DIAGNOSTIC TESTS

Assessing fever in the returned traveller

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SUMMARY

There are many causes of fever after travel, ranging from common and self-limiting to serious and life-threatening.

Priorities for management are to identify conditions that are life-threatening, treatable, or have public health implications.

Common diagnoses are malaria and dengue fever, respiratory illness and diarrhoeal illness.

Malaria is important to exclude in any febrile person who has travelled or lived in a malaria transmission area.

Careful assessment of travellers with fever involves a detailed history, a thorough examination and targeted laboratory investigations.

Patients with undifferentiated fever should be referred to an infectious disease physician.

Introduction

It is estimated that febrile illness (temperature greater than 38° C) occurs in about 2–3% of travellers, and accounts for about a quarter of post-travel presentations for medical care.[1] Fever after travel may be due to a wide spectrum of causes, many of which are minor and self-limiting, but could include serious, rapidly-progressive or potentially fatal causes. The severity of illness varies widely also, with presentations of patients with fever ranging from mild inconvenience to patients requiring urgent hospital admission. While most travel-related infections present within a few months of return, some infections can present many months or years after exposure, such as strongyloides or schistosomiasis.[2]

Causes such as malaria or meningococcal disease are treatable with early recognition and specific management. Infectious causes may be of public health concern, and require specific intervention to prevent spread. The management of post-travel fever should therefore be directed at identifying treatable causes, especially for potentially fatal or rapidly-progressive disease, and managing any potential for communicable spread.[3]

Laboratory testing is important in establishing a proper diagnosis, including drug sensitivity where relevant. Many exotic or tropical illnesses may present similarly or non-specifically, yet establishing the exact diagnosis and circumstances of infection can be important to both the patient and others. Overdiagnosis in the field is common. In a Tanzanian study, most febrile travellers were empirically diagnosed and treated for malaria.[4] Another study showed that many febrile travellers in Asia were labelled and treated for typhoid fever.[5] This may lead to incorrect labelling of 'treatment failure' and associated avoidable morbidity.

Causes

Common causes of travel-related fever include malaria, influenza, dengue fever, rickettsial infections, non-specific viral syndromes and bacterial diarrhoea.[6-9] Febrile illness, such as common infections, malignancy and autoimmune disorders, may be unrelated to travel. Fever may also have a non-infectious cause related to travel such as pulmonary emboli or drug reactions.

Infectious causes of fever after travel could have been acquired before, en route or even after the specific travel, so care with history-taking is important. Specific causes of fever vary depending on the patient's destination.[6] The largest study of unwell returned travellers, the GeoSentinel database, showed the following causes of fever in returned travellers:[7]

- systemic febrile illness – 35% (malaria, dengue, typhoid, rickettsia)
- unspecified febrile illness – 22%
- acute diarrhoea – 15%
- respiratory illness – 14% (pneumonia, bronchitis, sinusitis)
- vaccine-preventable illness – 3% (hepatitis A and B, typhoid).

While fever without local symptoms is common, it may be more difficult to diagnose than fever associated with localising syndromes. Common presentations with fever include a rash, jaundice, abdominal pain or eosinophilia.[1,8]

Assessing the patient

A thorough history and examination of the patient should be the first step to making a diagnosis. A useful guide to the evaluation and initial management of fever in a returned traveller is shown in Fig. 1.[2]

Patient history

The history should include the following:

- the medical history of the patient including age, past surgeries, drugs, allergies, vaccines, immune status (HIV, diabetes, pregnancy)
- a detailed account of the travel history, including destinations, activities and possible exposures (see Table 1), timeframes of travel, season at destination
- a detailed sequential history of the current illness, associated symptoms or signs, concurrent therapies, and whether other people have been affected. Information about the pattern of fever may be sought, although this is often not useful because of the use of antipyretics and antibiotics.

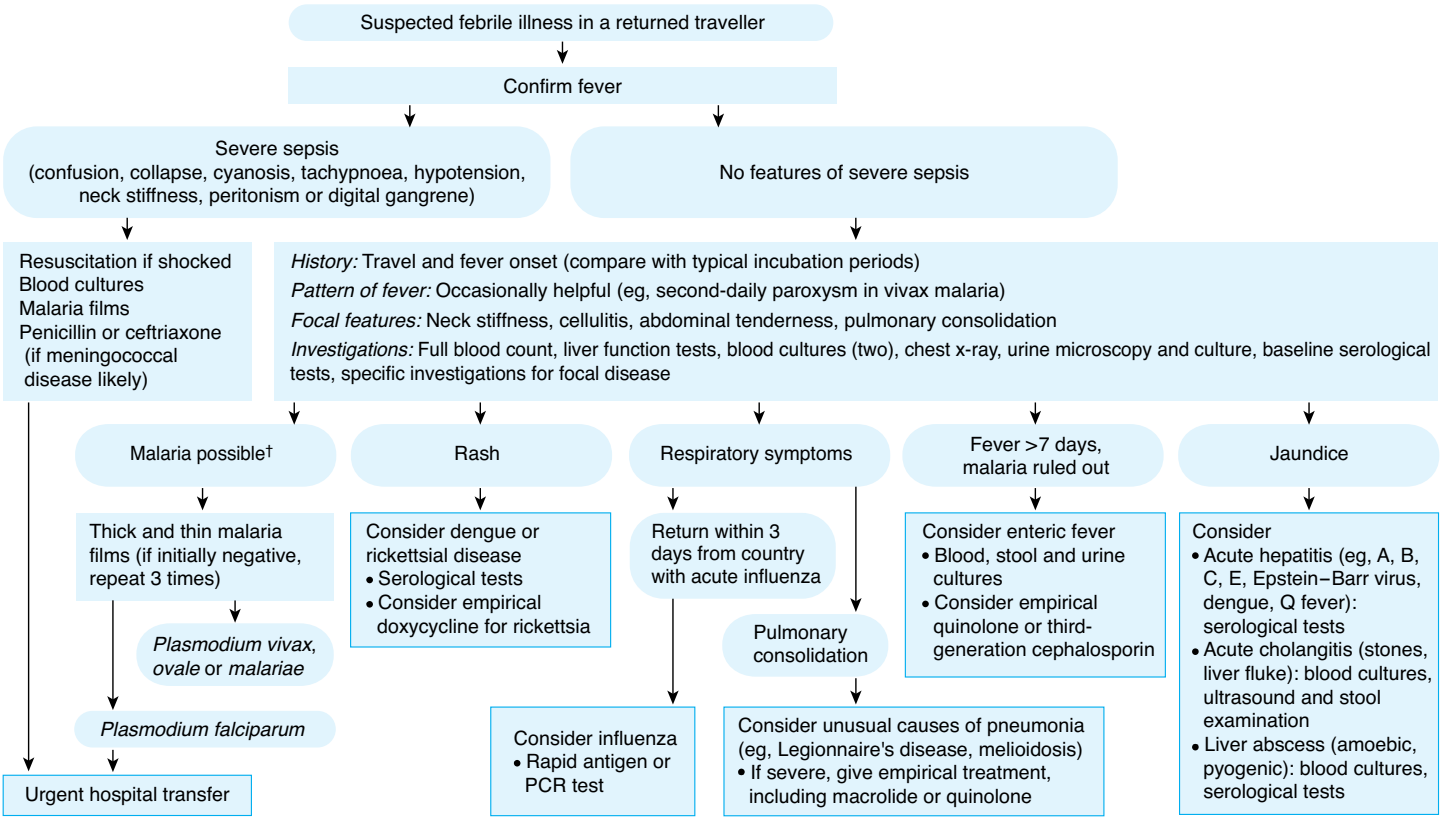
A checklist for history-taking in returned travellers is shown in Table 2.

It is important to identify if a traveller is a first or second generation emigrant traveller going back to visit friends and relatives, as these people have been shown to be at higher risk of travel-related morbidity.[9] This is because they have increased exposures to pathogens and decreased rate of preventative behaviours, such as vaccinations, before they travel.

Physical examination

Physical examination should include all systems. Important clinical features to look for include lymphadenopathy, hepatomegaly, splenomegaly, jaundice, anaemia, wheeze, rash or skin lesions, muscle or joint involvement, neck stiffness, photophobia, conjunctivitis, neurological signs or evidence of bleeding. Urine should be examined by dipstick initially for blood and glucose. Repeated examination may be required to monitor the evolution of symptoms and signs, and response to therapy.

Fig. 1 **Evaluation and initial management of fever in a returned traveller***



PCR polymerase chain reaction

* Evaluation should also include the differential diagnoses that would be considered in a non-traveller with fever

† Travel to high-risk area, rural or prolonged travel, non-compliance with prophylaxis

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Table 1 **Particular exposures and possible infections**

EXPOSURE	DISEASE
Drinking unclean water	Viral diarrhoea, shigella, salmonella, hepatitis A and E, giardia, polio, cryptosporidium, Guinea-worm
Skin contact in unclean water	Leptospirosis, schistosomiasis, free-living amoeba
Eating raw or improperly cooked food	Food-borne viruses and bacteria, wide range of parasites, brucellosis, listeriosis
Animal bites	Rabies, rat-bite fever, wound infections, simian herpes B-virus, cat-scratch fever
Animal contact	Q-fever, anthrax, toxoplasma, Hanta viruses, Nipah/Hendra viruses, severe acute respiratory syndrome, plague
Bird contact	Psittacosis, avian influenza
Mosquito bites	Malaria, dengue, yellow fever, arboviruses, viral encephalitis, filariasis
Tick bites	Rickettsia, borrelia, tick-born encephalitis, Q-fever, Crimean-Congo haemorrhagic fever, tularaemia, babesiosis
Fly bites	African trypanosomiasis, onchocerciasis, leishmaniasis, loa loa, sandfly fever, bartonella
Flea bites	Plague, murine typhus, tungiasis
Lice bites	Relapsing fever, epidemic typhus, trench fever
Mite bites	Scrub typhus, rickettsial pox
Triatomine bug bite	Chagas disease
Soil-skin contact	Hookworm, strongyloides, melioidosis, fungal infections, mycobacteria
Sexual contact	HIV, hepatitis A, B and C, sexually transmitted diseases
Injections, body-piercing	Hepatitis B and C, HIV, malaria, mycobacteria, leishmaniasis

Table 2 **Checklist for taking a history in returned travellers**

QUESTIONS	EXAMPLES
Country of origin and country of travel	Latent disease, possible exposures
Occupation, hobbies, activities	Farmer, abattoir worker, cave explorer
Prophylaxis	Immunisations, malaria prophylaxis, insect repellents
Treatments or procedures	Blood transfusions, injections, splenectomy, gastrectomy, tattoos
Drugs	Prescribed, over-the-counter, illicit
Diet	Seafood, raw food, traditional or homemade food
Sex	Unprotected sex, HIV partner, multiple partners, commercial sex
Allergies	Antibiotics, food, insect bites, plant
Bites	Insects, snake, animal, spider, human
Pets	Birds, dogs, cats, other
Family history	Diabetes, sickle-cell anaemia, tuberculosis

Clues to finding the cause of fever

The findings of the history and examination are then considered against the geographical distribution of infectious diseases and their incubation periods. Knowing the incubation period of certain diseases can assist in making the diagnosis, and while the exact date of exposure may not be determined, the departure and return dates may define the possible range of incubation periods, helping to rule in or out certain diagnoses (Table 3). For instance, an incubation period of less than two weeks rules out diseases such as amoebic liver disease, viral hepatitis, filariasis, visceral leishmaniasis and tuberculosis, whereas an incubation period beyond three weeks rules out dengue, rickettsia, haemorrhagic fevers and most bacterial infections including leptospirosis. Malaria can present from two weeks and up to months after return. Most cases (90%) of *Plasmodium falciparum* present within one month of return, whereas half of *P. vivax* cases present after one month.[2]

The presence of significant immune suppression also alters the possible range of infectious diseases as opportunistic infections must be considered. Other key physical findings may suggest certain diagnostic possibilities (Table 4). Remote travel within Australia also presents some risk of unusual communicable diseases (Table 5).

Laboratory tests

Initial screening of an undifferentiated fever should include:

- full blood examination with differential count and platelet count
- liver function tests
- thick and thin blood smears for malaria (could be supplemented by rapid tests where available)
- blood culture
- urinanalysis (infection, bilirubin)
- chest X-ray if patient is unwell.

Consider collecting an extra serum specimen to be held at the laboratory for future serology.

Routine screening may also help identify causes of potentially severe diseases such as malaria and typhoid. In addition to routine screening, extra investigations may need to be performed based on findings from the history and examination.[10]

Specific testing may be suggested by the clinical presentation, and guidance should be sought for the most appropriate specimen for the particular disease or phase of the disease.

Malarial smears

When malaria smears are ordered, it is preferable to refer to a recognised reference laboratory to minimise the chance of a false negative reading, as the experience of the technician is important. If malaria is suspected and the initial smear is negative, smears may need to be repeated at 24-hour intervals or sooner in severe disease. Negative smears can be due to low parasitaemia or can occur despite a high load with *P. falciparum* due to sequestration. Malaria should always be reconsidered if a traveller has returned from an area where transmission occurs, regardless of whether they took chemoprophylaxis,[11] or whether they are afebrile at the time of assessment.

Blood cell counts

The full blood examination and platelet count can be very helpful. Notably normal or low white cell counts occur in many infections including dengue, chikungunya, malaria, rickettsia and typhoid. Thrombocytopenia is seen in malaria, viral infections (especially viral haemorrhagic fevers including dengue) and in severe sepsis. Polymorphonuclear lymphocytosis usually reflects a bacterial infection, which could include leptospirosis or relapsing fever, but more often is due to common pyogenic organisms. Eosinophilia suggests invasive parasitic infection such as Katayama fever in schistosomiasis, or the migratory phase of some helminths or strongyloides. It also occurs in drug reactions and some fungal infections. Normal concentrations of non-specific markers such as C-reactive protein do not exclude serious illness.[1]

Other tests

Newer technologies like polymerase chain reaction-based tests may offer rapid and specific diagnosis, such as in dengue infection, but may also have a limited window to be positive. In general, positive bacterial specimens should be subjected to antibiotic sensitivity testing to guide therapy.

Referral and admission

When there is no clear diagnosis, patients should be referred to an infectious disease physician or major hospital for management. If the history and examination suggest a particular cause, patients can be managed outside hospital as long as there is access to diagnostics and prompt clinical review. Common conditions such as influenza or diarrhoea can generally be managed at home, but indications for referral for any illness should include suspected malaria, atypical presentations, or worsening clinical condition, in particular with onset of shock,

Table 3 **Average incubation periods for selected diseases**

INCUBATION PERIOD	DISEASES
Short (<10 days)	Arboviruses including dengue, chikungunya, bacillary dysentery, influenza, legionella, meningococcal, Marburg/Lassa fevers, plague, relapsing fever, rickettsial spotted fevers, scrub typhus
Intermediate (10–21 days)	African trypanosomiasis, brucellosis, hepatitis A and E, leptospirosis, malaria, typhoid, polio, epidemic typhus, Q-fever
Long (>21 days)	Hepatitis B, malaria, amoebic liver disease, visceral leishmaniasis, melioidosis, rabies, tuberculosis, filariasis, HIV, schistosomiasis

Table 4 **Key physical findings suggestive of cause of fever**

CLINICAL FINDING	POSSIBLE DIAGNOSES
Rash, maculopapular	Dengue, rickettsia, acute HIV, typhoid, scarlet fever, gonococcal, syphilis
Rash, petechial	Rickettsia, meningococcal, viral haemorrhagic fevers, leptospirosis
Eschars	Scrub typhus, tick-bite fever, anthrax, spider bites
Ulcers	Leishmaniasis, mycobacteria, anthrax
Jaundice	Hepatitis, malaria, leptospirosis, relapsing fever
Lymphadenopathy	Leishmaniasis, plague, rickettsia, brucellosis, toxoplasmosis, HIV, Lassa fever
Hepatomegaly	Malaria, leishmaniasis, schistosomiasis, liver abscess, typhoid, hepatitis, leptospirosis
Splenomegaly	Malaria, leishmaniasis, relapsing fever, trypanosomiasis, typhus, dengue, schistosomiasis, brucellosis

Table 5 **Unusual diseases present in Australia**

EXPOSURE	DISEASES
Mosquito	Alphaviruses – Ross River virus, Barmah Forest virus Flaviviruses – Murray Valley encephalitis, Kunjin virus, dengue, Japanese encephalitis
Tick	Queensland tick typhus, Flinders Island spotted fever
Mite	Scrub typhus
Soil and water	Melioidosis, leptospirosis
Animal	Australian bat lyssavirus, Hendra virus, Q-fever, brucellosis
Various	Mycobacteria – Bairnsdale ulcer, tuberculosis, leprosy, avian complex, trachoma

neurological, haemorrhagic or acute respiratory symptoms. Cases of poor response to treatment, persistent fever (fever for greater than seven days), or other chronic symptoms (greater than three weeks) should also be referred for specialist management.

Public health responses in Australia

Australia has 65 communicable diseases requiring notification by clinicians to state public health authorities. Many of these are diseases likely to be acquired through travel. Cumulative incidence is available through Communicable Diseases Intelligence reporting by the Australian Government Department of Health and Ageing.[12]

Quarantinable diseases, of which Australia currently has eight, include cholera, highly pathogenic avian influenza (H5N1), plague, rabies, severe acute respiratory syndrome (SARS), smallpox, the viral haemorrhagic fevers and yellow fever. Fortunately these are unlikely causes of fever in Australian travellers, although cholera and rabies have both caused recent outbreaks in tourist destinations. Quarantinable diseases are listed because they demand a major public health response.

The 2009 H1N1 pandemic highlighted the need to take a travel history when evaluating a patient with an undifferentiated influenza-like illness, and the requirement for an appropriate public health response.

Conclusion

Common diagnoses of fever in returned travellers are malaria, dengue fever, respiratory illness and diarrhoeal illness. Malaria is important to exclude in any febrile person who has travelled or lived in a malaria transmission area. Careful assessment of travellers with fever involves a detailed history, a thorough examination and targeted laboratory investigations. Patients should be referred to an infectious disease physician when a clear diagnosis is not made. <

Conflict of interest: none declared

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