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HOW I MANAGE THE FEBRILE RETURNING TRAVELLER*

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> Humanity has but three great enemies: fever, famine and war; of these by far the greatest, by far the most terrible, is fever.
>
> *Sir William Osler*

Throughout the centuries, the clinical diagnosis has been made or strongly suggested by the history, the presence of helpful physical findings and the observation of the patient. Like Osler, physicians since antiquity have viewed fever, an important clinical finding, as an entity worthy of unremitting attention.

An eighteenth century English diarist (Fanny Gurney, *Celia Book IV*, 1782) wrote that 'travelling is the ruin of all happiness'. Fortunately, this rather gloomy outlook is no longer widely held, as illustrated by the massive increase in public spending on travel and escalation in air travel by UK residents. Between 1991 and 1995 there was a rise to 22.9 million UK residents travelling abroad (International Passenger Survey, Office for National Statistics) and a 12.5 million rise in visitors to the UK over a similar period. Although Spain and France remain the most popular destinations, increasing numbers of British people (approximately three million in 1996) are travelling to the tropics and subtropics.

Fever is an important and common presentation of tropical disease and sometimes may be the only manifestation of serious illness. Indeed, 81% of travellers complaining of fever admitted to the Hospital for Tropical Diseases in London, in a period of six months had travelled to the tropics or subtropics (60% sub-Saharan Africa; 13% Indian sub-continent 8% South-East Asia).[1] This suggests that both primary and secondary care physicians need to be familiar with the management of patients arriving at, or returning to, this country with a febrile illness. It is only a fitting tribute to Sir Patrick Manson (1844-1922), the father of Tropical Medicine, born in Oldmeldrum, Aberdeenshire and a distinguished graduate of the University of Aberdeen, that the Royal College of Physicians of Edinburgh has chosen his Alma Mater as its host venue to address this important subject in a symposium.

Case History

A 42-year-old construction engineer returned from a one-month trip to Ghana. Ten days following his return he felt unwell with fever and a flu-like illness. He also admitted to occasional looseness of stool and anorexia. These symptoms did not improve with paracetamol and he consulted his local family doctor who referred him to the local hospital for assessment.

What are the key steps in evaluating the cause of this man's symptoms?

The evaluation of fever in travellers returning from a tropical country requires attention to ten points (Table 1):

KNOWLEDGE OF THE LIKELY AETIOLOGY OF THE FEVER

The most common infectious diseases that come to light after distant travel are not exotic infections such as Ebola or tuberculosis but rather, infections with a worldwide

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TABLE 1
Assessment of the febrile traveller: a ten point scheme.

1. Knowledge of likely aetiology of fever
2. Epidemiological knowledge of any concurrent outbreaks
3. Knowledge of incubation periods
4. Medical history
5. Travel history
6. Clinical examination
7. Investigation
8. Treatment
9. Notification
10. Prevention

distribution. The commonest are gastro-intestinal, with diarrhoea affecting up to 40% of short-term travellers to some destinations.[2] Fever in a returning traveller (Table 2) may either be due to a tropical infection or related to infections that are also common in non-travellers, such as urinary tract infections and upper respiratory tract infections including sinusitis and community-acquired pneumonia.[1,3] Legionnaires' disease does not account for most travel-associated respiratory infection.[2] Plausible reasons for increased rates of travel-related respiratory infections include prolonged exposure to low humidity in aircraft and close contact with large numbers of persons from many geographic regions, often in crowded or confined places.

However, unfamiliar infections do also occur following travel to temperate zones. For example, in travellers to the USA, relapsing fever, ehrlichiosis and Lyme disease are infections that may present with fever.[2] The commonest exotic infections in travellers returning from the tropics are malaria, enteric fever, viral hepatitis and dengue fever (Table 2).[1,3] Malaria is by far the most important cause of fever that has to be excluded; falciparum malaria can be potentially rapidly fatal but is curable with early recognition and appropriate treatment.[4-6]

TABLE 2
Aetiology of fever after travel to tropics.*

Diagnosis	% of patients
Tropical	
Malaria	42
Diarrhoeal illness	6.5
Dengue	6
Hepatitis	3
Enteric fever	2
Tuberculosis	2
Other	
Non-tropical	
Respiratory tract infection	2.5
Urinary tract infection	2.5
Pharyngitis	2
Other	
Undiagnosed	24.5†

*Based on data derived from published reports[1,3,4]
†Includes presumed viral and non-specific infections

One should also consider non-infective sources of fever such as drugs, neoplasms, connective tissue disease and pulmonary emboli, the latter particularly in long-haul travellers crammed into the tight quarters of an aeroplane or a coach - an economy class syndrome.

KNOWLEDGE AND EPIDEMIOLOGICAL INFORMATION ABOUT OUTBREAKS OF INFECTION WORLDWIDE.

The media have raised general awareness of outbreaks or epidemics of infection. They have widely reported Ebola in Africa, plague in India, diphtheria in Eastern Europe, Hatanvirus in the USA, meningococcal meningitis in Western Africa and in Muslim pilgrims visiting Mecca, and dengue in Asia and South America. Even though this information may not be readily available to the non-specialist clinician, an appreciation of where this information could be obtained would help in the diagnosis and management of the patient. Easily accessible sources of such specialist information include local public health departments, the Scottish Centre for Infection & Environmental Health (SCIEH), the TRAVAX computer database and regional infection units.

KNOWLEDGE OF INCUBATION PERIODS

Most returning travellers will present with fever within the first three weeks of their return: in the London study,[1] 71% of patients presented within 14 days of their return, and only 11% later than six months after. Most imported fevers are due to diseases with short (<3 weeks) incubation periods (Table 3).[4] An accurate travel history taken from the patients allows the doctor to determine the approximate duration of the presenting illness which will help to eliminate several possible differential diagnoses. For example, fever presenting more than three weeks after leaving the endemic zone will effectively exclude the arbovirus infections (dengue, yellow fever, the viral haemorrhagic fevers), typhus and plague.

However, some infections have variable incubation periods and malaria is particularly important in this respect. About one third of cases of malaria caused by *Plasmodium vivax* present within the first month of infection but almost ten per cent may not present until one year after exposure. Furthermore, although the majority of cases (90%) of falciparum malaria present within two months of a return from an endemic area, the increasing use of mefloquine chemoprophylaxis has delayed presentation,[7] often to three to four months after return.

TABLE 3
Incubation periods of secreted tropical infections.[4,5]

SHORT (< 3 WEEKS)	LONG (> 3 WEEKS)
Malaria	Malaria
Typhoid	Typhoid
Paratyphoid	Hepatitis A, B. E
Dengue fever	Amoebic abscess
Typhus (scrub, louse or flea borne)	Tuberculosis
Hepatitis A	Brucellosis
Leptospirosis	Filariasis
African trypanosomiasis	Acute schistosomiasis (Katayama fever)
Plague	HIV seroconversion
Relapsing fevers	Viseceral leishmaniasis
Haemorrhagic fevers (e.g. Lassa)	Q fever

MEDICAL HISTORY AND TRAVEL HISTORY

Junior doctors may fail to record important details of a patient's history and clinical findings in the medical records;[8] the taking and documentation of a good medical and travel history is of paramount importance if the correct diagnosis is to be established. The key components of a travel history are summarised in Table 4 and include questions designed to ascertain the full travel itinerary and activity, information about vaccination and the details of chemoprophylaxis. Questions in relation to the latter should include: Were you taking malarial prophylaxis? If so, which drug? At what dose and how often were you taking it? Are you still taking it?

TABLE 4
Travel history.

General questions	*Seek history of specific exposure*	
	Exposure	Infection
When did you travel? What were your arrival and departure dates?	Raw, undercooked or exotic foods	Enteric infections, hepatitis
Did you travel to urban or rural areas?	Drinking untreated water, milk, cheese	Salmonella, hepatitis, shigellosis, brucellosis
What was the purpose of your travel?	Fresh water swimming	Schistosomiasis, leptospirosis
Any travel companions unwell?	Insect bites	Malaria, dengue, etc
Sexual history during trip?	Animal exposures/bites	Rabies, Q fever, etc
What pre-travel vaccinations did you receive?	Exposure to infected persons	Lassa, Ebola, typhoid, meningococcaemia
Were you taking anti-malarial prophylaxis? Which drug did you take? Did you take it always? Are you still taking it and as instructed?		

The limitations of travel immunisation must also be appreciated. For example, the efficacy of all currently available typhoid vaccines is at best 70% and typhoid fever can be contracted despite vaccination.[9] These vaccines do not protect against *S. paratyphi*, a common cause of enteric fever in Asia and Eastern Europe.[10] A second and more detailed group of questions is designed to identify potential exposure to infection. For example, if one suspects acute schistosomiasis, disclosure of swimming in a fresh water lake, such as Lake Malawi in East Africa,[11] would confirm that a relevant risk had been taken.

The importance of taking a sexual history cannot be over-emphasised. Intercourse with new partners features in many people's travel; indeed, sexual tourism may be the primary reason for travel. About 60% of short-term Swiss tourists travelling to tropical Africa, Asia and Latin America, reported casual sexual contacts during their trip.[12] Many sexually transmitted diseases, including acute HIV seroconversion illness, can manifest as fever. Therefore, failing to ask about sexual activity during travel out of feigned politeness is not acceptable; this also applies to asking about misuse of injectable substances.

CLINICAL EXAMINATION

A thorough and meticulous examination is important. This should include the area behind the ears and the axillae, and a full pelvic and genital examination; these areas are often missed during a cursory examination, but could reveal potential skin signs and lesions. The key signs to look for are a throat exudate, rashes and other cutaneous lesions, jaundice, lymphadenopathy, hepatomegaly, splenomegaly and subcutaneous haemorrhage. These clinical signs and their associations are summarised in Table 5.[5,6]

TABLE 5
Possible clinical signs in selected tropical infections.

Clinical sign	Associated infection or disease
• Fever pattern	Not generally helpful, except in dengue fever (saddle back fever), typhoid (continuous fever) or fever every 48-72 hours (typical of non-falciparum malaria.)
• Throat exudate	Diphtheria, HIV seroconversion.
• Rash:	
Maculopapular	Dengue fever, HIV, rickettsial infections, hepatitis B, leptospirosis, brucellosis.
Isolated macular spots	Typhoid rose spots; transient, blanch with pressure, occasionally in gonococcaemia.
Eschar (painless ulcer with a black centre and erythematous margin)	Scrub or tick typhus, cutaneous diphtheria.
• Lymphadenopathy	HIV, rickettsial infections, brucellosis, dengue fever, Lassa fever, visceral leishmaniasis. (Not a feature of malaria.)
• Splenomeagaly	Malaria, relapsing fever, trypanosomiasis, typhoid, brucellosis, kala azar, typhus, dengue.
• Hepatomegaly	Amoebiasis, malaria, typhoid, viral hepatitis, leptospirosis.
• Haemorrhage	Viral haemorrhagic fevers, Rift Valley fever, dengue fever, yellow fever, meningococcal septicaemia.

INVESTIGATIONS

These can be divided into essential and selective laboratory tests. Essential tests are a complete blood count with differential count, and a thick and thin blood film for malarial parasites (see later for more detail), liver function tests, urinalysis, cultures of blood, urine and stool. The selective tests are those which should be restricted to certain pyrexial patients guided by the history and the findings on clinical examination(Table 6).

MANAGEMENT

This section will be confined to the most common hazards of travel. The number of British travellers to malarious areas has increased exponentially over the last few years; in consequence about 2,000 new cases with 10 deaths occur annually in the UK. The burden of malaria in Scotland remains significant with around 10-20 admissions annually to the regional infection units.[13,14] This presumably reflects the large number of Scots travelling to sub-Saharan Africa (40,000 visits in 1995) and Asia/Oceania (130,000 visits in 1995).

TABLE 6
Investigations useful in assessing the febrile traveller.

INVESTIGATION/abnormality *	Common selected associated infection or disease
Essential	
FULL BLOOD COUNT & PICTURE	
Neutrophilia	Bacterial enteritis, amoebiasis, pneumonia, leptospirosis.
Leucopenia	Arbovirus (especially dengue) infections, influenza, enteric fever, brucellosis.
Eosinophilia	Intestinal helminthiasis (worm), drug reaction, acute schistosomiasis (Katayama fever), filariasis.
Thrombocytopenia	Malaria, viral infections, brucellosis, leishmaniasis.
Parasites (thick & thin blood film)	Malaria.
LIVER FUNCTION TESTS	Significantly abnormal in acute hepatitis A, B, C, E; mild to moderately abnormal in Q fever, malaria, typhoid, dengue, HIV seroconversion, brucellosis, typhus and in any severe systemic infection.
BLOOD CULTURES	Enteric fever, invasive salmonellosis, pneumococcal pneumonia, urinary tract-derived bacteraemia.
STOOL CULTURE	Salmonellosis, campylobacteriosis, shigellosis, cryptosporidiosis.
URINALYSIS	Haematuria (schistosomiasis) urinary tract infection.
URINE CULTURE	Urinary tract infection.
Selective tests	
• Urinary antigen	Legionnaire's disease.
• Urine microscopy	Ova of schistosomiasis.
• 'Hot stool' microscopy	Ova, cysts & worms - amoebiasis, giardiasis, intestinal helminthiasis.
• Sputum microscopy & culture	Tuberculosis, pneumonia.
• Serology:	
Viral	Influenza, dengue serology, HIV, viral hepatitis, etc.
Bacterial	Q fever, chlamydia, mycoplasma, brucellosis, syphilis, Lyme disease etc.
Parasitic/helminth	Extra-intestinal amoebiasis (e.g. amoebic abscess), schistosomiasis, strongyloides, filariasis, trypanosomiasis, etc.
• Skin scrapings	Fungal infections, onchocerciasis (skin snip).
• Bone marrow aspirate-microscopy & culture	Visceral leishmaniasis, tuberculosis, trypanosomiasis.
• CSF	Meningitis.
• CXR	Pneumonia, liver abscess.
• Abdominal ultrasound	Abscess.

*None of these abnormalities are pathognomic

Malaria cannot be diagnosed with confidence on the basis of clinical features alone as these are usually non-specific. Immediate diagnosis is essential because falciparum malaria may progress rapidly to complicated disease, which may be fatal.

DIAGNOSIS AND MANAGEMENT OF MALARIA IN GENERAL PRACTICE

Key steps in establishing this diagnosis and managing the patient appropriately are:

- Blood must be taken and sent immediately to the haematology laboratory for examination of a thick and thin film. Delay in transport between the laboratory and surgery should be avoided, and it may be quite appropriate to alert the receiving haematologist to the request.
- The timing of taking the blood sample in relation to a peak of fever is less important.
- A 50% decline in countable parasitaemia can occur within 24 hours of taking the blood[15] and such a decline may make scanty parasitaemia even more difficult to detect. Additionally, delay may lead to deformities of the parasite that may make them unrecognisable to the inexperienced observer.
- If the film is confidently reported as showing *P. vivax*, *ovale* or *malariae*, then treat accordingly with chloroquine (chloroquine base - 600mg or for a child l0mg/kg for the first and second days, 300mg or for a child 5mg/kg on the third day).[16] Currently chloroquine resistance of *P. vivax* is confined to Papua New Guinea[17] ; *P. vivax* and *P. ovale* have hepatic parasites (hypnozoite stage) which are not eliminated by chloroquine. If complete eradication is not undertaken, then relapses of malaria may occur in subsequent months or years. Chloroquine treatment should be followed by primaquine (adult dose 15mg daily; child 0.25mg/kg/daily) for 15 days, or 21 days if *P. vivax* was acquired in S.E. Asia where primaquine resistance is common. Prior to instituting primaquine therapy the Glucose 6 Phosphate Dehydrogenase (G6PD) status of the patient should be checked as severe deficiency may lead to haemolysis. Patients deficient in G6PD may be treated instead with 300mg of chloroquine weekly for six months, or cautiously with primaquine 15mg weekly for four months.
- If there is uncertainty about the malaria species present, the patient should be treated as forfalciparum malaria.
- If the blood film is negative, although the likelihood of imminent progression or complicated disease is less, the film should be repeated on at least three occasions, 12-24 hours apart.
- Review of films by an experienced observer in cases where there is strong clinical suspicion but no diagnosis is crucial, as there is substantial inter-observer variation.
- If any of these steps are not possible or available, or if the patient has definite or possible *P. falciparum*, then the patient should be admitted to hospital for supervised management because of the potential progression of this infection to a complicated disease.
- It is usually advisable to consult the local infection specialist (consultant in infectious diseases) on each occasion.

Hospital management

The general measures that should be instituted are:

- Refer to infection specialist.
- Isolate patient in Infectious Disease Unit (if available) or a side-room in a general medical ward.
- Attend to fluid balance and replacement. Give analgesia.

- Prescribe antipyretics.
- Explain the diagnosis, and reassure patient and his family.

Specific measures

This subject has been extensively reviewed.[16] In the UK, for proven uncomplicated falciparum malaria the treatment of choice is oral quinine (adult 600mg t.d.s, child 10mg/kg t.d.s) for seven days, with either a single stat dose of Fansidar (three tablets for adults, for a child see product literature), or a seven day course of doxycycline (200mg once, then 100mg daily) if there is history of sulphonamide allergy or suspicion of Fansidar resistance (e.g. South-East Asia). Tetracyclines are contraindicated in children below the age of eight years or during pregnancy.

The management of complicated or severe malaria is beyond the remit of this paper. Any patient with impaired consciousness, prostration, parasitaemia of >2%, jaundice, hyperpyrexia or continued vomiting has severe malaria and should be referred urgently to a specialist.[16]

PREVENTION

Prevention of illness in any traveller should remain the priority. For example, avoiding mosquito bites by suitable clothing; use of insect repellents and impregnated mosquito nets are simple and effective measures. They prevent not only malaria but also anthropod-borne viral infections such as dengue fever which is currently hyper-endemic in the tropics and subtropics. Advice about the importance of taking the right type of prophylaxis, for the right duration, including continuing prophylaxis after the trip to cover the incubation period of falciparum malaria, cannot be overemphasised. This kind of information should be obtained from reputable sources - not travel agents, who can be notoriously unreliable.[18]

There is clear evidence that good up-to-date advice on prevention works. Unfortunately, concern about adverse reactions to mefloquine (lariam), a potent and highly effective anti-malarial for chloroquine-resistant zones such as a large part of sub-Saharan Africa including Kenya, has raised travellers' anxieties resulting in many taking no chemoprophylaxis or showing poor compliance. Although there is increasing evidence that mild to moderately severe side-effects, usually neuropsychiatric, are more common with mefloquine (1 in 140), as compared to chloroquine plus proguanil (1 in 1,100),[19] these are usually tolerable, reversible on discontinuing the medication; three-quarters of them occur by the third dose. Therefore, starting therapy two, if not three weeks, before travel is due, may allow their identification before departure as well as enabling adequate steady-state therapeutic concentrations to be reached. Above all if mefloquine is not tolerated, an alternative, albeit less efficacious regimen, must be sought. For example, the chloroquine and proguanil combination appears to provide only 65% protection in areas like East Africa.

Current UK restrictions about use of mefloquine in children and pregnancy are probably overcautious as recent USA recommendations allow mefloquine prophylaxis in the second and third trimester of pregnancy.[20] Regardless of the type of prophylaxis, none of which offers 100% protection, malaria should be still considered in the febrile traveller and the unwell patient must be educated to consider malaria and also to ask an attending clinician to consider this diagnosis!

NOTIFICATION

All the key travel-related infections: malaria; viral hepatitis; typhoid and paratyphoid fever and typhus, are notifiable diseases in Scotland and England and Wales. Once the diagnosis is established or there is a high level of clinical suspicion (even without laboratory confirmation) the diagnosis should be notified to the public health authorities so that accurate epidemiological information on the prevalence and geography of imported infections can be monitored. This is of critical importance if an assessment of the epidemiology of these infections, and the true impact and cost-effectiveness of various preventative strategies are to be made. Currently in the UK, of the key strategies for the prevention of imported infection - antimalarial chemoprophylaxis and vaccination against malaria and typhoid respectively - chemoprophylaxis remains the most cost-effective strategy.[21] The importance of simple hygiene precautions and avoidance of mosquito bites should also be emphasised.

KEY MESSAGES

- Fever in a returning traveller may be the presenting feature of either a tropical infection with malaria, typhoid, hepatitis and dengue fever being the most common, or of a cosmopolitan illness such as respiratory tract or urinary tract infection.
- Pulmonary embolism and drug fever are important non-infective causes of fever.
- Nearly three-quarters of patients who present with fever do so within three weeks of return to the UK.
- A detailed travel history must include any pre-travel vaccination, chemoprophylaxis compliance with recommended dose: this history-taking should be an integral part of the assessment of the febrile traveller.
- The efficacy of all currently available typhoid vaccines is at best 70%: typhoid can occur despite vaccination. These vaccines do not protect against *S. paratyphi*, a common cause of enteric fever in Asia and Eastern Europe.
- The exclusion of malaria should be a priority.
- Falciparum malaria is a medical emergency as in non-immune individuals it may progress rapidly to complications and fatality. All patients with proven or suspected falciparum malaria should be admitted to hospital.
- Initial investigations must include thick and thin blood films for malaria, complete blood count, liver function tests, cultures of blood, urine and stool.
- In the diagnosis of malaria a single film, delay in examining the film and poor observer experience may lead to a false negative diagnosis. Thrombocytopaenia and hyperbilirubinaemia are useful surrogate markers in film-negative malaria.
- Compliance with appropriate malaria prophylaxis is critical in the prevention of malaria.
- Notification of certain imported tropical infections is a statutory requirement in the UK.

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