**Acute schistosomiasis: Which molecular diagnostic test is best and why**

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**(See Major Article on Acute Schistosomiasis by Cnops et al. on Pages XXXX-XXXX)**

Each year, thousands of returning travellers and tourists typically report to clinics throughout Europe and the UK with various signs and symptoms of acute schistosomiasis following form exposure to schistosome cercariae in freshwater [1]. Unlike chronic schistosomiasis, which may have taken several months, or longer, to appear but has a proven set of diagnostic methods and tools available [2], reliable diagnosis of acute schistosomiasis within the first few months after last exposure to schistosome cercariae is problematic; as is precise incrimination of which species of infecting schistosome is, or are, responsible. It is against this unmet diagnostic challenge in acute schistosomiasis that the Cnop *et al.* [3] study is most insightful. Here they highlight both the detection and discrimination of infecting schistosomes within a cohort of returned Belgian travellers that were examined to an unusual degree of advanced diagnostic scrutiny.

Management of acute schistosomiasis can be of primary concern to those more worried patients, anxious about subsequent cerebrospinal complications [4], who may need extra reassurance as to why prompt treatment is withheld until 2-3 months later. This is to allow sufficient time (i.e. at least 12 weeks after last cercarial contact) for all juvenile schistosomes to mature and become most vulnerable to praziquantel treatment, the only available anti-schistosomal drug. Depending on severity, steroids may be co-administered with, or without, praziquantel in an attempt to manage concurrent inflammation and discomfort [5]. If praziquantel is given too soon, it is not fully-effective and should be repeated a month or two later. This ensures that all worms are successfully dispatched, arresting any disease progression before patient discharge.

Using a carefully designed protocol, Cnop *et al.* [3] report on a prospective diagnostic study that used a novel set of molecular DNA detection tools applied on sera, stool and urine, against existing serological assays and parasitological methods, to determine presence of various species of schistosome worms. Following a family doctor referral of a mother and her two children to the outpatient clinic of the Institute of Tropical Medicine, Antwerp, a cluster of 34 returned Belgian tourists, inclusive of 18 children, was identified. From travel histories, collectively this group was most likely exposed to schistosomes within a 1-3 day period whilst staying at an ecolodge in South Africa. Water contact was from building then sailing rafts. Framing this synchronicity of exposure(s) is particularly useful to develop a putative temporal dynamic of disease progression. It also provided a detailed snapshot of local transmission of schistosomiasis in this area on the border between Kwazulu-Natal and Mpumalanga.

Diagnosis of acute schistosomiasis, most typically presenting as Katayama syndrome, is most often revealed by clinical observation e.g. urticaria and angio-oedema, as well as, patients’ amnestic recall of signs and symptoms e.g. swimmer itch, dry cough, intermittent fever etc.. Many of these features were thought to result from an over stimulated immune system, from an initial response to immunogenic eggs as first shed into the vasculature by mature female worms. New doubt has been cast on this classic interpretation by the controlled human schistosome infection model. In this carefully manipulated experimentation only male cercariae of *S. mansoni* were used, thereby precluding any production of egg-antigens specifically, however, Katayama-like syndrome was still described and found correlated with escalating cercarial-dose [5]. Perhaps such hypersensitive, largely Ig-E mediated reactions, are directed towards worm antigens found in worm vomitus as they feed more copiously. Nonetheless, when both the numbers and timings of cercarial dosing are unknown, a precise diagnosis of acute schistosomiasis can be perplexing. Clinical diagnosis is upon a combination of exclusion criteria and detective acumen of rather non-specific, intermittent signs and symptoms, and even if florid, have to tie-in with the individual history and location of cercarial exposure(s). Accurate diagnostic biomarkers of schistosome are needed, ideally that also denote species, worm burden and occurrence of ‘single sexed’ infection.

Whilst there are a variety of *Schistosoma* DNA marker loci, two well-known multi-copy genomic regions, *Dra*1 and *Sm*1-7, offer sensitive targets, being demonstrated most useful in this study from gDNA extracted from serum, stool and urine [3]. Using these two loci in combination clearly demonstrated the presence of *S. haematobium* in all individuals and the likely presence of *S. mansoni* in one individual. Of note it that *Dra*1 is not unique to *S. haematobium* alone for it also occurs in closely related sister species, such as *S. mattheei* and the presence of this latter species, either as a mixed co-infection or as a *S. haematobium* x *S. mattheei* hybrid, was observed in three individuals. *Schistosoma mattheei* is usually found in livestock but has capacity to hybridise with *S. haematobium* [6, 7] which adds a new facet to the diagnostic triage of acute schistosomiasis. For example, is allergy associated with acute schistosomiasis enhanced by such worms of putative zoonotic origin?

From application of these molecular DNA markers it appeared that the *S. haematobium* infection was dominant and could be detected in 24/33 travellers by week 4-5 in the analysis of sera. Neither *Schistosoma* DNA nor schistosome ova were detected, at any timepoint, in either urine or stool, indicative of much lower detection thresholds of molecular DNA methods in excreta. Of note, half of the Belgian cohort seroconverted by week 7-8 [3] which adds some greater confidence to the pervasive nature of this group’s exposure to schistosomes for those more sceptical of molecular DNA detection methods. These findings demonstrate that *Schistosoma* DNA can be first detected in sera and can be used to confirm the clinical diagnosis of acute schistosomiasis.

As with all diagnostics, if there is sufficient incentive to embed a diagnostic method into routine travel clinic practice, it should meet the ASSURED criteria [8], perhaps with affordability being of principal concern. Unfortunately, without automation, such liquid handling and electrophoretic steps are drawbacks especially for large scale screening. However, another open question stands - how effective these methods assessing efficacy of treatment given that *Schistosoma* DNA signatures can endure after worm death. Whilst schistosome DNA might be a ‘quick’ marker of infection it is a ‘slow’ marker of cure. Other molecular targets such as the schistosome circulating anodic antigen (CAA), found in the vomitus of feeding worms, has merit as both sensitive marker of infection and cure but unfortunately cannot differentiate between schistosome species [5]. Thus, our diagnostic armamentarium for acute schistosomiasis, notwithstanding those infections caused by *S. japonicum* or other species within the *S. haematobium* group, remains incomplete.

It is sobering thought that across Europe and the UK only a few clinical diagnostic laboratories could undertake the methods reported by Cnops et al. [3]. It is also disappointing that the general priority given to schistosome diagnostics is surprising low despite its ubiquity and more importantly its potential severity, in terms of male and female genital schistosomiasis [9, 10]. At the very least, the Cnop *et al.* is a clear signpost for us to do better in our initial clinical triage and subsequent individual disease management plan.

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