Continuing Medical Education

FEVER AFTER A STAY IN THE TROPICS

Part 1 : diagnostic approach

E. Bottieau, J. Clerinx, R. Colebunders, A. Van Gompel

INTRODUCTION

Since world-wide travel and migration increased considerably in the last decades, physicians of industrialised countries may face various travel-related health problems or infectious diseases coming from all regions of the world. In 1997, about 650000 Belgian travellers had visited tropical and subtropical regions (1). After a short-term visit to developing countries, 15 % of 7886 Swiss travellers reported health problems, abroad or upon return, and 8 % consulted a doctor (2). In another study, up to 64 % of 784 American travellers experienced some illness during or after their travel, and febrile episodes were reported by 13 % of them (3). In travel clinics, fever represents the second cause of post-travel consultation after diarrhoea and has been reported by 20-37% of sick travellers in 2 observational studies (4,5). The diagnostic approach of fever in travellers usually challenges the attending clinician. First, the possible exposure to tropical pathogens broadens widely the differential diagnosis. In addition, fever and associated symptoms may not be specific enough to allow early diagnosis, or at least early distinction between a minor, self-limited process and a progressive, potentially life-threatening illness. Finally, physicians of European countries may be unfamiliar with tropical infections that the patient may have encountered while travelling.

As the possible causes of imported febrile illnesses are numerous and potentially severe, the clinician needs a logical approach in order to establish promptly an etiologic diagnosis. This article (part 1) describes the prevalence of the different illnesses reported in recent observational studies among travellers returning from the tropics, and discusses the required diagnostic work up for such patients. The second article (part 2) provides an updated knowledge of the most common tropical infections.

CAUSES OF FEVER

Only part of the febrile illnesses in returning travellers is due to tropical diseases. The spectrum of causes and prevalences varies widely according to population characteristics and travel destinations. Although many review articles have addressed the problem of imported fever (6-11), until 2000 only three series have specifically studied this topic (12-14). More recently, several series have been presented or published, and the main results are summarised in table 1 (15-20). Most of them are hospital-based, providing only limited information about the most common diagnoses in an ambulant setting. In addition, the characteristics of these studies vary considerably in terms of design, setting, criteria defin-

Instituut voor Tropische Geneeskunde,
Departement Klinische Wetenschappen,
Nationalestraat 155, 2000 Antwerpen, België

Adress for correspondence :
E. Bottieau
Institute of Tropical Medicine
Nationalestraat 155
B - 2000 Antwerpen
Belgium
Tel. + 32 3 247 64 28
Fax + 32 3 247 64 32
E-mail : EBottieau@poliklin.itg.be

Table 1 : Causes of fever in travellers/migrants

	MAC LEAN (12)	DOHERTY (13)	BASIAK (15)	BOTTIEAU (16)	CASTELLI (17)	LOPEZ-VELEZ (18)	O'BRIEN (19)	ZELLER (20)
Study period	1981-1988		1996-2000	01/04/00-31/03/01	09/98-01/01	1989-1999	01/01/97-31/12/99	01/11/99-30/10/00
Location	Canada	United Kingdom	Poland	Belgium	Northern Italy (multicentric)	Spain	Australia	France
Study design	not mentioned	prospective	retrospective	prospective	prospective	retrospective	retro/prospective	retrospective
Settings	OPD*/hospital	hospital	hospital	OPD*/hospital	hospital	hospital	hospital	OPD*/hospital
Number diagnoses	n = 587	n = 195	n = 197	n = 381	n = 541	n = 448	n = 232	n = 187
Period inclusion after return	(not mentioned)	(not mentioned)	(not mentioned)	12 months	18 months	(not mentioned)	(not mentioned)	12 days
TROPICAL INFECTIONS (%)								
Malaria	32	42	32	32	59	35	27	44
"enteritis"		36	27	19			14	
Bacillary dysentery	4,5	6,5	16	6,5		9,2		6
Dengue	2	6	3,5	1,5		4,9	8	2,5
Enteric fever	2	2	3	2,5		2,8	3	1,5
Amoebiasis				0,3				2
Katayama				2	2	0,7		
Rickettsiosis	1		3	2,5	2	4,5	2	
COSMOPOLITAN INFECTIONS (%)								
Respiratory tract infection	12		6	14,1	6,1	9,1	23	3,75
Urinary tract infection	4		10	4	3,7	2,9	2,5	6,5
Hepatitis A-E	6		2	1	2,2	2,6	3	
Meningitis	1		2	0,3			2	
Tuberculosis	1			2,5	2		0,4	
NON-INFECTIOUS (%)			1,6	0,9		2,8		
UNSPECIFIED (%)	25	25		22	20	20	9	19

OPD : outpatient department

ing fever, and period of inclusion after return. However, despite their differences and/or limitations, they confirm several important conclusions or bring some new insights.

The classic postulate in travel medicine ("first exclude malaria") remains relevant. Malaria represented about one third of all the causes of fever, with an understandable over-representation in hospital-based studies. The lower frequency of malaria in the Australian series (19) is probably related to differences in travel destination (more travellers to Asia). Fever in the returning traveller coming from a malaria-endemic area should then be assumed to be malaria until proven otherwise, even if some other cause seems evident on clinical grounds.

"Febrile enteritis" (after exclusion of malaria) is the other frequent diagnosis. In only a minority of cases, bacillary dysentery will be the cause of this condition. It should be suspected in the presence of white and/or red blood cells at the stool examination. Stool cultures may reveal the etiologic pathogen, mainly *Shigella* spp and *Campylobacter jejuni* in travellers. The other leading tropical causes of fever include enteric fever (typhoid and paratyphoid fever), dengue fever, rickettsiosis, and acute schistosomiasis (Katayama syndrome). They represent together up to 10 % of the diagnoses. The higher prevalence of dengue in the Australian study (19) is also explained by the higher proportion of travellers to Asia, in comparison with European series.

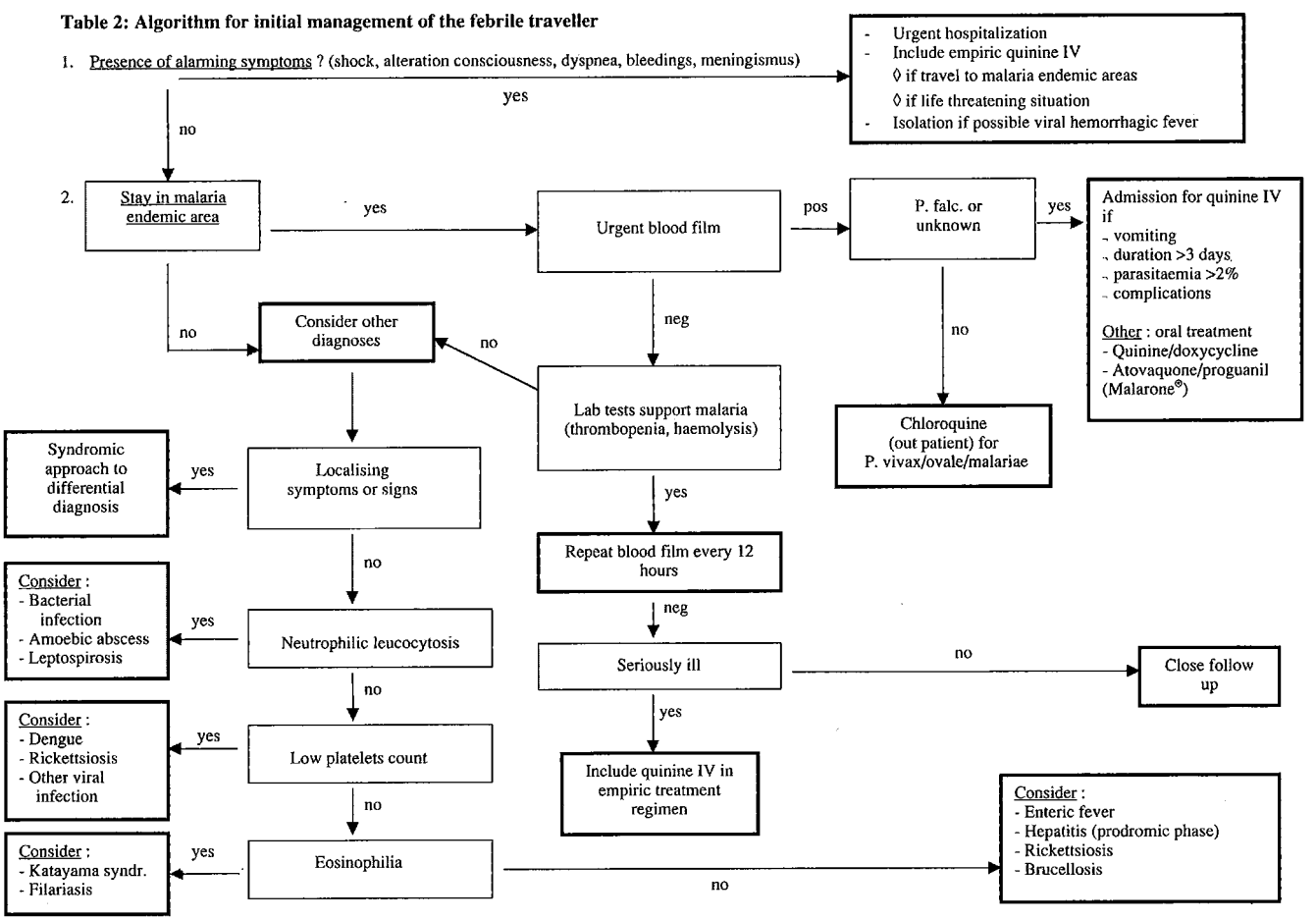
"Cosmopolitan" infections are also frequently observed. This is particularly true for the "respiratory" and "urinary" tract infections. In addition some cosmopolitan infections, such as Q fever, leptospirosis, or legionellosis occur much more frequently in travellers (21-23). The cause of fever remains unspecified in 20-25 % of the patients. These results are quite similar in the different series, despite some discrepancies in the definitions of "unspecified etiologies". The proportion of non-infectious diseases is extremely low in this specific situation. Sometimes travel-related thromboembolic affections may present with fever (personal observations).

When comparing recent studies with historical series, the decrease of hepatitis A as a cause of fever is remarkable, probably due to the availability and wide use of highly potent vaccines (24). Proportion of enteric fever remains low but stable, despite the availability of (less) protective vaccines. For reasons yet unclear, tuberculosis seems more frequently diagnosed than before, and this requires further analysis (25).

DIAGNOSTIC APPROACH

While evaluating a febrile traveller, two priorities have to be addressed: the early diagnosis of infections associated with significant morbidity or mortality if untreated (malaria, typhoid fever, amoebic abscess, meningococcal infections, ...), and the early recognition of transmittable diseases which raise public health concerns (tuberculosis, viral haemorrhagic fevers, meningococcal infections). Algorithms for the differential diagnosis should aim at excluding first these diseases (see table 2, adapted from Magill (7) and Jacobs (26)). A classical 3-step analysis is proposed.

Table 2: Algorithm for initial management of the febrile traveller



MEDICAL HISTORY

A febrile traveller should be questioned as any febrile patient regarding duration of fever, associated symptoms, underlying conditions (diabetes, immunodepression, ...), professional/occupational exposures (health care worker, veterinarian, ...), and sexual risks. For travellers, other specific information is required:

- **Visited areas**
  A detailed travel history is extremely important, and should include location and time of travel, as well as intermediate stops, to identify possible exposure to geographically focal pathogens. Updates on travel-related infections are available on line at the CDC web site: http://www.cdc.gov. under Traveller's' Health.

- **Incubation period**
  It is important to verify if the period between the last day of possible exposure (often the last day of travel) and the first day of fever is compatible with the minimum and maximum incubation time of the suspected diseases. It is a powerful tool in helping to refine and limit the differential diagnosis. If more than 1 month has lapsed since the day of return from a tropical stay, many infections can be excluded. In table 3 are listed the maximum incubation periods of some selected tropical diseases.

- **Vaccination and chemoprophylaxis**
  Information concerning vaccination status and use of chemoprophylaxis is helpful to suspect or exclude certain infections. A diagnosis of hepatitis A or yellow fever is highly improbable in case of adequate immunisation. The correct preventive intake of mefloquine, doxycycline, or the combination atovaquone/proguanil makes the diagnosis of acute *P. falciparum* malaria very unlikely, but can not eliminate it completely.

- **Specific exposures**
  A thorough inquiry of recreational activities during the travel can give sometimes the clue for a diagnosis, in a given clinical context (to name the most important : eating undercooked meat and trichinosis, visiting caves and histoplasmosis, bathing in fresh water and leptospirosis or Katayama fever, a tick bite and African tick typhus or relapsing fever, a tse-tse bite and trypanosomiasis,....). Patients should be questioned about their sexual behaviour during travel, because they may have been at risk of contracting a sexually transmitted infection (27). Some of these infections may present with fever: e.g. secondary syphilis, hepatitis B, primary HIV infection,... Fever in HIV-infected travellers or immigrants requires a specific diagnostic approach (Florence E. et al. *Acta Clin Belg,* in press).

PHYSICAL EXAMINATION

There are unfortunately few physical clues for the diagnosis of most tropical febrile illnesses. Some associated signs (lymphadenopathy, skin rash) can help narrowing the differential diagnosis. Some signs are highly suggestive for certain infections (a tertian or quartan fever pattern for malaria (28), a relapsing fever pattern for borreliosis (29)), or even pathognomonic (an eschar for African tick typhus (30), a trypanoma for east African sleeping sickness (31)). However, in imported pathology almost no diagnosis can be excluded (or asserted) only on clinical grounds. A physical examination is extremely important, as for usual approach, to identify signs of unfavourable prognosis (dyspnoea, impaired consciousness, petechiae, bleeding, hypotension, dehydration,...) requiring hospitalisation and further aggressive investigations. Febrile illnesses with haemorrhagic manifestations should be promptly evaluated for several life-threatening infections (complicated malaria, meningococcemia or other bacteremia, dengue haemorrhagic fever, leptospirosis,...). The possibility of a highly contagious viral haemorrhagic fever must also be kept in mind, in case of travel to endemic areas, and if the incubation period is short (less than 3 weeks) (33).

PARACLINICAL INVESTIGATIONS

The initial work-up in febrile patients returning from the tropics should usually include the following:

1. Complete blood count with differential
   a. Leucocytopenia: dengue and arboviroses, enteric fever, rickettsioses, severe bacteremia, visceral leishmaniasis,...
   b. Leucocytosis: bacillary dysentery, amoebic liver abscess, bacterial infections (respiratory tract, urinary tract, skin,...)

Table 3 : Incubation periods for selected tropical infections

Less than 3 (-4) weeks	Possible longer incubation (>1 month)
Arboviral infections* (Dengue, Yellow Fever, Japanese Encephalitis)	Malaria
Viral haemorrhagic fevers* (Lassa, Marburg/Ebola,...)	Amoebiasis
Rickettsioses* (tick-flea-louse-mite-borne typhus)	Brucellosis
Relapsing fevers* (tropical borreliosis)	Acute schistosomiasis
Hantavirus infections*	Filariasis
Leptospirosis	West-African sleeping sickness
Enteric fevers (typhoid and paratyphoïd fever)	Visceral leishmaniasis
Amoebiasis	Visceral larva migrans
Malaria	Viral hepatitis (A,B,C,E)
Meningococcal infections	Tuberculosis
Bacillary dysenteries	Secondary syphilis
East-African sleeping sickness	HIV infection
Q fever	Fascioliasis/Chonorchiasis
Legionnaire's disease	
Plague	
Trichinosis	
Brucellosis	
Measles	

* usually short incubation (< 10 days)

c. Eosinophilia (> 500/mm3): Katayama syndrome, Loeffler syndrome, acute filariasis, fasciolasis/clonorchiasis,...
d. Thrombocytopenia: malaria, dengue, east African sleeping sickness, visceral leishmaniasis,...

2. Elevation of liver enzymes: hepatitis A-E, enteric fever, yellow fever, Q fever, leptopirosis, CMV/EBV infection, acute HIV infection,...
3. Renal abnormalities: leptospirosis, hantaviroses, complicated malaria,...
4. Blood cultures : enteric fever, meningococcemia, melioidosis, other bacteremia,...
5. Blood smears: malaria, borreliosis, trypanosomiasis, filariasis,...

Other tests are to be considered, depending on associated symptoms, findings on physical examination and exposure history

- Urinalysis (and culture if abnormal sediment)
- Stool examination and culture: bacillary dysentery, amoebiasis, schistosomiasis
- Chest X-rays : pneumonia, pulmonary tuberculosis
- Serologic tests: dengue, Q fever, leptospirosis, viral hepatitis, brucellosis, HIV
- Abdominal ultrasonography: amoebic liver abscess
- Bone marrow aspirate/biopsy: visceral leishmaniasis, disseminated tuberculosis, brucellosis
- Examination of cerebrospinal fluid: bacterial meningitis, Japanese encephalitis,...

CONCLUSION

Physicians facing a febrile patient after a tropical journey may feel uncomfortable because of the wide differential diagnosis. Moreover, patient's complaints are most of the time not specific, and the physical examination is often unremarkable. Malaria should be first and quickly excluded by an appropriate microscopic exami-

nation, because the pre-test probability of malaria in febrile travellers returning from endemic areas is > 30 % in all published series. A reasonable diagnostic approach can then be proposed to the patient according to the exposures, signs, and symptoms (see also the excellent Swiss web site at http://www.fevertravel.ch).

REFERENCES

1. Van Gompel A, Van den Ende J. Import infectious diseases in Belgium. *Acta Clin Belg.* 1998; 53: 245-50.
2. Steffen R, Rickenbach M, Wilhelm U, Helminger A, Schar M. Health problems after travel to developing countries. *J Infect Dis.* 1987; 156: 84-91.
3. Hill DR. Health problems in a large cohort of Americans traveling to developing countries. J *Travel Med.* 2000; 7: 259-66.
4. Nothdurft HD, Loscher T. Imported infections in German travellers returning from tropical countries. Third Conference of the International Society of Travel Medicine, Paris, France, April 26-29, 1993; abstract 39.
5. Wetsteyn JC, Driessen SO, de Vries PJ, Cobelens FG, Kager PA. Tropical diseases and imported disorders in 1763 patients seen at the Outpatient Clinic for Tropical Diseases, Academic Medical Center, Amsterdam (1996-1997). *Ned Tijdschr Geneeskd.* 2000; 144: 2152-6.
6. Felton JM, Bryceson AD. Fever in the returning traveller. *Br J Hosp Med.* 1996; 55: 705-11.
7. Magill AJ. Fever in the returned traveler. *Infect Dis Clin North Am.* 1998; 12: 445-69.
8. Strickland GT. Fever in the returned traveler. *Med Clin North Am.* 1992; 76: 1375-92.
9. Suh KN, Kozarsky PE, Keystone JS. Evaluation of fever in the returned traveler. *Med Clin North Am.* 1999; 83: 997-1017.
10. Humar A, Keystone J. Evaluating fever in travellers returning from tropical countries. *Br Med J.* 4-13-1996; 312: 953-6.
11. Saxe SE, Gardner P. The returning traveler with fever. *Infect Dis Clin North Am.* 1992; 6: 427-39.
12. MacLean JD, Lalonde RG, Ward B. Fever from the Tropics. *Trav Med Advisor.* 1994; 5: 27.1-27.14.
13. Doherty JF, Grant AD, Bryceson AD. Fever as the presenting complaint of travellers returning from the tropics. *QJM.* 1995; 88: 277-81.
14. Klein JL, Millman GC. Prospective, hospital based study of fever in children in the United Kingdom who had recently spent time in the tropics. *Br Med J.* 1998; 316: 1425-26.
15. Basiak W, Kajfasz P. Fever in patients after return from tropical zone. 7th Conference of the International Society of Travel Medicine. Innsbruck, May 27 - 31, 2001; abstract PO12.06.
16. Bottieau E, Clerinx J, Van Gompel A, Colebunders R, Van Esbroeck M, Vervoort T. Fever after a stay in the tropics. *Clin Infect Dis.* 2001; 33: 1131, Abstract 251.
17. Castelli F, Beltrame A, Scaramuzza L, Saleria N, Bisoffi Z et al. Clinical syndromes associated with fever in the traveler. 7th Conference of the International Society of Travel Medicine. Innsbruck, May 27 - 31, 2001; abstract PO12.09.
18. Lopez-Velez R., Portero J.L., Turrientes M.C., Humar A. Fever in the returning traveler from the Tropics. 7th Conference of the International Society of Travel Medicine. Innsbruck, May 27 - 31, 2001; abstract PO12.05.
19. O'Brien D, Tobin S, Brown GV, Torresi J. Fever in returned travelers: review of hospital admissions for a 3-year period. *Clin Infect Dis.* 2001; 33: 603-9.
20. Zeller V., Didier B, Dos Santos G, Bossi P, Bricaire F, Caumes E. Causes of fever in patients returning from the Tropics. 7th Conference of the International Society of Travel Medicine. Innsbruck, May 27 - 31, 2001; abstract PO12.07.
21. Lever F, Joseph CA. Travel associated legionnaires' disease in Europe in 1999. *Euro Surveill.* 2001; 6: 53-61.
22. Potasman I, Rzotkiewicz S, Pick N, Keysary A. Outbreak of Q fever following a safari trip. *Clin Infect Dis.* 2000; 30:: 214-5.
23. van Crevel R, Speelman P, Gravekamp C, Terpstra WJ. Leptospirosis in travelers. *Clin Infect Dis.* 1994; 19: 132-4.
24. Behrens RH. Travel Trends, Malaria, Typhoid, Hepatitis A morbidity and prophylaxis use against imported infections in the UK: the change between 1991 and 1996. Sixth Conference of International Society of Travel Medicine, Montréal, June 1999. Abstract B09.
25. Cobelens FG, van Deutekom H, Draayer-Jansen IW et al. Risk of infection with Mycobacterium tuberculosis in travellers to areas of high tuberculosis endemicity. *Lancet.* 2000; 356: 461-5.
26. Jacobs M. Imported fever : a survival guide. *J R Soc Med.* 2000; 93: 124-8.
27. Hawkes SJ, Hart GJ. Travel, migration and HIV. *AIDS Care.* 1993; 5: 207-14.
28. Svenson JE, Gyorkos TW, MacLean JD. Diagnosis of malaria in the febrile traveler. *Am J Trop Med Hyg.* 1995; 53: 518-21.
29. Colebunders R, De Serrano P, Van Gompel A et al. Imported relapsing fever in European tourists. *Scand J Infect Dis.* 1993; 25: 533-6.
30. Raoult D, Fournier PE, Fenollar F et al. Rickettsia africae, a tick-borne pathogen in travelers to sub-Saharan Africa. *N Engl J Med.* 2001; 344: 1504-10.
31. Ripamonti D, Massari M, Arici C et al. African sleeping sickness in tourists returning from Tanzania: the first 2 Italian cases from a small outbreak among European travelers. *Clin Infect Dis.* 2002; 34: E18-22.
32. Florence E, Bottieau E, Lynen L, Colebunders R. Patients with HIV infection and fever : a diagnostic approach. *Acta Clin. Belg.* 2002; 57 (4) : 175-81.
33. Colebunders R, Van Esbroeck M, Moreau M, Borchert M. Imported Viral Haemorrhagic Fever with a potential for person-to-person transmission : review and recommendations for initial management of a suspected case in Belgium. *Acta Clin. Belg.* 2002; 57 (5) : 233-40.