

Parasitic diseases in the returning traveller

Parasitic infections often present with nonspecific symptoms.

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Travellers returning with parasitic diseases from endemic areas do not necessarily present with signs or symptoms specifically suggestive of a parasitosis – in most cases these are nonspecific (e.g. malaria presenting as a flu-like illness). Many features are shared with non-parasitic infectious diseases (e.g. signs and symptoms of amoebic liver ‘abscess’ may be identical to those of bacterial liver abscess(es)), and non-infectious diseases (e.g. in someone just returning from the tropics, classic signs of thyrotoxicosis may be misinterpreted as a febrile infectious disease because of the travel history). Moreover, a considerable percentage of travellers who acquired a parasitosis abroad may remain asymptomatic for a long time, sometimes for years.¹ It is therefore important not to focus exclusively on parasitic conditions, but also to consider non-parasitic entities as a differential diagnosis in the returning traveller.

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This article offers a concise overview of the major syndromes and how to diagnose them – because of space constraints, the therapeutic options are not discussed here.

Examining the symptomatic traveller

The febrile traveller

Malaria should always feature high on the list of differential diagnoses if a febrile patient returns from a malaria-endemic area, as it is a potentially life-threatening disease. The correct diagnosis is of paramount importance and effective treatment must be instituted immediately.

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Therefore, malaria features prominently in this article. However, there are pitfalls:

- Malaria endemicity may change rapidly, particularly in ‘fringe areas’ of plasmodial prevalence, leading to sentinel cases from areas previously thought to be malaria free.²
- Rare cases of airport/odyssean malaria may be acquired in locations where there is no autochthonous malaria.³

Five *Plasmodium* species cause disease in humans: *P. falciparum*, *P. vivax* (outside Africa), *P. ovale*, *P. malariae*, and *P. knowlesi* (the last has recently emerged and has so far only rarely been encountered in travellers returning from South East Asia).⁴

After an average incubation period of about 2 - 4 weeks (minimum ~10 days), infection with each species will lead to an initially similar febrile illness, but *P. vivax* and *P. ovale* hypnozoites may give rise to malaria episodes even years after exposure.

Sometimes, as in the case of *falciparum* malaria, but rarely with *P. knowlesi*, the disease may be characterised by fever and a wealth of possible accompanying signs and symptoms – suggesting a flu-like illness.^{4,5} Vomiting and/or diarrhoea may be misleading, delaying consideration of this important differential diagnosis and causing a critical delay in diagnosis and treatment. Malaria may be missed in patients who present after a prolonged incubation period.

Individuals who have acquired partial immunity through previous bouts of malaria develop a ‘parasitic threshold’ below which parasitaemia will not cause febrile disease, but the non-immune, malaria-naïve traveller will develop febrile disease at very low parasite counts (~10/μl). Fever as the lead symptom is often irregular at onset, particularly in cases of *falciparum* malaria.⁴

Unless the patient has already progressed to complicated disease, it is impossible to diagnose the correct species from the severity of symptoms. To describe two extremes – a falciparum malaria patient with a high parasitic burden and imminent end-organ complications may present in good clinical condition, whereas a patient with a low *P. malariae* parasite density may appear to be very ill. Although also nonspecific, splenomegaly may guide the attending physician towards the correct diagnosis.

A full blood count will regularly reveal a thrombocytopenia, yet the malaria patient will not bleed unless the disease is complicated by bacterial infections leading to disseminated intravascular coagulation (DIC), often with non-typhi salmonellae. The white cell count is typically normal. Anaemia – rightfully so – is the most-feared complication in children in endemic areas, and may not be evident at presentation. However, a raised lactate dehydrogenase (LDH) may hint at haemolysis. A wealth of diagnostic devices have been developed for malaria,⁶ but expert microscopy of Giemsa-stained thick and thin smears remains the 'clinical' gold standard (as opposed to the novel 'laboratory' gold standard – polymerase chain reaction (PCR) – that plays no significant role in the routine and emergency diagnosis of malaria). However, as microscopy has its drawbacks, alternative, rapid immunochromatographic malaria-antigen detection ('dipstick') tests have been developed and are increasingly used for routine diagnostic purposes in and outside endemic areas (Fig.1), including South Africa, where histidine-rich protein-2 (HRP2)-detecting tests (identifying *P. falciparum* but none of the other species) are in use. Although much more limited in terms of diagnostic potential compared with microscopy (not quantitative; not suited for follow-up; no identification of risk factors such as malaria pigment-containing leucocytes; no detection of additional/alternative infectious agents (Fig. 2)), they constitute an excellent diagnostic tool in the hands of those who are fully aware of the limitations of the method. Later-generation tests can detect falciparum and non-falciparum malaria.

The list of differential diagnoses to be considered in the returning febrile traveller is excessively long, comprising a few other (usually not life-threatening, with the possible exception of amoebiasis) parasitic diseases, but also a wealth of non-parasitic illnesses. Excellent overviews have been compiled by e.g. Speil *et al.*,⁷ Wilson and Schwartz,⁸ and Cook.⁹



Fig. 1. Examples for a positive (above) and a negative (below) histidine-rich protein-2 (HRP2)-detecting rapid immunochromatographic test ('dipstick test') used in South Africa to diagnose malaria caused by *Plasmodium falciparum*. (Courtesy of R Stewart, Johannesburg.)



Fig. 2. Thick smear prepared to screen patient blood for malaria, revealing *Loa loa* infection. (Courtesy of J Kammer, Lambaréné.)

The traveller with abdominal/gastrointestinal signs and symptoms

Abdominal pain, with or without fever, and with or without (bloody or watery) diarrhoea, may be the main complaint in travellers returning from the tropics. A range of parasitic diseases feature on the list of differential diagnoses, depending on the geographical area visited, specific history of exposure, and individual risk. However, it must be said that for most conditions, the risk for the local population is usually higher than that for the average traveller. An exception is infection with schistosomiasis

after leisure activities in infested freshwater (the water sports enthusiast returning from a sojourn on Lake Malawi is a classic example).

Cook⁹ provides a detailed overview on tropical gastrointestinal problems, including parasitic diseases.

Kala-azar, or visceral leishmaniasis, is relatively rarely encountered in returning travellers,¹⁰ but constitutes a risk particularly for the immunocompromised long-term traveller to endemic regions, especially the Mediterranean basin.¹¹ Visceral

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leishmaniasis, mainly caused by *Leishmania donovani* and *L. infantum*, should be considered outside endemic areas, particularly in individuals who have been resident in endemic areas of the Americas, Asia and (eastern) Africa and who present with sudden or gradual-onset or persistent fever and often gross (hepato) splenomegaly, anaemia, and (often chronic) diarrhoea, with emaciation, oedema, ascites and pleural effusions. Direct parasite detection in, or following culture of, bone marrow and splenic aspirations is ideal. Indirect but reliable alternative methods include PCR and antibody-detecting serological methods.

African trypanosomiasis (sleeping sickness) is not frequently seen as an imported condition. However, occasionally¹² clusters of diseased travellers surface in Europe as well as in South Africa, not infrequently heralding a sudden change in epidemiological patterns or hallmarking an outbreak. In some patients, a trypanosome chancre may still be seen. The majority of patients will present with neurological symptoms suggestive of African trypanosomiasis, and apart from a range of serological diagnostic tools, direct parasite detection on microscopy of blood and liquor is diagnostic. South American trypanosomiasis, or Chagas' disease, is rarely acquired by travellers.

Schistosomiasis is not infrequently encountered in travellers returning from endemic areas.¹³ However, except for haematuria in *Schistosoma haematobium* (occurring in vast areas of Africa; *S. japonicum* and *S. mekongi* transmission in specific areas of South East/East Asia), signs and symptoms are often discrete compared with those in cases of full-blown disease. Complications in belatedly diagnosed and treated individuals are still encountered in most endemic areas. Once the adult worms have established themselves, they begin to produce eggs. Dying eggs, which did not reach the lumina of either gut or urinary tract, cause a pathological condition by means of granulomatous inflammation. *S. mansoni* (endemic in vast areas throughout Africa, the Arabian peninsula, and foci in central/South America) and *S. intercalatum* infections (small foci in central/West Africa) may manifest with a variety of gastrointestinal symptoms such as chronic or intermittent, occasionally bloody diarrhoea. Secondary symptoms, including fever, fatigue and anorexia, may evolve in the chronically ill.

Diagnosis is either through direct detection of eggs passed with faeces or urine, in biopsy

material from affected organs, or by a range of serological methods.

Katayama fever is the acute presentation of schistosomiasis. A significant proportion of returning travellers who have contracted schistosomiasis will present early with skin lesions and fever characteristic of Katayama fever. This can be considered as schistosomal seroconversion syndrome hallmarking the onset of egg production in the human host. The initial 'classic' pathology in the course of schistosomal infection, cercarial dermatitis, is frequently missed as it will be mostly experienced during travel, with transient lesions caused by the infecting cercariae on penetration of the skin.

Hydatid disease is not confined to tropical areas, and little is known about travellers' risks of ingesting echinococci, particularly because of the prolonged asymptomatic period and its worldwide occurrence.

Entamoeba histolytica may lead to bloody diarrhoea, causing severe disease (the differential diagnosis would comprise non-parasitic causes of bloody diarrhoea) and constituting a medical emergency.¹⁴ More critical amoebic liver abscesses may rapidly evolve and swiftly reach the dimension of a life-threatening condition. Direct detection of parasites in adequately handled stool samples in amoebic colitis, or aspirate from a hepatic lesion (to be avoided unless therapeutically indicated owing to imminent rupture into adjacent body cavities), confirms the diagnosis. Serological methods together with ultrasound imaging of the hepatic region are reliable in guiding towards the correct diagnosis, yet initiation of therapy in suspected cases must not be delayed.

Other enteric amoebae are indicators of ingestion of contaminated water rather than causative agents of intestinal disease. Similarly, *Giardia lamblia* causes asymptomatic infection in most cases, but may lead to bouts of diarrhoea, weakness, weight loss, abdominal pain and less frequently to other related signs and symptoms. Among the various diagnostic techniques at hand, direct parasite detection of either trophozoites or cysts is optimal.

An endless variety of helminths can be contracted via the faecal-oral route, leading to manifestations ranging from asymptomatic infestation, or harmless yet irritating symptoms (perianal itch in *Enterobius* infections), to hookworm-related anaemia. Travellers, depending on their risk of exposure, may present on

their return with complaints suggestive of an intestinal helminthiasis. Among the diagnostic methods at hand, direct detection of helminths or eggs offers proof.

Liver flukes, other trematodes and cestodes may be acquired during travel.¹⁵ Many of these are not confined to particular areas; therefore acquisition at home rather than during travel is often a possibility.

The traveller with eosinophilia

Eosinophilia, almost always in conjunction with a raised IgE level, is either found in patients presenting with signs and symptoms of disease or on screening of an otherwise asymptomatic returning traveller (see below). Eosinophilia encompasses a wide range of differential diagnoses, including a wealth of non-infectious conditions such as adverse drug effects, allergies, rheumatological disorders (which lead the list of differential diagnoses in affluent, temperate regions of the world that are seemingly largely devoid of helminths), and helminthic infections, particularly with tissue-dwelling parasites.¹⁶ Fascinatingly, the ranking within a list of differentials depends largely on the global region visited. For example, a patient with a migrating subcutaneous (Calabar) swelling and a conspicuous eosinophil level returning from West Africa will most likely be suffering from loiasis. A patient presenting with exactly the same constellation of symptoms, usually with some latency after a sojourn in Thailand (or circumscribed parts of South America) and after ingestion of raw fish dishes (or else unusual meats such as bullfrog meat) would most likely be diagnosed as having gnathostomiasis.

The traveller with a skin condition

Occasionally, cutaneous, and rarely mucocutaneous leishmaniasis is seen in travellers returning from various global endemic areas (servicemen may be at particular risk).¹⁰ Sometimes the diagnosis is not easily established. Ideally, scrapings from underneath the undermined lesion's edge reveal amastigotes, but a wealth of confirmatory indirect methods exists.

Ectoparasitic infestation, ranging from ticks and lice such as *Phtirus pubis* (*papillon d'amour*), is among possible unwanted travel souvenirs.¹⁷ *Tunga penetrans* may lead to painful lesions under toenails (many beaches, e.g. along the East African coastline, are heavily infested). Myiasis caused by *Dermatobia hominis* (South

Long-term travellers should be screened on return.

The returning traveller

America) or *Cordylobia anthropophaga* (Africa) and many other species can cause painful boils. Often patients feel a wriggling sensation within lesions, and witness the evasion of the mature larvae from the skin. The condition is as embarrassing and painful as it is harmless. Most (tissue-dwelling) filariases (apart from a few blood-dwelling species such as *Mansonella perstans* which cause little harm), including onchocerciasis, loiasis and bancroftian filariasis, cause distinct pathologies including characteristic and extensive skin lesions (in long-standing disease). However, they are only infrequently encountered in travellers who visit endemic areas for a short period. Nevertheless, cases may be missed or misdiagnosed owing to a long latency of onset, or misinterpretation of early symptoms, which only remotely resemble full-blown disease usually depicted in textbooks, sporting full-blown pathology in individuals permanently living in endemic areas.¹

Cutaneous larva migrans, as caused by canine *Ancylostoma* spp. deposited by defaecating dogs, e.g. on tropical beaches, are irritating, but harmless. In cases of missed diagnosis, the larvae cease migrating through the subcutaneous tissues, being unable to penetrate to deeper tissues, and die spontaneously.

Screening the asymptomatic returning traveller

Clerinx and van Gompel¹⁸ provide a comprehensive overview of this topic. In brief, short-term travellers will rarely require screening on return unless they were

at particular risk and follow-up is required, e.g. after extensive freshwater contact in one of the great lakes of eastern Africa. Others may have encountered health problems during travel, but return symptom free, seeking clarity on what may have afflicted them *en route* and wondering whether they are harbouring a 'blind passenger' from abroad. However, long-term travellers, both private or business, should be screened on return. A thorough history and retrospective risk assessment will indicate further investigations. A comprehensive physical examination and a screening laboratory examination, including a full blood count, transaminases and renal function tests, as well as exposure-specific seromarkers, will guide the attending physician with regard to findings that are suggestive of an imported (parasitic or non-parasitic) condition.

References

1. Grobusch MP, Göbels K, Teichmann D, Bergmann F, Suttrop N. Early-stage elephantiasis in bancroftian filariasis. *Eur J Clin Microbiol Infect Dis* 2001; 20: 835-836.
2. Jelinek T, Corachan M, Grobusch MP, et al. Falciparum malaria in European tourists to the Dominican Republic. *Emerg Infect Dis* 2000; 6: 537-538.
3. Frean JA, Blumberg L. Odyssean and non-mosquito-transmitted forms of malaria. In: Schlagenhauf-Lawlor P, ed. *Traveller's Malaria*. 2nd ed. Hamilton: BC Decker Inc., 2008: 343-351.
4. Grobusch MP, Kremsner PG. Uncomplicated malaria. *Curr Topics Microbiol Immunol* 2005; 295: 83-104.
5. Jelinek T, Schulte C, Behrens R, et al. Imported falciparum malaria in Europe: Sentinel surveillance data from the European Network on surveillance of imported infectious diseases. *Clin Infect Dis* 2002; 34: 572-576.
6. Grobusch MP, Burchard GD. Diagnosis of malaria in returned travellers. In: Schlagenhauf-Lawlor P, ed. *Traveller's Malaria*. 2nd ed. Hamilton: BC Decker Inc., 2008: 284-299.
7. Speil C, Mushtaq A, Adamski A, Khardori N. Fever of unknown origin in the returning traveller. *Infect Dis Clin North Am* 2007; 21: 1091-1113.
8. Wilson ME, Schwartz E. Post-travel care: fever. In: Keystone JS, Kozarsky PE, Freedman DO, Nothdurft HD, Connor BA, eds. *Travel Medicine*. 2nd ed. London: Mosby, 2007: 513-521.
9. Cook GC. Tropical gastroenterological problems. In: Cook GC, Zumla A, eds. *Manson's Tropical Diseases*. 21st ed. London: WB Saunders, 2003: 111-147.
10. Weitzel T, Mühlberger N, Jelinek T, et al. Imported leishmaniasis in Germany 2001-2004: data of the SIMPID surveillance network. *Eur J Clin Microbiol Infect Dis* 2005; 24: 471-476.
11. Alvar J, Aparicio P, Aseffa A, et al. The relationship between leishmaniasis and AIDS: the second 10 years. *Clin Microbiol Rev* 2008; 21: 334-359.
12. Jelinek T, Bisoffi Z, Bonazzi L, et al. Cluster of African trypanosomiasis in travellers to Tanzanian national parks. *Merg Infect Dis* 2002; 8: 634-635.
13. Grobusch MP, Mühlberger N, Jelinek T, et al. Imported schistosomiasis in Europe: Sentinel surveillance data from TropNetEurop. *J Travel Med* 2003; 10: 164-169.
14. Pritt BS, Clark CG. Amebiasis. *Mayo Clin Proc* 2008; 83: 1154-1159.
15. Teichmann D, Grobusch MP, Göbels K, et al. Acute fascioliasis with multiple liver abscesses. *Scand J Infect Dis* 2000; 32: 558-560.
16. Wolfe MS. Eosinophilia in the returning traveller. *Med Clin North Am* 1999; 83: 1019-1032, vii.
17. Davis RF, Johnston GA, Sladden MJ. Recognition and management of common ectoparasitic diseases in travellers. *Am J Clin Dermatol* 2009; 10: 1-8.
18. Clerinx J, van Gompel A. Post-travel care: Post-travel screening. In: Keystone JS, Kozarsky PE, Freedman DO, Nothdurft HD, Connor BA, eds. *Travel Medicine*. 2nd ed. London: Mosby, 2007: 502-512.

In a nutshell

- The list of differential diagnoses to be considered in the returning febrile traveller is long, including parasitic, non-parasitic infectious diseases, and non-infectious conditions.
- A considerable proportion of travellers who acquired a parasitosis abroad may remain asymptomatic for a long time, sometimes for years.
- Malaria should feature highly among diagnoses to be considered in a febrile traveller returning from endemic areas.
- Five *Plasmodium* spp. cause human disease, i.e. *P. falciparum*, *P. vivax* (outside Africa), *P. ovale*, *P. malariae*, and *P. knowlesi* (in circumscribed foci in South East Asia).
- Malarial fever as lead symptom is often irregular at onset, particularly in falciparum malaria.
- Kala-azar (visceral leishmaniasis) is relatively rarely encountered in returning travellers.
- African trypanosomiasis (sleeping sickness) is not frequently seen as an imported condition. However, occasionally clusters of travellers who contracted African trypanosomiasis are seen in Europe as well as in South Africa.
- Schistosomiasis is not infrequently encountered in returning travellers, but signs and symptoms are often discrete.
- *Entamoeba histolytica* may cause bloody diarrhoea and/or organ (liver) abscesses, thus potentially leading to death.
- Eosinophilia can be the key finding pointing towards a helminthic infection (usually in conjunction with a raised IgE level).
- Cutaneous larva migrans, tungiasis and myiasis can all cause considerable discomfort but are comparably harmless.
- A symptomatic, returning short-term traveller will rarely require a health screening on return.
- Long-term travellers should be assessed on return.