An approach to fever in the returning traveller

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Abstract

The traveller who presents with fever on return requires a comprehensive assessment. This paper outlines the salient features in assessing these patients. A detailed history, examination and knowledge of diseases prevalent in the areas that were visited is essential if one is to arrive at a diagnosis and institute appropriate treatment or referral.

Malaria remains the first differential diagnosis in travellers returning from an endemic area irrespective of precautions taken.

The most common illnesses that result in a fever in travellers are presented and a resource list is provided.

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Introduction

The patient who presents to the practitioner with unexplained fever, whatever the setting, creates considerable anxiety for the physician. Such situations require a methodical approach, which is fundamental in all aspects of good clinical medicine: a detailed history, thorough clinical examination, formulation of a hypothesis/differential diagnosis, and testing of the hypothesis, with revision until a final diagnosis is achieved.

This applies equally to the situation when one is faced with a returning traveller who presents with a febrile illness, particularly if travel has included the tropics or subtropics, as the diseases that might have been contracted can be rapidly fatal. Travellers who cross borders may be exposed to a host of pathogens to which they have no previous exposure, making them fully susceptible to these infections.

There are additional factors that can change the hypothesis dramatically, and knowledge of these factors is essential if a rapid diagnosis is to be made and appropriate treatment instituted. Even more important is that the cause of the fever may have major public health implications.

The purpose of this paper is not to explore the countless causes of fever in a returning traveller, but to highlight those aspects that can aid and facilitate the diagnostic process. A comprehensive guideline to evaluating fever in returning travellers and migrants has been published and the reader is referred to this guideline for more detailed information.[1] An on-line version is available that includes a flowchart and a decision chart.[2] These guidelines deal only with travellers returning from the tropics or subtropics with a febrile illness and do not include children under the age of eight years or the immunocompromised. Ubiquitous infections, such as hepatitis A, influenza or pneumococcal pneumonia, are not discussed in detail.

The facts

The adage "common things occur commonly" still holds true for the returning traveller who presents with a fever. For those travellers returning from the tropics or subtropics, malaria heads the differential diagnosis list.

In a study of 622 travellers returning from the tropics[3] it was found that

- Tropical diseases are not the leading cause for consultation. A total of 230 diagnoses (36.1%) were related to tropical diseases, the main being malaria, schistosomiasis, amoebiasis and gastrointestinal disorders caused by intestinal nematodes, and dengue fever.
- Malaria was diagnosed in 21% of the 257 travellers who presented with a febrile illness.
- The presenting illness may not be related to travel and the practitioner might become so focussed on the travel aspect that common causes for a fever are overlooked.
- The illness in question might be related to an existing chronic medical problem or to a previous infectious disease that are unrelated to travel.

Key questions

Key questions that should be asked that can assist greatly in narrowing down the possible list of causes for the febrile illness:

- Is this malaria?
- What diseases are prevalent in the towns/countries visited?
  Knowledge of the prevalence of diseases and outbreaks of diseases in the countries, towns and rural areas that were visited is important and the travel history can narrow the differential diagnosis considerably.
  In a study undertaken by the GeoSentinel Network, malaria was one of the most frequent causes of a systemic febrile illness without localising signs in travellers returning from the developing world. Further, there is an emergence of rickettsial disease, particularly *Rickettsia africae*, in travellers to sub-Saharan Africa (these were more common than typhoid fever) and, in travellers to Asia, parasitic causes for diarrhoea are more common than bacterial.[4]
- Is the illness related to the most recent travel or to previous travel?
  Despite the fact that the traveller might have returned some months prior to presenting with a fever, the travel history cannot be ignored, as some illnesses have long incubation periods.
- Is it unrelated to travel?

Key factors

Travel history

Without a detailed travel history (this also impacts on disease profile), it is virtually impossible to formulate a differential diagnosis. The history must include:

- A detailed travel itinerary
  This must include travel within the past year, as the infection might not be related to the most recent travel.
  The departure date and dates of entry into various countries visited and dates of departure.
  These dates are an important reference in comparison to incubation periods when considering specific diseases prevalent in the regions visited.
  Details of the towns visited and whether or not travel included rural areas must be obtained.
  Ascertain the mode of transport to and from the destination and transport used at the destination.
- Purpose of trip
  The business executive will be exposed to a different disease profile than someone who spent time as an aid worker in a refugee camp or as a backpacker/adventure traveller.
- Precautions and chemoprophylaxis
  Ascertain specific precautions that were taken, including chemoprophylaxis and personal precautions.
  Adherence to appropriate, effective prophylaxis must be ascertained.
- Immunisations
  When and which immunisations were administered (for example, the bivalent rather than quadrivalent meningococcal vaccine might have been administered. Neither may be effective if the patient is a college student exposed to a serogroup not covered by either vaccine, e.g. serogroup B).
  Have the necessary booster doses been given?
- Accommodation
  The type of accommodation is crucial, as this too will change the likelihood of various infectious diseases. Was it a five-star hotel with air-conditioning or rural and tented accommodation? Were bed nets available, were they used and were they impregnated with an insect repellent? What was the condition of the bed net?
- Contact with animals
  Rabies can have a long incubation period and the small nibble from a dog might have been forgotten.
- Activities undertaken
  Participation in activities such as swimming, contact with fresh water, scuba diving and mountain climbing need to be ascertained. Schistosomiasis prevalence in sub-Saharan Africa is high and returning travellers might present with Katayama syndrome.
- Insect bites
  Tsetse fly, tick, mosquito, black fly and other arthropod bites may be relevant to the present illness.
- Dietary/food consumption
  Did the traveller eat at local restaurants, purchase food from street vendors or was it self-prepared? Did the traveller purchase food locally? What storage facilities were available?
- Disease prevalence
  What diseases are prevalent and what outbreaks have recently occurred in the countries visited?
  It is impossible for the practitioner to be totally knowledgeable regarding disease outbreaks. It is imperative that access to online information services is available so as to source this information. The World Health Organization and the centres for Disease Control and Prevention regularly publish disease outbreak information online.[5,6]
- Previous medical history
  This should include previous travel history as the febrile illness might not be related to the most recent travel.
  Has the traveller had any previous febrile history that was unexplained?
  Previous history of infectious diseases is important, such as malaria, schistosomiasis, Epstein Barr virus infection, tick bite fever, hepatitis A, which could narrow the differential diagnosis considerably
- Chronic ailments
  Cardiac disease, diabetes, tumours, hypertension, asthma and other chronic illnesses can all result in complications and infections that are not related to travel. However, travel might expose the patient to other common viral or bacterial infections.
- Present medication
  Medications and chemoprophylaxis can interact. Gastrointestinal disease may affect absorption and therefore reduce the efficacy of the medications.
- Immune status
  Many patients who are undergoing chemotherapy or are on immunomodulating drugs are travelling and frequently this aspect is overlooked. Patients with various stages of HIV infection also embark upon travel and opportunistic infections could also be the cause for fever in these travellers.[6] Knowledge of immune status is therefore critically important.
- Surgical history
  Splenectomised patients are more likely to develop severe malaria or pneumococcal disease.

Was help sought while away?

It is estimated that 8% of travellers to the developing world require medical attention while away or on their return home.[7]

Is this episode related to a problem that developed whilst away? Ascertaining what treatment was prescribed is sometimes difficult, as the traveller invariably has thrown away the medication containers. Regrettably, it is seldom that the treating practitioner provides documentation regarding the illness and details of the management, including the medication prescribed.

History of the current illness

It is important to establish the time of onset of fever and associated symptoms in order to establish a relationship between possible exposure, incubation period and development of symptoms.

Associated symptoms and signs
Headache is particularly severe in malaria, meningitis, Epstein-Barr virus infections, rickettsial infections and psittacosis.

The following infections should be considered in travellers who present with a rash and fever:
- Typhoid fever
- Dengue, West Nile and Sindbis fever and other arbovirus infections
- Rickettsioses
- Relapsing fever
- Primary HIV illness
- Katayama fever

A rash, associated with the history of swimming in fresh water, might lead one to consider a diagnosis of Katayama syndrome, whereas a rose rash and a relative bradycardia would support a diagnosis of typhoid fever.

Fever presenting with specific skin lesions may offer a diagnostic clue, e.g. the chancre associated with a tsetse fly bite and sleeping sickness (Trypanosomiasis), the tache noire of tick bite fever or a more mundane spider bite with toxic systemic involvement.

Anthrax may present with a skin lesion and systemic illness, including fever.

Myalgia is prominent and severe in some viral haemorrhagic fevers, whereas photophobia occurs in arboviral infections, rabies and leptospirosis.[7]

The presence of abdominal pain must be elicited. In children, malaria can present with abdominal pain and features of gastroenteritis. If the presentation of typhoid fever is fairly late into the illness, it can present with an acute abdomen and surgical referral will be required. The possibility of an amoebic liver abscess must be considered if there is tenderness in the right upper quadrant, but it should be borne in mind that acute cholecystitis could be the cause of the abdominal pain and tenderness.

In an Australian study of hospital admissions, jaundice did not feature as a major symptom or sign in returning travellers with a febrile illness.[8] However, jaundice and fever may be the presenting symptom or a subtle sign in complicated malaria. Viral hepatitis may likewise present with varying degrees of fever and jaundice, especially in older children and adults. Jaundice and fever may be a feature in varying stages of many other infectious diseases, including septicaemia due to many causes and non-infectious haematological or neoplastic disorders.

Eosinophilia and fever form an important, notable combination in many travel- and non-travel-related diseases alluded to in a comprehensive review article on illness in the returned traveller by Ryan et al.[9]

Specific febrile illnesses

Malaria
Malaria remains the first differential diagnosis in a traveller returning from a malaria-endemic area, irrespective of precautions taken. Chemoprophylaxis and personal precautions reduce the risk of contracting malaria considerably, but are not 100% effective. Adherence to the chemoprophylaxis regimen might not have been good and there are other factors that could interfere with absorption of the drug, such as vomiting and diarrhoea, rendering it ineffective.

The standard method for malaria diagnosis remains microscopic examination of stained blood smears. QBC and *Plasmodium* antigen rapid tests are extremely helpful, but have distinct limitations. Most rapid cassette-type tests check only for *P. falciparum* (95% of malaria in Africa) and one should not be satisfied with a negative test, as the infection could be due to *P. ovale, P. malariae* or *P. vivax* malaria. Certain rapid antigen tests do include all the malaria species and these may be preferable to use in areas with a high prevalence of non-*falciparum* malaria, with the caveat that such tests are less sensitive than the *falciparum*-specific tests and are easily misinterpreted.

An initial negative test does not exclude malaria, as all methods can be negative in the early stages and parasitaemia might not be detectable. Non-*falciparum* malaria results in a low parasitaemia, frequently making microscopic confirmation difficult. The presentation of non-*falciparum* malaria is less severe, with a low-grade fever that can lead one to erroneously discount the possibility of malaria

A full blood count is extremely useful, as a thrombocytopenia is almost invariably present in malaria. If no other laboratory-confirmed diagnosis has been established, the malaria blood films, antigen and QBC fluorescence tests must be repeated.

The test results should be obtained within three hours. Waiting until the next day is unacceptable, as deterioration can be rapid and treatment must be initiated urgently. Once the diagnosis has been confirmed it must be borne in mind that malaria is a notifiable disease and that the Department of Health must be informed via the local health authority.

Treatment

Comprehensive guidelines for the treatment of malaria in South Africa are available from the Department of Health and are published online.[10]

Who should be hospitalised?
Pregnant women, children under the age of five years, the elderly and immunocompromised are at high risk for severe malaria and should be hospitalised. Any patient with any of the following indicators of severe malaria should also be hospitalised:
Clinical features
- Impaired consciousness
- Respiratory distress
- Jaundice
- Bleeding
- Shock

Biochemical features
- Hypoglycaemia (blood glucose <2.2 mmol/l)
- Acidosis (plasma bicarbonate <15 mmol/l)
- Liver impairment: a threefold rise in the transaminases
- Signs of renal failure (serum creatinine >240 umol/l)

Haematological features
- Parasitaemia of more than 5%
- Haemoglobin <6 g/l or haematocrit <20%
- DIC
- The presence of *P. falciparum* schizonts in the peripheral blood smear

Katayama fever
Katayama fever is the acute presentation of schistosomiasis, which is prevalent in sub-Saharan Africa and parts of southeast Asia: the endemic areas have been defined well.[11] In a study of expatriates and tourists near Lake Malawi, it was found that the one-day absolute risk of acquiring schistosomiasis was between 52% and 74%.[1]

Katayama fever may closely mimic malaria and, unless there is a high index of suspicion, the condition is often not diagnosed and travellers

are not treated appropriately. Symptoms, which typically commence about four to six weeks (or even as soon as two weeks) after exposure, include fever, rigors, sometimes a fine urticarial rash and bronchospasm. Hepatosplenomegaly is sometimes found. Serology, except as a baseline, is unhelpful in this situation, as it may take three months for these tests to become positive.[12]

The diagnosis of Katayama fever is based on the following:

- History of exposure
- Urticarial rash
- Fever
- Bronchospasm
- Eosinophilia
- Negative malaria tests (smear, antigen tests, QBC fluorescence tests)

Searching for ova in the urine and faeces is unhelpful, as the ova only appear from about 45 days after exposure. Treatment in the acute phase is with high-dose corticosteroids. Praziquantel may be administered in the acute phase under steroid cover or deferred. Serological confirmation can be obtained at about six weeks. If praziquantel has been administered in the acute phase (this can lead to exacerbation of the symptoms), treatment might need to be repeated.

Respiratory tract infections

Respiratory tract infections account for 11% of travellers presenting with a febrile illness. The organisms involved are similar to those causing illness in non-travellers, but there is a higher proportion of atypical infections, such as legionellosis.

Consider histoplasmosis in adventure travellers who may have been spelunking.

Regarding avian influenza, a patient with respiratory symptoms who has been in South East Asia or other risk areas should be questioned about close contact (within one metre) with live or dead domestic fowl, wild birds or pigs in any environment, including poultry markets, or close contact (touching/speaking distance) with a case of severe respiratory illness or unexplained death in one of the affected areas. Local health authorities should be notified immediately about suspected cases.

Helminth infections should also be borne in mind, as these can cause respiratory symptoms with fever due either to the migration of the larvae through the lungs or a hypersensitivity reaction. An eosinophilia present in the blood count would aid in the diagnosis.

Typhoid fever

Travellers who have visited South Asia and developing countries in Asia, Africa, the Caribbean and South America are at the greatest risk for contracting typhoid fever.[13] The incidence is ten times higher in India and north Africa than in other tourist destinations.[1] A history of the patient's eating habits whilst away is important.

Presentation is variable, from a mild infection that develops over a few days, to severe or life-threatening disease, and the symptoms and signs will vary depending on when the traveller presents. The onset of fever is gradual, with headache, insomnia, malaise and anorexia. Constipation is more common than diarrhoea in adults and older children.[14] As the illness progresses, the fever is sustained, abdominal pain develops and hepatosplenomegaly is found. The rose spots that blanch on compression, which are easily noticeable in white-skinned patients, develop on the skin of the trunk in about 50% of patients and a relative bradycardia is typical. Stool and blood cultures must be obtained urgently. Serology lacks specificity, but may be helpful in some circumstances, e.g. if the patient has received antibiotics. The Widal test is non-specific and often falsely positive, causing much anxiety and incorrect diagnosis in many travellers in Africa. Typhoid fever is a notifiable disease and the Department of Health must be informed.

Dengue fever

Dengue fever is caused by a mosquito-borne flavivirus of which there are four serotypes. Patients present with a high fever, severe muscular pains, and sometimes a macular rash. The rash is inconsistent and is not a reliable sign. Many other arboviral infections (e.g. Rift Valley, West Nile, chikungunya and sindbis, among others) present in the same way. Dengue haemorrhagic fever and shock syndromes occur in patients who have been re-infected with a different serotype: this is unlikely to occur in the transient traveller. There is significant risk for travellers to dengue epidemic areas and regions where outbreaks have occurred. It is widespread in the tropical and subtropical regions of central and South America and south and south-east Asia, as well as in Africa. Dengue is usually confirmed by serological tests (IgG and IgM) It should be noted that false positive serology can arise in those travellers who have been inoculated against Japanese encephalitis and yellow fever.[15] There is no specific treatment for arbovirus infections, but in the case of dengue patients must be monitored carefully to ensure that no haemorrhagic manifestations occur, which would then necessitate hospital admission.

Chikungunya virus disease

Chikungunya virus disease has recently occurred in epidemic form in India and some Indian Ocean islands. It is transmitted by mosquitoes, particularly *Aedes* species, which bite during daylight. Fever and arthralgia, the latter persisting for weeks or months after the acute illness, are common presentations.

Rickettsial diseases

Tick bite fever, the most common rickettsial disease in Africa, presents in two forms. *Rickettsia conorii* infection (boutonneuse fever) is largely a peri-urban disease. *Rickettsia africae* infection (African tick bite fever) is more common in rural areas, and frequently occurs in hikers and campers. The former infection tends to be more severe, with a prominent rash, while the latter is generally milder, with multiple eschars that may be present and rash frequently absent. The incubation period is six to twelve days. An initial prodrome of severe headache and fever, frequently accompanied by nightmares, is followed three to five days later by the rash. At the site of the bite there is a characteristic eschar ('tache noir'), usually associated with painful regional lymphadenopathy. Prominent lymphadenopathy may be present in the absence of an obvious eschar. The rash is typically maculopapular, and the distribution is on the trunk and limbs, classically involving the palms and soles. In older patients, and in severe disease, the rash may be haemorrhagic. A negative serology test result in the first week of illness is common. Optimum treatment is with doxycycline, and a short course should even be considered in young children and pregnant women. Erythromycin is much less effective. There is limited experience with the new 4-fluorinated quinolones and macrolides. If treatment is delayed, tick bite fever may be complicated by multi-organ failure and disseminated intravascular coagulation (DIC).

Travellers in tropical Asia and the Western Pacific region may be exposed to scrub typhus, a frequently severe mite-transmitted rickettsial infection. Key clinical features are headache, fever, an

eschar, lymphadenopathy, myalgia and conjunctivitis; rash and deafness affect about half and a third of patients respectively. Pneumonitis may progress to fatal acute respiratory distress syndrome if diagnosis and treatment are delayed.

There is no vaccine that prevents any of the African rickettsioses transmitted by ticks.

Other tick-borne diseases
In certain parts of Africa, including South Africa, tick bites may lead to Crimean-Congo fever, an often deadly viral illness that presents after an incubation period of only one or two days with fever, malaise and a rash that quickly becomes haemorrhagic and may lead to rapid deterioration and death.

In certain parts of eastern Europe and near Asia, infected ticks in wooded areas transmit vaccine-preventable European tick-borne encephalitis, caused by a virus.

The practitioner should not forget that Lyme's disease is transmitted by ticks in many parts of the world, including the USA, Europe and parts of Africa. The disease may present as an acute febrile episode, but often has a more insidious onset and chronic prolonged course.

African trypanosomiasis
East African trypanosomiasis (sleeping sickness) is an acute, often fulminating condition with a substantial mortality. Transmission to tourists has occurred recently in game reserves in Tanzania, Malawi and Kenya, and in the Zambezi Valley in Zimbabwe. The vectors are tsetse flies, which are aggressive and deliver an unmistakably painful bite, often through clothing. A distinct erythematous trypanosomal chancre may form a few days afterwards at the site of the bite. Systemic disease is an acute febrile illness, not unlike malaria. Disease may be rapidly complicated by myocarditis, coagulation disorder, including DIC, and central nervous system invasion. Trypanosomes in the blood may be scanty and easily missed unless the laboratory is warned of their possible presence. Specific treatment in the form of suramin or melarsoprol (in the case of CNS invasion) is mandatory, but is toxic and must be given under expert supervision, preferably in an intensive care unit.

Bleeding and fever
This combination in a traveller immediately suggests viral haemorrhagic fever (VHF), but rickettsial and other viral and bacterial infections, particularly meningococcal septicaemia, are more common and need to be considered urgently. Labelling a patient '?VHF' often means that appropriate investigations and treatment are not done because of inappropriate caution on the part of medical staff. Conversely, patients may be evacuated or admitted under the wrong diagnosis; thus, an undiagnosed Ebola virus case may be flown in from central Africa as a bleeding peptic ulcer patient, for example. A detailed discussion of the presentation and management of VHF is outside the scope of this article. If the diagnosis of VHF is suspected, the patient should be isolated (but not neglected), and appropriate barrier nursing measures taken by medical and nursing staff while expert advice is sought. The number of people in contact with the patient should be minimised to help with control measures should a dangerous pathogen prove to be involved.

Conclusion

The returning traveller who presents with a febrile illness should be managed appropriately. A detailed travel history is the cornerstone to eliminating or honing in on possible infections: knowledge of the prevalence and outbreaks of diseases in the country/towns that were visited is paramount.

In those travellers returning from the tropics or subtropical areas, malaria remains the most important consideration. However the fever could equally be due to another life-threatening but treatable infectious disease or even be unrelated to travel.

An initial negative malaria test does not exclude malaria, and these tests should be repeated until a positive test is obtained or a positive diagnosis of another infection has been made.

Particular care should be taken with children, pregnant women, the elderly and the immunocompromised, as these patients are at particular risk for severe malaria and hospital admission is advised, irrespective of the presenting stage of the illness.

Patients who present with shock, respiratory distress or features of haemorrhagic disease must be referred for urgent hospital admission. If in doubt, consult the National Institute for Communicable Diseases or a practitioner with an interest in travel medicine.

Resources

The Department of Health: http://www.doh.gov.za/
The National Institute for Communicable Diseases: http://www.nicd.ac.za/
The South African Society of Travel Medicine (SASTM): www.sastm.org.za
Travax (Scotland): http://www.travax.scot.nhs.uk/registered/index2.asp (this requires SASTM membership)
CDC Traveler's Health: Outbreaks http://wwwn.cdc.gov/travel/default.aspx
CDC Health Information for Travel 2008
Weekly Epidemiological Record Bulletin: http://www.who.int/wer
WHO Epidemic and Pandemic Alert Response: http://www.who.int/csr/en/
WHO International Travel and Health 2007: http://www.who.int/ith/en/
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