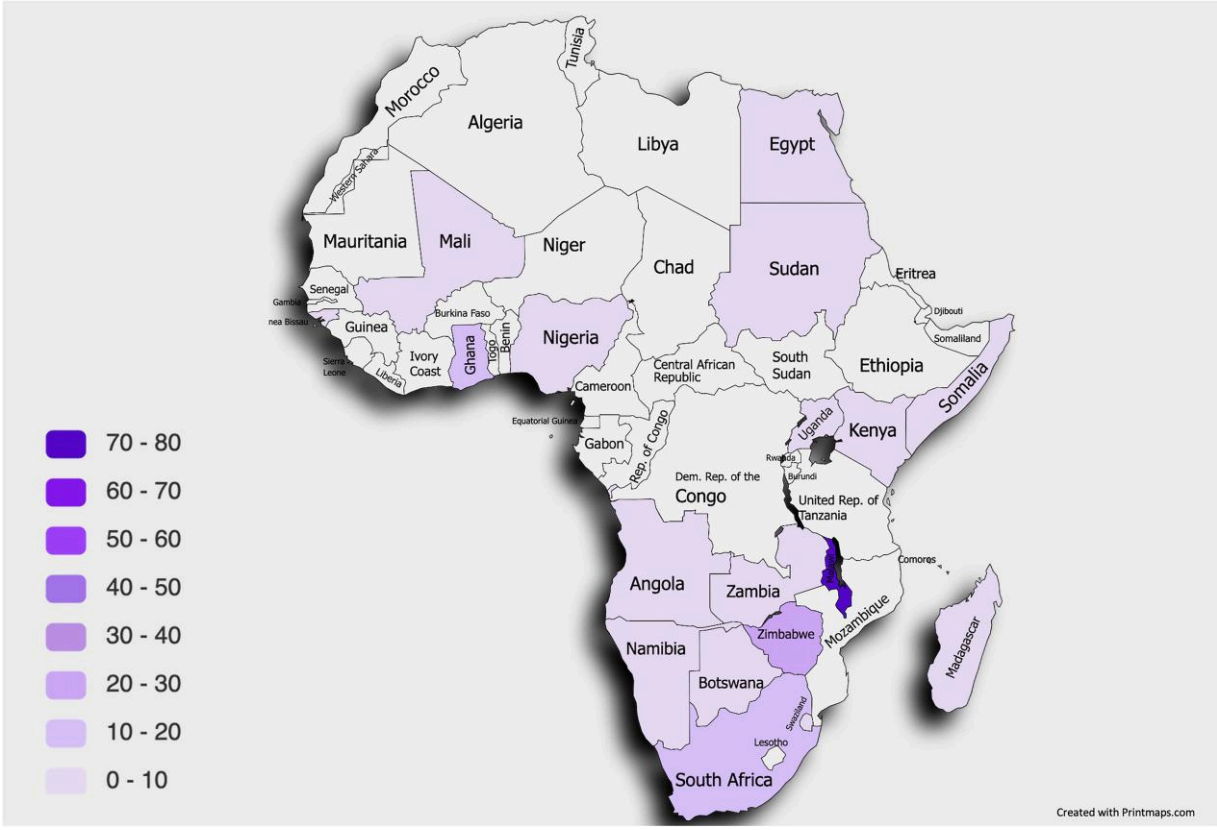

Figure 2. Location of likely acquisition of imported urogenital *Schistosoma haematobium* infections at the Hospital for Tropical Diseases between 1998-2018.

(HTD) review. Referrals were made to gynecology (4%, 3/62 female patients in total) and nephrology (1 patient).

Pragmatic Pathways for the Investigation and Management of Patients with *S haematobium* Infection

Significant variation in clinicians' approach to investigation and management of patients with confirmed *S haematobium* infection was demonstrated. We devised a robust pathway to guide physicians' investigation based on the observed local practice. A new diagnostic tool was integrated into the pathway. Circulating anodic antigen (CAA) is a marker of adult worm regurgitated waste, demonstrating the presence of live worms, and therefore a useful marker for successful treatment.

Figure 3 outlines a proposed pathway for investigation of patients potentially exposed in schistosomal endemic settings, using the resources currently available in a UK setting. Figure 4 outlines a proposed urological approach to follow-up, based on expert opinion. It is pragmatically constructed to minimize unnecessary cystoscopy where possible. Given the absence of evidence based on the frequency of cystoscopy, this is based on expert opinion.

In addition we have

- Developed patient information leaflets to improve the consistency of information, particularly around safety netting advice.
- Created an ultrasound standard operating procedure linked to World Health Organization schistosomiasis grading with radiology colleagues.
- Curated a prospective database for auditing follow-up of new cases and the utility of CAA testing.
- Formulated a female genital schistosomiasis pathway with links to sexually transmitted infection testing facilities and gynecology (see associated publication by Rafferty et al).

DISCUSSION

Between 2008 and 2018, there has been a decline in the number of cases of *S haematobium* diagnosed at the Hospital for Tropical Diseases in returning travelers and migrants. This may in part be due to schistosomiasis control initiatives and mass drug (praziquantel) administration programs reducing the burden of infection in endemic regions [20]. This is also reflected in other associated studies, such as declining schistosomiasis associated cases of eosinophilia in returning travelers at this center, demonstrating a paucity of this particular imported infection [21].

These data support existing literature demonstrating that migrants have the highest burden of infection and are most likely to have urinary tract abnormalities on imaging/cystoscopy. We have a large African diaspora population in the United Kingdom, and the imported case burden is reflective of this

Table 1. Patient Characteristics, Investigations and Follow up of Patients Diagnose With Confirmed *S.haematobium* Infection at the Hospital for Tropical Diseases Between 1998–2018.

	Holiday n = 93	Visiting Friends/Relatives n = 5	Business n = 26	Migrant n = 57	Not Specified n = 5	Overall n = 186
Age, y, median (range)	24 (3–54)	24 (22–46)	28 (19–46)	25 (11–54)	33 (24–36)	25 (3–72)
Male (%)	54 (59%)	3 (60%)	14 (54%)	48 (84%)	5 (100%)	124 (67%)
Weight (kg)	72 (52–106)	74 (64–82)	73 (61–111)	68 (31–103)	74 (66–103)	70 (31–111)
Duration in schistosomiasis endemic country[a]						
0–6 mo	50	0	8	0	3	61 (33%)
6–12 mo	32	2	5	0	0	39 (21%)
>12 mo	10	3	12	57	0	82 (44%)
Duration of symptoms to diagnosis, mo (range)	3 (0.25–144)	12 (6–24)	5 (0.25–60)	13 (1–265)	12 (3–180)	6 (0.07–270)
Clinical presentation						
Asymptomatic	28	1	7	5	1	42 (23%)
Katayama fever	2	0	1	0	0	3 (2%)
Hematuria	47	2	15	48	2	114 (62%)
Hematospermia[b]	5	0	2	1	1	9 (7%)
Lumpy semen[b]	7	0	0	0	1	8 (6%)
Testicular pain[b]	2	0	1	4	0	7 (6%)
Diarrhea	6	0	2	2	0	10 (6%)
Lethargy	20	0	7	5	4	36 (19%)
Fever	7	0	1	1	2	11 (6%)
Itch	3	0	1	1	0	5 (3%)
Abdominal pain	12	3	3	10	0	28 (15%)
Gynecological issue[c]	2	0	0	1	0	3 (5%)
Investigations						
Terminal urine						
Viable *S haematobium* ova seen	72	4	22	46	5	149 (80%)
Nonviable *S haematobium* ova seen	19	1	4	8	0	32 (17%)
Viability not commented on	1	0	0	2	0	3 (2%)
Histopathology—*S haematobium* ova seen	15	0	4	21	0	40 (22%)
Eosinophils Median ($\geq 0.5 \times 10^9$/L)	0.46 (41)	0.42 (2)	0.56 (15)	0.4 (20)	0.33 (1)	0.44 (79)
Urinary tract ultrasound Abnormal/normal	5/25	0/2	3/8	10/11	0/2	18/48
Cystoscopy Abnormal/normal	10/3	4/0	3/1	21/1	0/0	37/5
Complications						
Squamous cell bladder cancer	0	0	0	1	0	
Urinary tract abnormality	9	2	1	11	0	
Infertility	1	1	0	5	1	
Service aspects						
Lost to follow-up	22	1	5	25	0	
Re-referred after discharge	2	0	1	6	0	

[a]N = 182.

[b]n = 124.

[c]n = 62.

highly endemic region. A TropNet 20-year retrospective study showed similar results, concluding that sub-Saharan Africa was the most common place of infection. In that study, of 31 patients across 8 centers, 58.1% had hydronephrosis and 16% had bladder cancer [22]. Our case review demonstrates migrants were the traveler group with the highest rates of being lost to follow-up, resulting in planned investigations and treatment not taking place. Having a 1-stop shop clinic, with investigation and treatment performed on the same day, would be an advantageous service for this transient population.

Variation in clinician approach to management of urogenital schistosomiasis has been described previously in Europe and is an expected result of an evidence-light area of medicine [14]. Italian specialists advocate noninvasive ultrasound monitoring to review the response to treatment [22], stating that bladder wall lesions resolve 3–6 months after treatment with praziquantel [11, 12]. The 2023 Italian guidelines recommend that histological diagnosis should be sought only if there is presence of "lesions or signs such as hematuria persistent after 6 months after treatment" [23]. Delay in diagnosis of a urological malignancy in a patient with confirmed schistosomiasis infection would be challenging to defend in many litigious healthcare settings, so our threshold for referral to urology is lower in comparison.

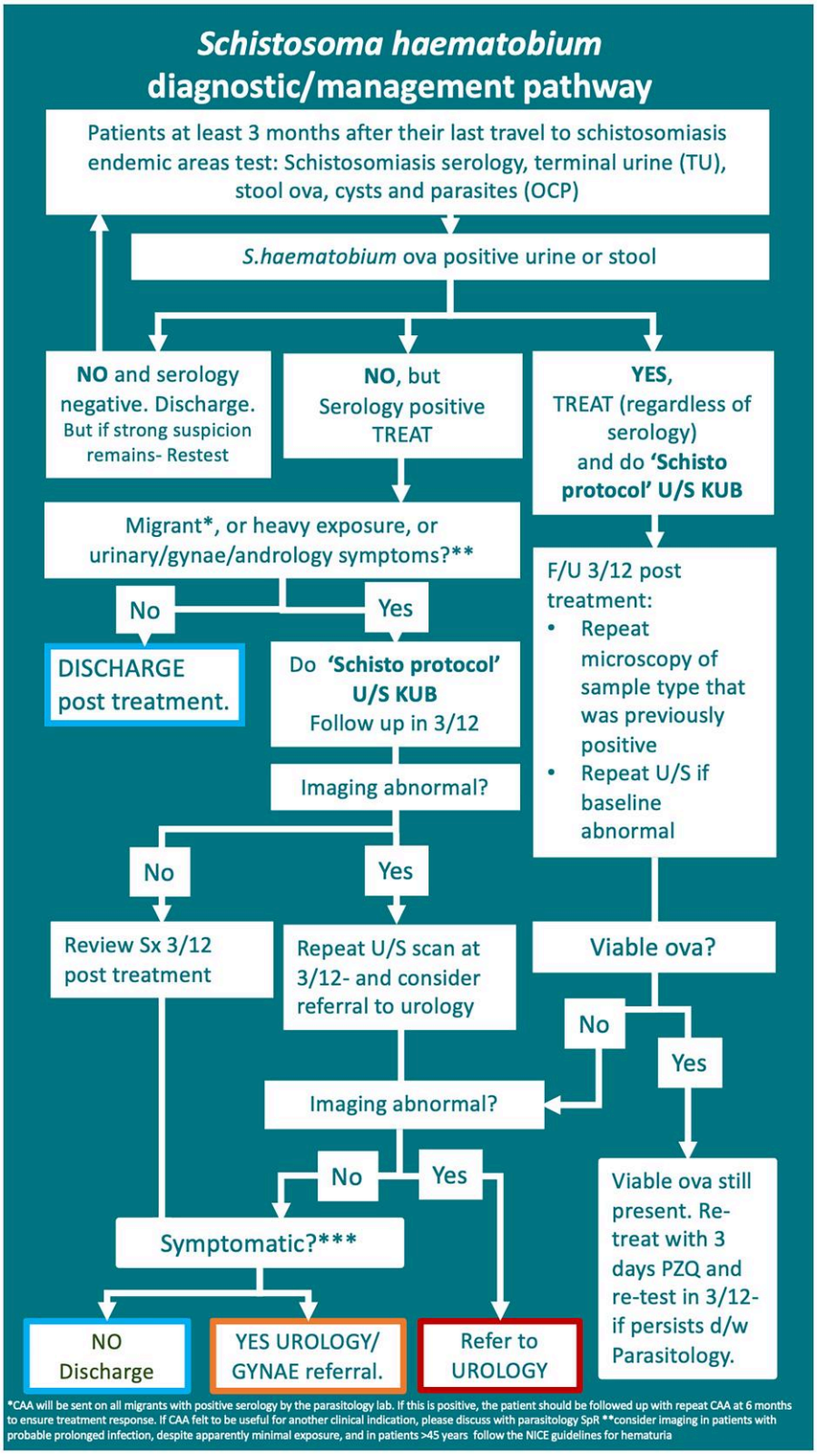

Figure 3. Hospital for Tropical Diseases *Schistosoma haematobium* diagnostics/management pathway.

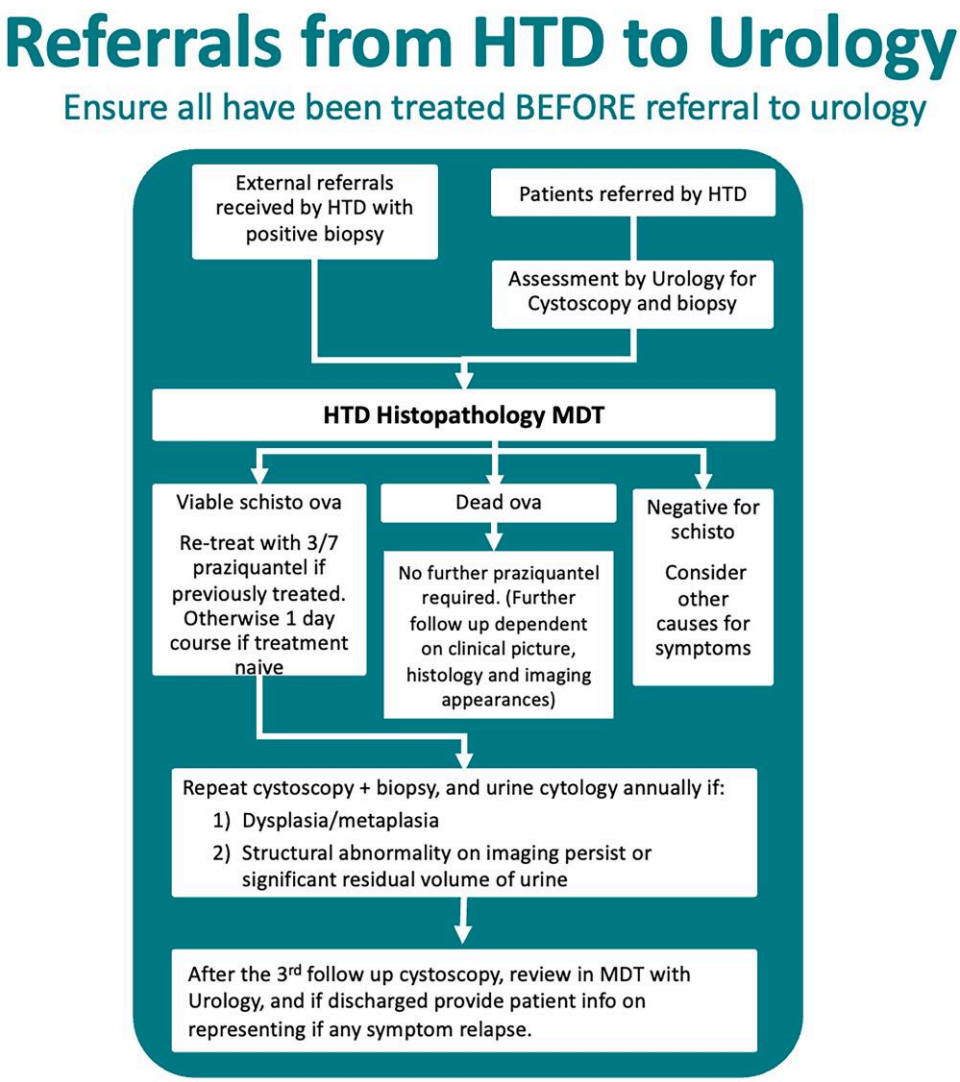

Figure 4. Referrals from the Hospital for Tropical Diseases (HTD) to urology.

The decline in numbers of *S haematobium* cases is blunting clinicians' experience of evaluating patients with this condition. Overcautious physicians may overinvestigate, and when this involves invasive tests (e.g., repeated cystoscopy), it may result in procedural complications and limit the patients' adherence to further follow-up. On the other hand, not monitoring patients sufficiently could result in missed complications, including altered urinary tract anatomy, bladder cancer, and infertility.

It is imperative to investigate and follow-up patients at highest risk of malignant transformation secondary to schistosomal infection. This is logistically difficult because the cohort, predominately migrants, with chronic, high-burden infection is also the most challenging group to retain in the health care system. Prioritizing follow-up, ease of access to testing and treatment of this group is important for service provision. Providing adequate patient information at discharge is also imperative, to ensure individuals seek medical advice if they develop any symptoms consistent with relapse/repeat infection or sinister complications.

Different diagnostic approaches, particularly for urinary testing, such as polymerase chain reaction or loop-mediated isothermal amplification have high sensitivity and specificity. They are more sensitive than urine filtration and are more specific than serum enzyme-linked immunosorbent assay antibody detection in low burden traveler infections. CAA in serum has demonstrated particular value (97% sensitivity) in diagnosing acute infections in Belgian travelers and showing response to therapy [24].

Absence of some data and suboptimal documentation has contributed to loss of uniform details in this cohort in keeping with the challenges of retrospective case review (particularly in a predigitalized era). Changes in access to investigations over the decades covered by this case-note

review makes patient management comparisons more challenging.

CONCLUSIONS

The number of diagnoses of confirmed *S haematobium* infection is declining at the Hospital for Tropical Diseases, London. Migrants with prolonged time in endemic regions were most likely to be symptomatic and to have infection complications. However, holiday makers and business and family/friend-associated travel were also associated with anatomical changes associated with infection. While we await a more robust evidence base for the investigation and management of patients with *S haematobium* in non-endemic settings, we put forward a pragmatic pathway based on the current diagnostic capabilities in the United Kingdom.

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