THE RETURNING TRAVELLER WITH FEVER

As numbers of visitors returning from exotic destinations in less developed parts of the world increase, the challenges to the physician grow.

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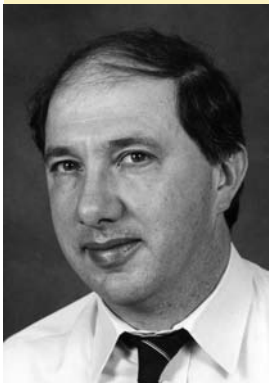

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Travellers face a number of health risks during their journeys. The majority of incidents are related to trauma or to underlying co-morbid disease, most commonly cardiovascular disease. Infectious diseases however are a significant problem and range from the potentially life-threatening, such as malaria, to those that are more mundane, such as travellers' diarrhoea. This article will focus on the traveller who returns with a suspected infectious disease and will discuss a diagnostic approach, before describing important syndromes and their common causes.

HISTORY

Pyrexial illness is a presentation of most travel-associated infectious diseases, but many common infections such as influenza and pneumonia also occur in the tropics or may be acquired *en route* to and from exotic regions. Patients may also have chronic or recurrent medical problems that are unrelated to their tropical exposure. In approaching a pyrexial patient, therefore, a general medical history should elicit the presence of underlying conditions, particularly those associated with increased risk of infections such as diabetes, malignancy, HIV infection, splenectomy, and pregnancy. Specific questions about the current illness are listed below. The travel history, both recent and past, is of vital importance. Duration of illness in relation to known incubation periods helps to include or eliminate certain infections. Areas visited and the nature of the travel may suggest likely exposures, e.g. business travel in city hotels has a different risk profile compared with river-rafting adventures.

History — important questions

- Symptoms and sequence of symptoms
- Travel departure and return dates
- Purpose of travel (elicit specific details): business, leisure, missionary, military, expatriate
- Onset of illness in relation to travel
- Countries visited, including stopovers, and specific areas within the country
- Season and climate
- Type of travel: e.g. overland, air, sea, backpacking
- Type of accommodation: e.g. camping, hotel
- Pre-travel immunisations: what and when
- Prophylaxis, including chemoprophylaxis, e.g. malaria: type and compliance with drugs

- Exposures: see Table I
- Past illness: general plus specific illnesses such as hepatitis A
- Co-morbid disease, medication
- Immunosuppression: specific illnesses or drug-induced, previous splenectomy
- Specific symptoms: fever (onset of fever, fever pattern), headache, rigors, photophobia, conjunctivitis, arthritis, arthralgia, myalgia, presence of rash or skin lesions (see below), lymphadenopathy, gastrointestinal symptoms (diarrhoea, presence of blood, vomiting), jaundice, and haematuria.

PHYSICAL EXAMINATION

A thorough physical examination is essential, and together with the history, will direct the choice of further radiological and laboratory investigations (Table II). A full blood count and examination of blood smears is a nearly obligatory basic investigation. The physician should focus initially on those infections that carry the greatest morbidity and mortality, those that are treatable and those that pose a public health risk.

UNDIFFERENTIATED FEVER

Diagnosis and management of malaria in travellers is urgent, and should be considered in anyone returning from a malaria transmission area with symptoms of a flu-like illness, fever, rigors, headache and/or myalgia, irrespective of the season or whether chemoprophylaxis was taken. The risk of contracting malaria is highest in Africa and Oceania, followed by Asia and Latin America. Most large cities in South and Central America and Southeast Asia are malaria-free but this is not true of Africa (apart from South Africa, the Kenyan capital Nairobi, Gaborone in Botswana, Windhoek in Namibia and Harare in Zimbabwe). *Plasmodium falciparum* is the commonest species in Africa and overall the most serious, frequently progressing rapidly to complicated disease. Most travellers with malaria present 7 - 21 days after exposure but incubation periods may be prolonged by inappropriate chemoprophylaxis or poor compliance, and clinical illness may be delayed in patients with non-falciparum malaria. A blood smear or rapid antigen detection test is usually sufficient to confirm the diagnosis, but a negative test does not exclude malaria and repeat tests may be necessary. Thrombocytopenia is frequent, even in uncomplicated cases. Choice of treatment depends on severity of disease and the likely drug resistance pattern of the parasite. Chloroquine-resistant *Plasmodium falciparum* is a problem globally. Artemisinin combination therapy is considered highly effective, with quinine and doxycycline as an alternative for malaria acquired in Africa. Chloroquine and primaquine are effective for most strains of *Plasmodium vivax* with the exception of some resistance in Oceania and Papua New Guinea.

Typhoid fever characteristically presents insidiously with fever, headache,

Table I. **Specific exposures and associated infections**

Type of exposure	Associated infections
Bites	
Mosquito	Malaria, dengue, yellow fever, encephalitis, filariasis
Tick	Borreliosis (Lyme disease, relapsing fever), rickettsioses (tick bite fever, typhus, Rocky Mountain spotted fever); Congo-Crimean haemorrhagic fever, Q fever, tularaemia, encephalitis, ehrlichiosis
Fly	African trypanosomiasis, onchocerciasis, leishmaniasis, bartonellosis, myiasis, loiasis
Flea	Plague, tungiasis, murine typhus
Triatomine bugs	American trypanosomiasis (Chagas' disease)
Mammal	Rabies, rat-bite fever, tularaemia, anthrax, Q fever, cellulitis
Ingestion	
Water (untreated)	Hepatitis A/E, cholera, Norwalk/caliciviruses, *Salmonella, Shigella, Giardia,* poliomyelitis, *Cryptosporidium, Cyclospora,* dracunculiasis
Dairy (unpasteurised)	*Brucella*, tuberculosis, *Listeria* Enteric bacteria (*Salmonella, Shigella, E. coli, C. jejuni,* etc.)
Raw or undercooked food (meat, fish, vegetables)	Helminths (*Ascaris, Trichinella, Taenia* – including cysticercosis, whipworm, *Capillaria, Angiostrongylus*), protozoa (amoebiasis, toxoplasmosis)
Freshwater skin contact	Leptospirosis, schistosomiasis, *Acanthamoeba*, or *Naegleria*
Sand/dirt/mud skin contact	Hookworm, cutaneous larva migrans, visceral larva migrans, leptospirosis
Sexual contact	HIV, hepatitis B/C, syphilis, gonorrhoea, *Chlamydia*, herpes, papillomavirus

Table II. **Differential diagnosis of physical findings for some febrile diseases**

Physical finding	Differential diagnosis
Lymphadenopathy	Plague, HIV, rickettsioses, brucellosis, leishmaniasis, dengue, lymphogranuloma venereum, Lassa fever
Hepatomegaly	Malaria, leishmaniasis, amoebic liver abscess, typhoid, hepatitis, leptospirosis
Splenomegaly	Malaria, leishmaniasis, trypanosomiasis, typhoid, brucellosis, typhus, dengue
Jaundice	Hepatitis, malaria, leptospirosis, relapsing fevers, cholelithiasis, pancreatitis
Petechiae/ecchymosis	Meningococcaemia, yellow fever, dengue, rickettsioses, viral haemorrhagic fevers
Wheezing	Löffler's syndrome, Katayama fever, tropical pulmonary eosinophilia

Table III. **Skin lesions associated with infections**

Skin lesion	Differential diagnosis
Maculopapular	Arboviruses, acute HIV, rickettsia, syphilis, typhus, bartonellosis, typhoid, rubeola, rubella, scarlet fever, cercarial dermatitis, scabies, arthropod bites
Petechiae/ecchymoses	Rickettsiae, meningococcaemia, viral haemorrhagic fevers, dengue, leptospirosis
Eschar	Tick bite fever, scrub typhus, anthrax, African trypanosomiasis, tularaemia, spider bites
Nodules	Onchocerciasis, bartonellosis, myiasis
Ulcers	Leishmaniasis, tropical ulcers, anthrax, tularaemia, cutaneous diphtheria, ecthyma, syphilis, yaws, tuberculosis, granuloma inguinale, lymphogranuloma venereum, arthropod bite
Migratory	Cutaneous larva migrans, larva currens, gnathostomiasis, loiasis, myiasis, paragonimiasis, sparganosis

chills, and abdominal pain. There is frequently a paucity of clinical signs and fever may be the most prominent clinical finding. An irritable cough, change in mental state, and splenomegaly may be noted. Rose spots are uncommon. Characteristically there is leucopenia, with neutrophilia and eosinopenia, thrombocytopenia and a modest increase in hepatic transaminases. The diagnosis is best confirmed by isolating *Salmonella typhi* on blood culture. Isolation from stool or urine is supportive but not absolutely diagnostic as it may merely indicate the carrier state. A four-fold rise in agglutinating antibodies to the O capsular antigen is highly suggestive. Quinolones are highly effective. Alternative agents include third-generation cephalosporins, chloramphenicol and ampicillin. Antibiotic resistance is a significant problem in Southeast Asia.

East African trypanosomiasis is generally an acute, often fulminating condition with a substantial mortality. Transmission to tourists has occurred recently in game reserves in Tanzania, Malawi and Kenya. The vectors are tsetse flies, which are aggressive and deliver an unmistakably painful bite, often through clothing. At the site of the bite a trypanosomal chancre may form a few days afterwards. Systemic disease is an acute febrile illness, not unlike malaria. Disease may be rapidly complicated by myocarditis, coagulation disorder including disseminated intravascular coagulation (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.

FEVER AND RASH

Travel-related infectious diseases are commonly associated with skin lesions or rashes. Important aids to diagnosis are the nature of the lesion, distribution of the rash, appearance of the skin lesion in relation to the course of clinical illness, and the presence of other clinical signs and symptoms (Table III). More than 150 arboviruses affect humans. Arboviruses tend to be seasonal and regional in their distribution so a history of travel to a specific geographical area often provides the clue to the specific causative arbovirus. Many present with a characteristic clinical syndrome of fever, rash and arthritis.

In southern Africa, important arboviral infections include West Nile, Sindbis and Chikungunya. Dengue is increasingly seen in travellers returning from endemic areas. Culicine mosquitoes transmit Sindbis, West Nile and Chikungunya viruses. Fever, polyarthropathy involving both small and large joints, severe myalgia and rash are usual features. Arthritis may persist for several months to 2 years. Malaise, conjunctivitis and pharyngitis

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may be noted. Rash is prominent and in Sindbis is typically maculopapular, with a characteristic halo surrounding each individual macule or papule (Fig. 1). Rash is variable in West Nile infection, ranging from maculopapular to discrete roseolar spots, diffuse small spotted exanthem or even mottling of the skin. Diffuse lymphadenopathy is common.

In the northern hemisphere, West Nile infections more commonly present as encephalitis. The rash of Chikungunya is generally a fine diffuse macular or papular rash that spreads centrifugally, often to the palms and soles.
Dengue is caused by a flavivirus transmitted principally by daytime biting *Aedes aegypti* mosquitoes. Recently, epidemics of dengue have occurred in Southeast Asia, notably in Thailand, Indonesia and Vietnam, on the Indian subcontinent, and in Central and South America. In Africa, dengue

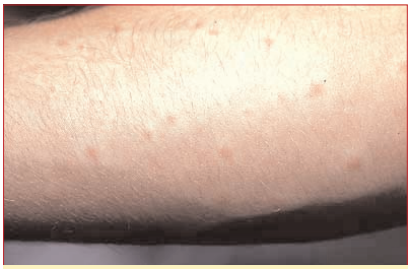

Fig. 1. Sindbis rash, showing 'halo' around the lesions.

Table IV. **Causes of eosinophilia and fever in returning travellers**

Disease or condition	**Substantiating evidence, caveats, and clinical points**	**Suggested investigations**
Acute schistosomiasis	History of transient skin itching, tingling or papular rash; dry cough common; eosinophilia earliest sign, parasite ova only appear weeks or months later	Schistosomiasis serology, repeat in a week if low/negative
Strongyloidiasis	Transient urticarial rashes (larva currens); abdominal pain; nausea, diarrhoea, weight loss in more severe cases	Stool (and sputum, if disseminated disease suspected) examination for larvae; serology not available in SA
Trichinosis	History of eating raw or undercooked meat; presents with nausea and vomiting, followed by myalgia, and periorbital oedema; uncommon complications are myocarditis, meningoencephalitis	Muscle needle biopsy; serology not available in SA
Gnathostomiasis	History of eating raw/undercooked fish, crabs, crayfish, birds, typically acquired in Far East, SE Asia but also recently in Africa; presents as larva migrans syndrome Albendazole (21 days) has proven successful	Surgical removal of larvae (difficult); specific serological test available in Thailand only
Löffler's syndrome	Transient parasitic pneumonitis, presents with fever, cough, wheezing; most commonly due to *Ascaris lumbricoides* larvae migrating through lung; less commonly, hookworm infection and strongyloidiasis	Chest X-ray shows transient infiltrates
Toxocariasis	Typically in children with history of pica and contact with dogs; presents with fever, hepatomegaly, wheezing; sometimes cardiac and neurological dysfunction; ocular form can mimic retinoblastoma	Liver function tests (hyper-gamma-globulinaemia); *Toxocara* serology

occurs in East and West Africa. Local transmission in South Africa has not been reported although occasionally vectors have been imported in tyres from endemic areas. The incubation period is 3 - 8 days, and presentation is abrupt with headache, fever, chills, myalgia, arthralgia, and retro-orbital pain. On day 3 - 5, fever reduces and a morbilliform rash appears on the trunk, spreading to the face and extremities. Characteristically, the rash tends to blanch (Fig. 2). Petechial haemorrhages may appear, but do not necessarily indicate the complication of dengue haemorrhagic fever. Leucopenia and thrombocytopenia are common findings. The diagnosis of arboviral infections is confirmed during the first week of illness by virus isolation from blood. Seroconversion may be demonstrated after the first week of illness. Management of arboviral disease is generally symptomatic.

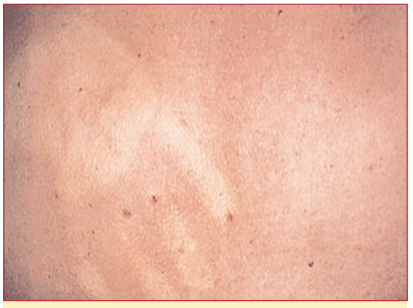

Fig. 2. Dengue rash, showing blanching on pressure.

There are two forms of tick bite fever, the commonest rickettsial disease in Africa. *Rickettsia conorii* infection (boutonneuse fever) is largely a peri-urban disease. *Rickettsia africae* infection (African tick bite fever) is more common in rural areas, frequently in hikers and campers. The former tends to be more severe with a prominent rash, while the latter is generally milder, multiple eschars may be present and rash is frequently absent. The incubation period is 6 - 12 days. An initial prodrome of severe headache, fever and frequently nightmares, is followed 3 - 5 days later by the rash. At the bite site the characteristic eschar (Fig. 3) is generally noted, and usually associated with painful regional lymphadenopathy. The rash is typically maculopapular, and the distribution is on the trunk and limbs, classically involving the palms and soles (Fig. 4).

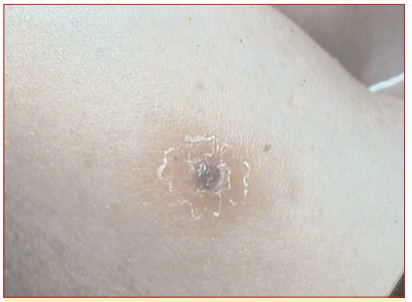

Fig. 3. Eschar of tick bite fever.

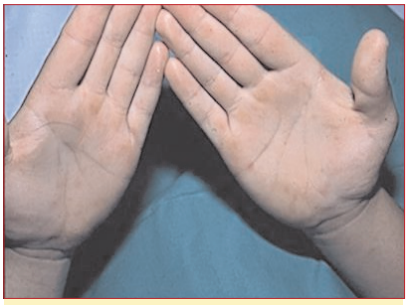

Fig. 4. Rash of tick bite fever, involving palms.

In older patients, and in severe disease, the rash may be haemorrhagic with petechiae and even ecchymoses. The disease is confirmed by the specific serological test. A negative result in the first week of illness is not uncommon, and repeat serology is indicated. The Weil-Felix test is neither sensitive nor specific for tick bite fever. Optimal treatment is 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 DIC.

FEVER AND EOSINOPHILIA

Eosinophilia, defined as an absolute eosinophil count of > 400/µl, is associated with several infections, mainly parasitic, that may present with a febrile illness (Table IV). Schistosomiasis is the commonest cause in returning travellers. In general, protozoan infections do not produce eosinophilia; exceptions are *Isospora belli* and *Dientamoeba fragilis*. Non-parasitic infectious diseases causing eosinophilia include chronic tuberculosis, resolving scarlet fever, bronchopulmonary aspergillosis and histoplasmosis. There are many non-infectious causes of eosinophilia that may coincidentally be present in a patient with fever (e.g. lymphomas, leukaemias, other malignancies, drug allergies, toxins, dermatological, pulmonary, and idiopathic conditions). Typhoid fever is classically associated with an absence of peripheral blood eosinophils; systemic steroid therapy also usually suppresses an eosinophilic reaction of any aetiology.

LABORATORY INVESTIGATIONS

A full blood count gives valuable information regarding aetiology as well as severity of disease. Leucocytosis is suggestive of bacterial infection, leucopenia is frequent in malaria, typhoid and arboviral infections and thrombocytopenia is invariable in malaria. Eosinophilia is most likely to be due to a helminthic infection. Peripheral blood smears for malaria are mandatory in febrile travellers from malaria risk areas. A liver function test is frequently very useful. The remaining investigations are guided by the suspected diagnosis based on history and travel. Cultures should ideally be submitted prior to starting antibiotics. Interpretation of serological investigations should take into account the sensitivity and specificity of the test, and they may need to be repeated to demonstrate seroconversion or increase in titre.

MANAGEMENT

The potentially most dangerous and common causes of fever in returning travellers should be looked for first and managed accordingly. Specific treatment is ideally given only once the diagnosis is confirmed, influenced however by the severity of the clinical disease and the likelihood of a specif-

ic disease. Drug-resistant organisms are a major problem globally and the likely sensitivity pattern of the specific organism acquired in a specific locale must be taken into account.

Further reading

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IN A NUTSHELL

Thorough history of illness and travel movements is essential.

Ask about existing medical conditions.

Focus initially on diagnosing infections that are dangerous for patient and community.

Skin lesions are important clues to many travel-related infections.

Malaria must always be considered in a traveller with fever and flu-like symptoms.

Tick bite fever is common in travellers in Africa, and the typical rash may be absent.

Fever, rash and arthritis is suggestive of arboviral infections.

Fever and eosinophilia is commonly due to acute schistosomiasis (Katayama fever).

Full blood count, blood smear examination, and liver function tests are obligatory initial investigations.

Getting a diagnosis before treatment is ideal, but must be balanced against the need to treat severe illness.