

Fever in the returned traveller

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Abstract

The diagnosis of fever in the returned traveller is an important challenge to the physician. An accurate travel history and knowledge of the incubation period of common diseases is required to assess the risk of infection with a specific infectious agent. Although many febrile illnesses are benign and self-limiting, failure to diagnose malaria and enteric fevers may have disastrous consequences. All patients returning with fever should have thick and thin blood films for malaria and blood cultures performed. Other haematological and biochemical tests are useful in identifying a group of patients in whom empirical anti-microbial therapy is indicated. Thought must be given to the isolation of patients and notification of certain suspected or proven diseases to the local Consultant for Communicable Disease Control. Preventative measures in those likely to travel again should be discussed.

Keywords

Travel, fever, malaria, typhoid, prophylaxis.

Introduction

Each year millions of tourists travel abroad from the United Kingdom (U.K.) and an increasing number venture to 'less safe' areas outside Europe and North America. On their return a small proportion of travellers are referred to hospital with a fever of unknown aetiology. A careful history, examination and appropriate investigations, often in discussion with the microbiology laboratory, are required. Whilst a fever may be associated with a benign self-limiting illness, failure to diagnose and specifically treat other infections, such as malaria and typhoid, may have disastrous consequences.

History

The onset, duration and exact nature of the symptoms should be elicited. A travel history should ascertain places visited, mode of travel, exposure to potential hazards and risk of acquiring specific infections. A businessman staying overnight at the Nairobi Hilton has less risk of contracting an exotic illness than a backpacker travelling through sub-Saharan Africa. Eating food at local markets and drinking unbottled water increases the risk of bacterial enterocolitis, giardiasis and amoebiasis.

Other hazards include time spent in rural areas where anopheles mosquitoes and malaria are more prevalent. Contact with freshwater may result in schistosomiasis or leptospirosis, camping or sleeping in log cabins are risk factors for tick bites and therefore typhus (rickettsiosis) and relapsing fever (borreliosis). The bites of tsetse flies, the carrier of trypanosomiasis, are often acquired on safari and are memorably painful. Sexual contact with locals is a risk factor for acquisition of primary HIV infection, acute Hepatitis B and other sexually transmitted infections. A history of consumption of unpasteurized dairy products is helpful in assessing the risk of brucellosis.

Health-care workers (HCW) are exposed to additional hazards. Tuberculosis, not normally associated with travel, may be nosocomially acquired through droplet infection and needle-stick injuries may result in primary HIV and acute Hepatitis B infection. HCW are at risk of acquiring viral haemorrhagic fevers (eg. Marburg and Ebola) if they have nursed patients with severe bleeding in sub-Saharan Africa within 21 days of presentation. Cavers and pot holers are at risk of histoplasmosis or rabies from bats. Pathogens associated with exposure to animals include chlamydial infection (psittacine birds), leptospirosis (rodents) and Lassa Fever (rodents). An immunisation history is important but vaccine efficacy is variable and type dependent. Protection against malaria in East Africa with chloroquine and proguanil is diminishing and may be 70% or less; recent guidance states that mefloquine, doxycycline or Malarone are the preferred drugs of choice.¹ The date of return to the U.K. and knowledge of the incubation period of common infectious diseases is helpful in determining the probability of a specific diagnosis. These are summarised in Table 1.

Patients often complain of non-specific symptoms such as fever, myalgia and headache. Textbooks claim that the periodicity of fever may give a clue to the underlying cause but this is rarely the case. Myalgia, characteristic of many viral illnesses (eg. Dengue fever), is a common early feature of severe bacterial sepsis (eg. Meningococcal disease). Headache, photophobia and meningism is

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Short (<10 days)	Long (>21 days)
<i>Amoebiasis</i>	<i>Amoebiasis</i>
Bacterial enterocolitis	<i>Brucellosis</i>
<i>Brucellosis</i>	Hepatitis A and B
Diphtheria	HIV infection
+Haemorrhagic fevers	EBV infection
Dengue fever	<i>Malaria</i>
Lassa	~Q fever
Marburg/Ebola	~Schistosomiasis
Influenza	Secondary syphilis
Legionnaire's disease	<i>Trypanosomiasis</i>
<i>Malaria</i>	Tuberculosis
+Psittacosis	
Streptococcal pharyngitis	
Meningococcal disease	
<i>Trypanosomiasis</i>	
+Typhoid and Paratyphoid	
+Typhus (Rickettsiosis)	
~ Incubation period may be as short as 2 weeks	
+ Incubation period may be longer than 10 days but rarely exceeds 21 days	
The incubation period of Crimean-Congo Haemorrhagic Fever (CCHF) and leptospirosis is commonly 10-21 days	
Where the incubation periods overlap, the diseases are highlighted in italics	

Table 1. Incubation period of diseases associated with fever in the returned traveller.

suggestive of viral or bacterial meningitis. As travellers often return with infections commonly acquired at home, patients should be routinely asked about the presence of sore throat, cough and sputum production. Change in bowel habit is a common symptom and in large bowel infections the stool may be bloody, contain mucus and be associated with a fever. Diarrhoea, although unusual, may occur in malaria and typhoid and can also occur with any form of abdominal sepsis (eg. appendicitis or diverticulitis) occasionally requiring surgical intervention. Frequency, dysuria and nocturia are symptoms of lower urinary tract infections (UTIs) more common in returned travellers because of dehydration. The formation of renal calculi may predispose to pyelonephritis that classically presents as fever, rigors, and loin pain.

Examination

The skin should be examined for the presence of soft tissue infection, possibly superinfecting insect bites, or a rash. The features of a rash may be particularly helpful in providing a clue to the underlying disease (Table 2). Although not specifically associated with any illness, the conjunctivae should be examined for signs of anaemia, jaundice and petechiae, and the cervical, axilla and inguinal areas palpated for lymphadenopathy. Auscultation of the heart may reveal regurgitant murmurs, consistent with infective endocarditis and focal chest signs are compatible with bacterial pneumonia. Abdominal examination should be undertaken; tender hepatomegaly in a jaundiced patient occurs with acute viral hepatitis and intercostal point tenderness is suggestive of an amoebic liver abscess. Splenomegaly is associated with acute or chronic malaria, schistosomiasis and visceral leishmaniasis, where there

Generalised:	Restricted:
Maculopapular: Dengue Ebola Enteroviruses Hepatitis B Primary HIV infection Infectious mononucleosis Typhus	Maculopapular: Typhoid Meningococcaemia
Petechial: Dengue Infectious mononucleosis Leptospirosis Meningococcaemia Relapsing fever Typhus Viral haemorrhagic fevers	Eschar: Typhus Trypanosomiasis Cutaneous anthrax
Vesicular: Chickenpox Enteroviruses	

Table 2. Rashes in the returned traveller.

may be massive splenomegaly. An altered mental state may be an early sign of cerebral malaria or typhoid. Once excluded, meningitis and viral encephalitis need to be considered.

Common illnesses causing fever in the returned traveller

Malaria and enteric fevers are the most important tropical infections to consider, not only numerically but also because of their lethal potential. Other important causes of imported fevers are considered below, but the notion that they are exotic is erroneous. Many patients present with focal bacterial infections with and without bacteraemia, diseases that could have been acquired at home.

Malaria

Nearly 2000 cases of malaria are diagnosed in the U.K. each year. The symptoms are variable and non-specific and any traveller with fever returning from a malarious region within the last three months should be appropriately investigated (see below). Patients with malaria may present atypically with cough, jaundice or diarrhoea. If the patient has been compliant with chemoprophylaxis the diagnosis is more difficult and prophylaxis should be stopped whilst investigations are carried out.

Non-falciparum malaria is a relatively benign illness. Failure to diagnose falciparum malaria may result in severe complications including:

- cerebral malaria
- adult respiratory distress syndrome (ARDS)
- renal failure
- coagulopathy
- circulatory collapse (shock) and death.

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The risk is greatest in non-immune individuals when the parasitaemia is equal or greater than 2% of infected red blood cells.

Enteric fevers

The majority of cases of typhoid (*Salmonella typhi*) and paratyphoid (*Salmonella paratyphi*) seen in the U.K. are acquired in the Indian subcontinent. Patients characteristically complain of headache, cough, abdominal pain and constipation although at the onset of fever, constitutional symptoms may be mild. Classically the patient has a relative bradycardia compared to the temperature. Rose spots and splenomegaly may be present in the second week of illness. Culture of the organism from the blood or stool (and occasionally urine) provides a definitive diagnosis. The treatment of choice is ciprofloxacin if the organism is sensitive, although many isolates from the Indian subcontinent are increasingly quinolone resistant.²

Dengue fever

Dengue, transmitted by day-biting *Aedes* mosquitoes, is prevalent throughout South-East Asia, Central America and the Caribbean. The incidence of disease is increasing due to urbanisation and climatic changes. Its traditional name, 'break-bone fever' aptly describes the clinical picture of fever, severe myalgia, arthralgia and retro-orbital headache. There may be a blanching macular or a non-blanching petechial rash and bleeding gums whilst brushing teeth may provide a diagnostic clue. In common with malaria, patients may present with a thrombocytopenia and defervescence coincides with a recovery in platelet count and disappearance of the virus as detected by PCR.³ Travellers previously exposed to dengue infected with a different viral serotype are at risk of dengue haemorrhagic shock syndrome (DHSS), a cross reactive immunological phenomenon, caused by extravasation of plasma into pleural and peritoneal cavities.

Viral haemorrhagic fevers (Excluding Dengue fever)

In contrast to Dengue fever, Lassa, Ebola, Marburg and Crimean-Congo Haemorrhagic Fever (CCHF) are rare with one imported case occurring every 10 years in the U.K. However, the attending physician must be aware of this diagnostic possibility, particularly in a patient with spontaneous bleeding where malaria has been excluded. Major epidemiological risks include contact with a known or suspected case and return from a high-risk area within 21 days, commonly rural sub-Saharan West Africa. Case-fatality is high as is the risk to medical, nursing and laboratory staff. Patients must therefore be transferred to one of two high security isolation facilities sited in London or in Newcastle.⁴ Treatment is essentially supportive although ribavirin has been used in Lassa fever and may improve prognosis.

Amoebic liver abscess

Amoebiasis is a disease of the tropics and subtropics. The patient typically complains of fever and right upper

quadrant pain (but not diarrhoea) often months after travel to an endemic country. Fingerpoint tenderness between the intercostal spaces indicates that the abscess is close to the skin. The right lobe is predominantly affected and disease occurs more commonly in men. Ultrasound examination and serology are the basis of diagnosis and treatment is with metronidazole and an amoebicide, dilanoxide furoate, to eradicate intraluminal cysts. Aspiration of the abscess is not required unless rupture into the pleural or peritoneal cavities are imminent.

Rickettsial diseases (Typhus)

A large proportion of Tick typhus (*Rickettsia prowazekii*, *Rickettsia conorii* and *Rickettsia africae*) is acquired in Africa's safari parks. The tick bite is painless and easily missed. Patients characteristically develop a febrile illness with headache, myalgia, a macular rash and lymphadenopathy. Serology is the mainstay of diagnosis and clinical response to doxycycline is rapid. Failure to diagnose and treat promptly may result in severe vasculitic complications including renal failure, gangrenous extremities and bowel perforation.

Viral hepatitis

Hepatitis A and B are the commonest causes of viral hepatitis in the returned traveller and may cause a low grade fever. Hepatitis A is acquired via the faecal-oral route and its incubation period is 2-6 weeks. Hepatitis B is both sexually transmitted and acquired percutaneously via contact with blood or infected body fluids. Patients infected with Hepatitis A and B commonly present with a low grade fever, jaundice and tender hepatomegaly. At presentation, transaminases are markedly elevated before returning to normal. Fulminant hepatic failure rarely occurs. Unlike Hepatitis A where there are no chronic carriers, ten percent of adults infected with Hepatitis B become chronic carriers and are at risk of developing liver cirrhosis and hepatocellular carcinoma. Both infections are preventable through immunisation.

Leptospirosis

Exposure to fresh water contaminated with rodent urine is a risk factor for leptospirosis. Most cases are mild, but certain serotypes are associated with a severe form of illness or Weil's Disease, characterised by hepatorenal failure and bleeding with disseminated intravascular coagulation (DIC). Although the organism may be seen in the urine on darkground microscopy within the first week of illness, the diagnosis is generally made by serology. Treatment is with a beta-lactam antibiotic or doxycycline and is only effective if given in the early stages of disease.

Schistosomiasis

Most travellers returning to the U.K. acquire schistosomiasis through freshwater exposure in Africa, commonly Lake Malawi. Some patients develop 'swimmers itch' at the site of entry of the invasive form and 4-8 weeks later Katayama fever, an acute febrile illness characterised by fever, headache, myalgia, cough and

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urticaria. Early diagnosis of *S. mansoni* and *S. japonicum* is important, as once liver fibrosis develops treatment with praziquantel is of little benefit. Chronic *S. haematobium* is associated with squamous cell carcinoma of the bladder.

Sexually transmitted diseases

Primary HIV infection may present with fever, rash, lymphadenopathy and orogenital ulceration. If this diagnosis is not actively considered, patients remain undiagnosed and may, only years later, present with an opportunistic infection.⁵

Focal bacterial infections with or without bacteraemia

Upper respiratory tract infections

Diphtheria should be considered in travellers returning from areas of high prevalence such as Eastern Europe and Russia but this is rarely associated with fever. Bacterial pharyngitis, often caused by *Streptococcus pyogenes*, occasionally necessitates admission to hospital. The common presentation is with a unilaterally enlarged palatine tonsil and exudate associated with fever, headache and tender cervical lymphadenopathy. Severe infections may have features similar to meningitis and failure to examine the throat may result in unnecessary lumbar puncture.

Lower respiratory tract infections

Pneumococcal pneumonia is the commonest cause of community acquired pneumonia seen in patients at home or travellers from abroad. The patient characteristically presents with cough, haemoptysis, pleuritic chest pain and a high fever that responds dramatically to a single dose of antibiotic. Respiratory signs may be absent at presentation only to appear 24 hours later. In the absence of previous antibiotics, blood cultures are positive in 30% of cases. Of the atypical pneumonias, *Legionella* is the most severe and likely to cause hospital admission. The history is often subacute and confusion is a common feature. Epidemiological clues, in addition to travel abroad, include contact with jacuzzi's and hot water spa's and working or residing in an air-conditioned environment. Tuberculosis should be considered in any patient with a low grade fever, night sweats, poor appetite and weight loss.

Soft tissue infections

The foreign traveller not uncommonly returns with soft tissue infections. Predisposing lesions such as insect bites may become superinfected and athlete's foot may also provide a portal of entry. Localised skin infections (boils, carbuncles and furunculosis) are caused by *Staphylococcus aureus* whereas streptococcal infections (eg. group A but also group C and G) more commonly cause cellulitis. Patients may present with fever, constitutional symptoms and a raised white cell count, only for cellulitis to declare itself the following day. Group A streptococcal infections occasionally cause necrosis or are associated with bacteraemia and shock. An anti-Streptolysin O titre

(ASOT) is generally required for a retrospective diagnosis. Blood cultures and wound swabs are often sterile. *S. aureus* is rarely isolated from blood cultures unless the organism has disseminated to a distant site, commonly joints, bone or heart valves.⁶

Gastrointestinal infections

Campylobacter, shigella and non-typhi salmonella species are the commonest causes of bacterial enterocolitis associated with fever in the returned traveller. Shigella and campylobacter species may present as a dysenteric illness but rarely cause bacteraemia. In contrast, non-typhi salmonellosis can cause bacteraemia, especially in the elderly and immunocompromised.⁷

Urinary tract infections (UTI's)

In lower UTI's and pyelonephritis a variety of organisms can be cultured from the urine. *Escherichia coli*, the commonest uropathogenic coliform, may cause bacteraemia and seeding to the spine may occasionally occur, particularly in the elderly.

Investigations

Investigations are best considered as haematological, biochemical, microbiological and radiological. These are described below.

Haematology

Thick and thin blood films, the mainstay of malaria diagnosis, are the most important haematological investigations. Three films, taken on consecutive days, are required to effectively exclude malaria. Blood films are also used for the diagnosis of borreliosis (relapsing fever) and trypanosomiasis (sleeping sickness) although the sensitivity is poor. The white cell count (WCC) and differential count are the most important parameters in helping to determine the cause of infection. A raised WCC with neutrophilia suggests pyogenic bacterial infection whereas a normal or low WCC suggests viral or intracellular bacterial infections (Table 3). Occasionally, at presentation, the WCC is normal only to rise dramatically after the initiation of antibiotics. Acute malaria and dengue fever are the two most common infections associated with thrombocytopenia. The presence of atypical lymphocytes is most commonly associated with illnesses such as EBV, CMV, toxoplasmosis and primary HIV infection. In the returned traveller eosinophilia, a marker of helminth infection, is generally an incidental finding and not the cause of fever.

Biochemistry

Urea and creatinine may be elevated due to dehydration or as a direct consequence of infection, a poor prognostic marker. Elevated transaminases are the hallmark of viral hepatitis, an elevated bilirubin and alkaline phosphatase are caused by biliary tract sepsis and obstruction. Minor abnormalities of any liver enzymes can occur with any bacteraemia.

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Brucellosis
#Dengue fever
Enteric fever (Typhoid or paratyphoid)
#Malaria
Non-typhi salmonella enterocolitis
Primary HIV infection
Schistosomiasis
Viral haemorrhagic fevers
Ebola
Lassa
Marburg
Crimean Congo Haemorrhagic Fever
Commonly associated with thrombocytopenia

Table 3. Imported diseases associated with normal WCC.

Pulse >120/min
WBC > 15 or neutrophils >12 x 10 ⁹ / litre
Fever > 39°C or rigors
BP < 90/60, or a postural drop, or cold peripheries
Any rash
Drowsiness or neck stiffness
Hypoxia, acidosis or respiratory distress
Diarrhoea or vomiting
Aching limbs or acute inability to stand
Renal or liver impairment
CRP >100mg/litre
Disseminated intravascular coagulopathy
Two or more from the list above indicate the need for empirical antimicrobial therapy

Table 4. Clinical and laboratory parameters associated with severe infection.

Microbiology and Serology

Blood cultures must always be taken in patients presenting with a pyrexial illness. Depending upon localising symptomatology, cerebrospinal fluid, sputum, throat swabs and urine should be cultured. Certain organisms will not grow on standard non-selective agar (eg. *Corynebacterium diphtheriae* and *Legionella pneumophila*) and where these infections are suspected the laboratory requires warning. Where antibiotics have been administered prior to admission the diagnosis is dependent upon PCR and antigen detection tests (eg. Meningococcal disease⁸). More fastidious bacteria are commonly diagnosed serologically, often retrospectively. A serum sample should always be saved at the time of illness so that seroconversion can be documented.

Treatment

Where possible, treatment should be withheld until cultures are taken and a specific diagnosis made. In severely ill cases, treatment with broad spectrum antimicrobial agents should be initiated and clinical symptoms, signs and blood tests can help to identify a subset of patients in whom this is appropriate (Table 4). Antibiotic policies, based on likely common pathogens and their susceptibility patterns, are invaluable in guiding junior doctors in the safe and effective use of antibiotics. These should take account of the increasingly prevalent multiple drug resistance of organisms acquired abroad (eg. Penicillin-resistant pneumococci, ciprofloxacin resistant

Chickenpox	Isolate until last vesicle has healed
Diarrhoea and vomiting of unknown aetiology	Until cessation of diarrhoea and vomiting
Hepatitis (undiagnosed)	7 days after onset of jaundice for Hepatitis A. Patients with Hepatitis B do not require isolation
Meningitis (undiagnosed)	Isolate until cause is found
Meningococcal septicaemia	Isolate for 48 hours after commencing treatment
Streptococcus pyogenes	For 24 hours after commencing treatment
Tuberculosis (pulmonary)	14 days after commencing treatment. If MDR TB, isolate until culture negative
Typhoid	Isolate on admission to hospital
Viral haemorrhagic fevers	Transfer to high security infectious diseases unit
The above list is not comprehensive. Further information is available from the local Consultant in Communicable Disease Control (CCDC) and the Department of Health publication 'Immunisation against Infectious Diseases'. ¹⁰	

Table 5. Diseases associated with fever in returning travellers requiring isolation.

Typhoid). Empirical therapy should be modified in the light of results obtained from the microbiology laboratory.

Uncomplicated falciparum malaria, often equating to a parasitaemia of < 2%, should be treated with oral quinine or Malaroner, each tablet containing 250 mg atovaquone and 100mg proguanil. Severe falciparum malaria or patients with persisting vomiting should be treated with intravenous quinine. Artemisinin derivatives are a useful alternative although are not widely available in the U.K. In patients with a parasitaemia greater than 30%, or lower if severely ill, consideration should be given to exchange transfusion.⁹

Isolation and Infection Control

All patients returning from overseas with a fever should be considered infectious and admitted to a side room, preferably negative pressure, until the diagnosis is apparent. Here, appropriate staff should wear plastic aprons and gloves, and if there is a risk of acquiring disease through droplet inhalation facial masks should be worn. Once the diagnosis is known (eg. malaria) patients may be safely moved and nursed on the open ward. Implementation of an infection control policy is dependent upon available facilities and a risk assessment applied to individual cases. Handwashing before and after patient contact and safe disposal of sharps is always of utmost importance. Very few infections require permanent isolation. Patients with the greatest need for isolation in negative pressure siderooms are summarised in Table 5.

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Diphtheria	Paratyphoid and Typhoid fever
Dysentery (amoebic or bacillary)	Scarlet fever
Encephalitis (acute)	Tuberculosis
Food poisoning	Typhus
Leptospirosis	Viral haemorrhagic fever
Malaria	Viral hepatitis
Meningitis	Whooping cough
Meningococcal septicaemia (without meningitis)	Yellow fever
The above list is not comprehensive and other infections acquired at home or abroad are notifiable by law	

Table 6. Notifiable diseases at home or in returned travellers.

Discharge

As the patient recovers from a febrile illness, certain or presumptive diagnoses must be notified to the local Consultant in Communicable Disease Control (Table 6). This allows epidemiological data to accrue on infectious diseases that should be reported to microbiologists and physicians in a timely fashion. Advice should be given concerning risk reduction on future travel overseas. For example, adherence to chemoprophylaxis and the use of insecticides including impregnated bed nets should be discussed with patients recovering from malaria planning future trips overseas. The immunisation history should be reviewed and advice given on the need for boosters or other immunisations.

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Conclusion

Diagnosing the cause of fever in returned travellers remains an exciting challenge to the physician. A detailed history and knowledge of the incubation period of common diseases allows the risk of infection with a specific agent to be assessed. Malaria and enteric fevers must always be excluded. It is therefore essential that blood films and blood cultures are taken from every patient. In addition to clinical symptoms and signs, haematological and biochemical parameters are helpful in identifying a group of patients in whom empirical antimicrobial treatment should be initiated. Communication with the microbiology laboratory facilitates a timely diagnosis that, more often than not, is neither exotic nor obscure as infections that are commonly acquired at home often feature in the differential diagnosis. Thought must be given to the isolation of patients and notification of certain suspected or proven infections. Further measures to prevent infection in patients likely to travel again should be discussed.

Acknowledgements

We would like to thank Dr N.M. Price for his helpful comments whilst preparing this manuscript.

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