CHAPTER 5

Tropical Fevers: Part A. Viral, bacterial, and fungal

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1. INTRODUCTION

Pyrexial illness is a presentation of many diseases particularly associated with tropical environments, but one should remember that many common infections, such as influenza and tuberculosis, also occur in the tropics or may be acquired *en route* to and from exotic locales. Febrile patients may also have chronic or recurrent medical problems that are unrelated to their tropical exposure, including non-infectious disease e.g. autoimmune or malignant conditions.

In approaching a pyrexial patient, therefore, a general medical history should aim to elicit the presence of any underlying conditions, particularly those associated with increased risk of infections such as diabetes, neoplastic conditions, HIV infection, splenectomy, and pregnancy. The history of the current illness will determine the duration (acute or chronic) and pattern, if any, of fever; signs and symptoms which may be important in suggesting possible aetiologies are headache and other central nervous system involvement; myalgia and arthralgia; photophobia and conjunctivitis; skin rashes and localised lesions; lymphadenopathy, hepatomegaly, and splenomegaly; jaundice, and anaemia. The geographic and travel history, both recent and past, is of course of vital importance. The onset of illness in relation to known incubation periods and time of possible exposure can help to include or eliminate various infectious diseases (see Table 1).

The areas visited and the nature of the travel may also be helpful in suggesting the likely exposures, e.g. business travel confined to city hotels has a different risk profile compared to river-rafting adventures. Arthropod bites, sexual exposure, occupational risks, animal contact, and immunization and drug history should be specifically asked about. Recent outbreaks of the severe acute respiratory syndrome (SARS), and current concerns about H5N1 avian influenza, make questions about contact with ‘wet markets’ and live poultry in Asia obligatory in persons with fever and respiratory symptoms. Knowledge of current outbreaks of infectious diseases in various geographic areas may be helpful, and there are such internet-based resources, e.g. ProMED, and WHO Epidemic and Pandemic Alert and Response (http://www.who.int/csr/don/en/).

Some specific exposures and associated infections are shown in Table 2.

Table 1. Usual incubation periods of some febrile infectious illnesses

Short: **≤ 10 days**	**Intermediate:** **7 – 28 days**	**Long:** **> 4 weeks**	**Variable:** **Weeks to years**
Anthrax Arbovirus infections Avian influenza Boutonneuse fever Crimean-Congo Haemorrhagic fever Chikungunya Dengue Histoplasmosis Legionellosis Marburg/Ebola Haemorrhagic fever Meningococcal disease Plague Psittacosis Rat-bite fever Relapsing fever SARS Tularaemia Yellow fever Yersiniosis	Acute schistosomiasis Bartonellosis Brucellosis Ehrlichiosis Hepatitis A, C, E Haemorrhagic fever with renal syndrome Acute Human immunodeficiency virus (HIV) seroconversion Lassa fever Leptospirosis Malaria (falciparum, ovale, vivax) Poliomyelitis Q fever S. American Haemorrhagic fevers Toxoplasmosis Acute trypanosomiasis (East African, American) Typhoid and paratyphoid fever Typhus	Brucellosis Hepatitis B (A, C, E) Leishmaniasis Malaria (malariae) Trypanosomiasis (West African)	Amoebiasis Brucellosis Chronic schistosomiasis Chronic trypanosomiasis Filariasis HIV Melioidosis Systemic fungal infections Rabies Tuberculosis

An initial thorough physical examination is essential, and together with the history, will direct the choice of further radiological and laboratory investigations. A full blood count and examination of blood smears is a nearly obligatory basic investigation. Repeated examination to assess evolution of existing clinical signs, and development of new ones, is important.

Table 3 shows differential diagnoses of important physical findings that may be associated with some febrile illnesses.

Table 4 lists conditions that may be suggested by skin lesions in a febrile patient.

Table 2. Specific exposures and some associated infections

Type of Exposure	Associated infections
Bites	
Mosquitoes	Malaria, dengue, yellow fever, viral encephalitis, filariasis, many arbovirus infections
Ticks	Borreliosis (Lyme disease, endemic relapsing fever), rickettsioses (tick bite fever, typhus, various spotted fevers); Congo-Crimean haemorrhagic fever, Q fever, tularaemia, tick-borne encephalitis, ehrlichiosis, babesiosis
Biting flies	African trypanosomiasis, onchocerciasis, leishmaniasis, bartonellosis, loiasis, sandfly fever
Fleas	Plague, tungiasis, murine typhus
Mites	Scrub typhus, rickettsialpox
Lice	Relapsing fever (epidemic), epidemic typhus, trench fever
Triatomine bugs	American trypanosomiasis (Chagas' disease)
Mammals	Rabies, rat-bite fever, tularaemia, anthrax, Q fever, bite wound infections, simian B virus infection, cat scratch disease
Bats	Rabies (Central and South America only); rabies-related viruses; Nipah and Hendra viruses
Birds	Ornithosis
Fish	Erysipeloid, non-cholera vibrios
Asian 'wet markets' with live animals, poultry	Severe acute respiratory syndrome (SARS); avian (H5N1) influenza
Exposure to rodents and their excreta	Hantavirus infection, Haverhill fever, Lassa fever, leptospirosis, monkeypox, pasteurellosis, campylobacteriosis, yersiniosis
Ingestion	
Water (untreated)	Hepatitis A/E, cholera, noroviruses/calciviruses, salmonellosis, shigellosis, giardiasis, poliomyelitis, cryptosporidiosis, cyclosporiasis, dracunculiasis
Dairy (unpasteurised)	Brucellosis, tuberculosis, listeriosis, Q fever, enteric bacterial infection (*Salmonella* spp., *Shigella* spp., *Escherichia coli, Campylobacter jejuni*, etc)
Raw or undercooked food (meat, fish, vegetables)	Helminth infections (ascariasis, trichinellosis, taeniasis, trichuriasis; cysticercosis; gnathostomiasis, capillariasis, angiostrongyliasis; lung, liver and intestinal flukes), protozoa (amoebiasis, toxoplasmosis); numerous foodborne viruses and bacteria
Freshwater skin & mucous membrane contact	Leptospirosis, schistosomiasis, free-living amoebic infection (*Acanthamoeba* spp., *Naegleria fowleri*, *Balamuthia mandrillaris);* environmental mycobacterial infection (e.g. *M. marinum*)
Sand/dirt/mud skin contact	Hookworm, strongyloidiasis, cutaneous larva migrans, leptospirosis, tungiasis, melioidosis; environmental mycobacterial and fungal infections
Injections, tattoos & body piercing, transfusions, acupuncture	Hepatitis B/C, HIV, malaria, mycobacteria (e.g. *M. fortuitum*, *M. chelonei*)
Sexual contact	HIV (including acute HIV seroconversion illness), hepatitis B/C, syphilis, salpingitis, perihepatitis, herpes, disseminated gonococcal infections; other sexually-transmitted infections are not usually associated with fever

Table 3. Differential diagnosis of physical findings for some infectious febrile diseases

Physical finding	Differential diagnosis
Lymphadenopathy	Plague, HIV, rickettsioses, brucellosis, leishmaniasis, dengue, Lassa fever, infectious mononucleosis, tuberculosis, toxoplasmosis, tularaemia, anthrax, cat scratch disease, melioidosis, West African trypanosomiasis, lymphatic filariasis
Hepatomegaly	Malaria, leishmaniasis, schistosomiasis, amoebic or pyogenic liver abscess, typhoid, hepatitis, leptospirosis, tuberculosis
Splenomegaly	Malaria, leishmaniasis, trypanosomiasis, typhoid, brucellosis, typhus, dengue, acute or chronic schistosomiasis, tuberculosis, toxoplasmosis, tularaemia, anthrax
Jaundice	Hepatitis, malaria, leptospirosis, relapsing fevers, cholelithiasis, pancreatitis, etc (see Table 9)
Wheezing	Löffler's syndrome, Katayama fever, tropical pulmonary eosinophilia

Table 4. Skin lesions associated with febrile infections

Skin lesion	Differential Diagnosis
Maculopapular rash	Arboviruses, acute HIV, rickettsiae, secondary syphilis, typhus, bartonellosis, typhoid, rubeola, rubella, scarlet fever, infected scabies, arthropod bites, disseminated gonococcal or meningococcal infections
Petechiae/ecchymoses	Rickettsioses, meningococcaemia, viral haemorrhagic fevers, yellow fever, dengue, leptospirosis, septicaemia and disseminated intravascular coagulopathy
Eschars	Tick bite fever, scrub typhus, anthrax, tularaemia, spider bites
Localised subcutaneous swellings	African trypanosomiasis ('chancre'), Chagas' disease ('chagoma')
Nodules	Onchocerciasis, bartonellosis, leprosy, atypical mycobacteria, erysipyloid, rat-bite fever, erythema nodosum
Vesicles or vesiculopustular lesions	Rickettsialpox, African tick bite fever, parvoviruses, enteroviruses, monkeypox, cowpox, orf, varicella, Sindbis, herpes simplex, herpes zoster
Ulcers	Leishmaniasis, tropical ulcers, anthrax, tularaemia, cutaneous diphtheria, ecthyma, tuberculosis, infected arthropod bites, non-TB mycobacterial infection (e.g. *M. ulcerans*)
Migratory lesions	Strongyloidiasis (larva currens), gnathostomiasis, loiasis, paragonimiasis, sparganosis

Having touched on the general approach to the febrile patient, we turn to viral, bacterial, and fungal diseases that should be considered in a patient with the combination of a febrile illness and tropical exposure. Our emphasis is on rapidly establishing a likely diagnosis, so we will use a syndromic approach, namely, undifferentiated fever, fever and rash and/or arthralgia, fever and hepatitis, haemorrhagic fever, and fever and central nervous system signs. Organism- or disease-specific clinical, laboratory and treatment details will be found in other chapters of this primer or in other texts. Likewise, important parasitic and rickettsial infections are dealt with in other sections of this primer.

2. UNDIFFERENTIATED FEVER

Fever without specific symptoms or localising signs is a common early feature of many infections, and clinical clues to the cause of illness are likely to emerge as time progresses. Frequent clinical re-evaluation is therefore necessary. In the early stages of this process it is important to specifically consider infections that require urgent intervention (malaria, meningococcal disease, typhoid, viral haemorrhagic fever, rickettsiosis, generalised sepsis).

The common causes of undifferentiated fever following tropical exposure are malaria, dengue, rickettsial infections, leptospirosis, enteric fever, and cosmopolitan infections like respiratory, urinary, and gastrointestinal infections. Important early laboratory investigations are blood smears for malaria, a full blood count, urea and electrolytes, blood cultures, urinalysis, and liver function tests. A polymorphonuclear leukocytosis suggests a bacterial aetiology such as leptospirosis, relapsing fever, or common pyogenic infections that are localised (abscess, pneumonia, septic arthritis) and/or generalised (septicaemia). Common organisms (e.g. streptococci, staphylococci, *Candida* spp.) may localise in unusual sites (e.g. heart valves, subphrenic space, bone, prostate, brain) and special imaging techniques (ultrasound, MRI, CT, radionuclide scans) may be required. Neutropenia suggests malaria, viral infections, typhoid, or severe sepsis. Thrombocytopenia frequently occurs in malaria, viral infections including viral haemorrhagic fevers (VHF), and severe sepsis. Eosinophilia suggests invasive helminth infection or drug reaction, but there are many other causes, both infectious and non-infectious. In the context of this chapter, chronic tuberculosis, scarlet fever, histoplasmosis, and bronchopulmonary aspergillosis may all be associated with eosinophilia.

Tables 5 to 7 list some important fungal, bacterial and viral infections that may need to be considered in a patient with an appropriate history. Cosmopolitan conditions like influenza, tuberculosis, pneumococcal and other respiratory infections, sexually transmitted and urinary tract infections, and childhood viral exanthems are not listed, but should be kept in mind, as previously mentioned.

Table 8 lists frequent HIV-associated causes of fever in the tropics.

Table 5. Fungal diseases that may present initially as undifferentiated fever

Fungal disease	Substantiating evidence, caveats, and clinical points	Suggested investigations
Histoplasmosis	History of contact with bird or bat guano, e.g. in caves; acute cough, chest and joint pain; chronic pulmonary form resembles TB; disseminated form usually in AIDS patients	Chest x-ray (diffuse infiltrate in acute form; consolidation and cavitation in chronic); skin or mucous membrane lesion microscopy, culture and histology; bone marrow aspirate culture and histology in disseminated form
Blastomycosis	Mainly in North America, also Africa, India, Middle East; chronic skin, bone and lung disease; clinically resembles TB, actinomycosis or nocardiosis	X-rays of bones and lung; microscopy, culture and histology of pus or biopsy material
Coccidioidomycosis	History of visits to semi-desert areas in Americas; primary infection presents with cough, chest pain, weight loss, spontaneous resolution; prolonged pneumonia and dissemination is risk for the immunocompromised	As for histoplasmosis
Paracoccidioidomycosis	Tropical and subtropical S. & C. America; lung, mucosal, and skin involvement; may disseminate widely throughout viscera	As for histoplasmosis
Penicillium marneffei infection	Confined to China and SE Asia; disease resembles disseminated histoplasmosis; affects both normal and immunocompromised patients	As for histoplasmosis
Disseminated sporotrichosis	HIV is risk factor for disseminated cutaneous infections	Culture, histopathology of biopsy
Cryptococcosis	Meningitis, pulmonary, and disseminated forms occur; HIV is the major risk factor	India ink stain of CSF; latex agglutination, culture; histopathology of biopsies

Table 6. Bacterial diseases that may present initially as undifferentiated fever

Bacterial disease	Substantiating evidence, caveats, and clinical points	Suggested investigations
Enteric fever (typhoid and paratyphoid)	Constipation more common than diarrhoea in early infection; relative bradycardia; normal or low WCC; eosinophils absent; psychiatric symptoms may occur; dry cough is common; splenomegaly; liver enzymes moderately raised	Blood culture; bone marrow culture; urine & stool culture; FBC/diff; liver functions; Widal or TMXY, repeat in a week if necessary, but remember patient may have been vaccinated
Pyogenic liver abscess	Patients generally older than for amoebiasis; diabetes is a risk factor; multiple abscesses more common than in amoebiasis	Amoebic serology, repeat in a week if low/negative; blood cultures; chest X-ray; abdominal CT or MRI or ultrasound scans
Atypical pneumonia (legionellosis, Q fever, chlamydial and *Mycoplasma* infections	Mental confusion, diarrhoea, hypotension, electrolyte disturbances are typical of legionellosis; *Mycoplasma* infections may be complicated by erythma multiforme, haemolysis, arthritis; Q fever: there may be history of animal contact	Chest x-rays; blood cultures; serological tests for atypical pneumonia agents; *Legionella* urine antigen test; U&E and LFTs
Leptospirosis	Early (4-7 days): non-specific flu-like illness, conjunctivitis, myalgia; leukocytosis (unlike viral hepatitis); in later immune phase, serious complications may occur eg jaundice, hepatorenal failure, myocarditis, pulmonary haemorrhage, ARDS	Culture and dark-field microscopy of blood not usually available; serology positive after 5-6 days of illness; FBC/diff; LFTs
Melioidosis	Especially SE Asia, n. Australia; underlying disease, notably diabetes or chronic renal failure; also alcohol abuse, chronic liver or lung disease; short history, septicaemia, metastatic abscesses in lungs, liver, spleen	Blood, sputum, pus culture; chest x-rays; serological test available in some countries
Brucellosis	Ingestion of unpasteurised milk or soft cheese; contact with parturient or aborting animals; meat and abattoir exposure; early illness is non-specific, hepatosplenomegaly may be present; localisation to bone, joints, CNS, genitourinary tract, or heart valves	Blood culture (may take up to 6 weeks to culture); bone marrow aspirate; pus or biopsy culture; serology
Rickettsial infections	Eschars are sometimes not detected in routine examinations; rashless tick bite fever is well described; Q fever does not produce a rash but may present as hepatitis	Weil-Felix test is obsolete; specific rickettsial IFA tests should be requested; Q fever serology; LFTs

Table 7. Viral diseases that may present initially as undifferentiated fever

Viral disease	Substantiating evidence, caveats, and clinical points	Suggested investigations
HIV seroconversion	Injection, transfusion, IV drug abuse, sexual history; presence of palatal petechiae and pleiomorphic rashes	HIVserology: screening and confirmatory tests, especially HIV antigen test
Avian influenza (H1N1)	Specific clinical and epidemiological information must be elicited; see below	See below
Severe Acute Respiratory Syndrome (SARS)	History of close contact with a suspected or probable case of SARS, or travel or residence in an area with recent local transmission, is required for diagnosis. Presents with fever, malaise, cough, dypnoea, which in some cases progresses to respiratory failure; sometimes diarrhoea	Serology, PCR or isolation is done in specialised laboratories only
Viral hepatitis (A-E)	Dietary, blood, injection, or sexual exposure history important; all can present with fever, headache, fatigue, anorexia, nausea, vomiting, abdominal discomfort or pain, dark urine, pale stools, jaundice; subclinical infections common	LFTs; hepatotropic virus serology; herpes virus group, arboviruses, adenoviruses, other viral serology; investigations for bacteria eg leptospires, mycobacteria, rickettsiae; may be indicated
Infectious mononucleosis syndrome	Acute fever, sore throat, lymphadenopathy, fatigue; pharyngeal exudates and petechiae, splenomegaly; mild hepatomegaly, jaundice rare. HIV seroconversion, CMV and toxoplasmosis can cause the same clinical picture	FBC/diff (lymphocytosis, atypical lymphocytes); EBV serology
Q fever	History of animal contact (direct or indirect); febrile illness which may progress to hepatitis and/or atypical pneumonia	Q fever serology; chest X-rays, LFTs
Arbovirus infections	See fever, rash, arthralgia syndrome, below	
VHFs	See VHF syndrome, below	
Rabies/other lyssaviruses	Non-specific prodromal symptoms include fever, headache, myalgia, fatigue, sore throat, gastrointestinal symptoms, irritability, anxiety, insomnia. History of animal exposure	Virus culture or PCR: saliva, CSF, skin, brain biopsy material; IF staining of tissue; seroconversion occurs relatively late
Novel paramyxo-viruses: Nipah (NiV) and Hendra (HeV) viruses	NiV causes severe and often fatal febrile encephalitis; animal hosts are fruit bats, pigs; NiV outbreaks have occurred in Malaysia and Bangladesh; HeV is also found in fruit bats; causes ‘flu-like illness or meningoencephalitis; only 2 fatal human cases of HeV, in Australia	Clinical, geographical, and occupational history important in considering diagnosis. BSL-4 facilities required for lab investigations: RT-PCR, cell culture, ELISA
Poliomyelitis	Nonspecific febrile illness in 10% of infections. Nigeria, India, Pakistan and Afghanistan still have endemic disease; recent imported outbreaks in Namibia, Angola, DRC, Nepal	Seroconversion; isolation of virus from stool

3. AVIAN INFLUENZA

In view of current pandemic fears and the response to the threat, avian influenza is briefly discussed in this separate section. Clinical symptoms and signs are non-specific; hence the importance of the geographic, travel and occupational history in selecting patients for further investigation. The following guidelines are suggested for use in decision making regarding testing of suspected human infection with avian influenza H5N1 during the present phase 3 of the pandemic alert period.

The risk of infection in returning travellers from currently affected countries is very low. All cases that meet the criteria outlined below or in whom advice is required should be discussed with the relevant public health/communicable disease authorities and laboratories, before submitting specimens. For updates on countries currently reporting outbreaks in wild/domestic fowl: http://www.oie.int/eng/en_index.htm

Patients meeting the following criteria should be considered for diagnostic testing.

Any individual with:

Criteria A – Clinical criteria
Clinical signs and symptoms specifically suggestive of **avian influenza (H5N1)** infection in humans:
Fever ≥38^{0}C
AND
≥ 1 of the following:

- Symptoms/signs of lower respiratory tract infection including viral pneumonia
- Watery diarrhoea, vomiting, abdominal pain

AND

Criteria B – Epidemiological risk factors - travel
History of travel within **8 days** prior to onset of symptoms to an area currently affected by avian influenza (H5N1):
For updates: www.who.int/csr/disease/avian_influenza/en/ or http://www.oie.int/eng/en_index.htm
AND
Had **close** contact (**within 1 metre**) with live or dead domestic fowl, wild birds or pigs in any environment including poultry markets OR has been in close contact (touching/speaking distance) with a case of severe respiratory illness/unexplained death in one of the affected areas.

OR
Criteria A AND
At least one of the following:

Criteria C – Epidemiological risk factors - local

- Individual is a health care worker who has treated the above or is part of a cluster of unexplained respiratory illness
- Individual is a laboratory worker who has potential exposure to influenza A (H5N1)
- Individual is working in a veterinary/agriculture team that is directly involved in conducting surveillance for avian influenza in birds

See websites (in box above) for guidelines for collecting and sending human specimens for laboratory investigations for avian influenza.

Table 8. Causes of infectious HIV-associated tropical fevers

Infection	Substantiating evidence, caveats, and clinical points	Suggested investigations
Tuberculosis	Often extrapulmonary or disseminated	Microscopy and culture from site of localisation, if any; blood culture; bone marrow culture
Bacteraemia	*Salmonella* spp. and *Streptococcus pneumoniae* particularly common	Blood culture
Recurrent bacterial pneumonia	*S. pneumoniae* is common	Blood culture
Atypical mycobacteriosis	*M. avium* complex is common	Blood culture, bone marrow
Cryptococcosis	Meningitis and/or disseminated infection including skin involvement	CSF microscopy, culture; blood culture; bone marrow culture, microscopy; blood antigen test
Pneumocystis jirovecii pneumonia	Dry cough, progressive hypoxia are typical; there may be atypical presentation because of concurrent bacterial infection or tuberculosis	Chest X-ray; blood gases; specific identification of the organism in bronchial washings, tracheal aspirate, or induced sputum
Disseminated mycosis	See Table 5	
Cytomegalovirus	Disseminated infection: pneumonitis, retinitis, enteritis, colitis, hepatitis	Virus isolation, antigen detection, PCR on blood, biopsy tissue, respiratory secretions, urine; serology
Toxoplasmosis	Usually reactivation disease; CNS disease (encephalitis) is typical. CNS tuberculosis and tumours are other possible causes of the clinical picture	CT, MRI, brain biopsy; serology
Other tropical opportunistic infections	Includes nocardiosis, bartonellosis, *Rhodococcus* spp., leishmaniasis, disseminated strongyloidiasis	

4. FEVER, ARTHRALGIA AND RASH

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 4). The triad of fever, arthralgia/myalgia and rash is typical of many arbovirus infections. There are more than 500 known arboviruses; more than 150 can affect humans, but only about 26 are important human pathogens. A few (all mosquito-borne) are capable of causing epidemics: Venezuelan equine encephalitis, chikungunya, Ross River, o'nyong-nyong, Mayaro, yellow fever, dengue, Japanese encephalitis, Rift Valley, and West Nile viruses. 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. Most arboviruses cause inapparent or mild infection (fever, flu-like

symptoms). Many present with a characteristic clinical syndrome of fever, headache, arthralgia and/or myalgia, and sometimes a rash. A few are associated with encephalitis or haemorrhagic complications. Table 9 compares some of the common arboviral infections. Recently, epidemics of dengue have occurred in South East Asia, notably in Thailand, Indonesia, and Vietnam, on the Indian sub-continent, and in Central and South America. Dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) are only a risk when subsequent infection with a different dengue virus serotype occurs. The diagnosis of arboviral infections is confirmed during the first week of illness by virus isolation or RT-PCR from blood. Seroconversion may be demonstrated after the first week of illness. Management of arboviral disease is generally symptomatic.

Table 9. Features of West Nile, Sindbis, chikungunya, dengue, and Ross River virus infections

	West Nile	**Sindbis**	**Chikungunya**	**Dengue**	**Ross River**
Geographic distribution	Africa, N. America, Europe, Middle East, India, Russia	Africa, India, SE Asia, Russia, Europe, Australia	Africa, India, SE Asia, Philippines; recently, Indian Ocean islands	Throughout tropics	Australia, S. Pacific islands
Common clinical presentation	Headache, fever, malaise, polyarthralgia, myalgia, rash. Conjunctivitis, retroorbital pain and photophobia may be present. In some infections, arthralgia may persist for months; large and small joints may be involved				
Rash appearance	M/P*, varies from discrete spots to diffuse mottling	M/P or vesicular; pale halo around lesion is typical	Fine, diffuse M/P, spreads centrifugally	Morbilliform, blanching, spreads centrifugally; petechiae may appear	M/P in most patients
Other clinical features	Encephalitis, especially in elderly in N. America		Mild haemorrhagic syndrome: only SE Asia and India	Capillary leakage may lead to DHF* or DSS*	Causes epidemic polyarthritis
***Abbreviations:** M/P = maculopapular; DHF = dengue haemorrhagic fever; DSS = dengue shock syndrome					

5. FEVER AND HEPATITIS

Many of the conditions previously discussed or mentioned in the tables present with febrile hepatitis. Some of the more important ones are shown in Table 10. On the basis of the bilirubin and liver enzyme levels, the illness may fall into one of the categories below; however, mixed pictures can occur. Herpes hepatitis is often particularly severe and rapidly progressive, and may occur in apparently immunologically normal persons; typical mucocutaneous lesions of herpes are usually absent in these cases.

Table 10. Causes of fever and hepatitis or jaundice

Pattern of Jaundice	Diseases
Prehepatic (haemolytic)	Severe falciparum malaria
	Haemoglobinopathies
	Glucose-6-phosphate dehydrogenase deficiency
	Haemobartonellosis
	Haemolytic-uraemic syndrome (*E. coli* 0157; *S. dysenteriae*)
Hepatic	Severe falciparum malaria
	Leptospirosis
	Viral hepatitis A-E
	Typhoid
	Septicaemia, pneumonia, liver abscess
	Relapsing fever
	Yellow fever, other haemorrhagic fevers
	Typhus, other severe rickettsial infections
	Q fever
	Brucellosis
	Epstein-Barr virus infection
	Herpes simplex virus
Posthepatic	Ascending cholangitis
	Common bile duct obstruction
	Cholecystitis: bacterial, cryptosporidial, drug-induced

6. FEVER AND HAEMORRHAGE

Some bacterial infections can present as, or be complicated by, haemorrhage: meningococcal septicaemia, leptospirosis, plague, rickettsial infections, or any severe bacterial sepsis complicated by disseminated intravenous coagulopathy. Urgent clinical assessment and if appropriate, empiric treatment, is essential in managing this syndrome, as rapid progression to severe or fatal disease may occur (especially in meningococcal septicaemia). This discussion will concentrate on viral haemorrhagic fevers (VHFs). In general these are characterised by high death rates and tendency to spread from person to person, but mild (therefore often unrecognised) infections may occur. Some are arboviruses, some are transmitted from animals, and for some, the reservoirs and/or vectors are unknown (Table 11).

General clinical features are a short incubation period (less than 10 days) but may be longer (up to 21 - 35 days) in arenavirus and hantavirus infections. There is often a sudden high fever, severe headache, dizziness, facial flushing, conjunctivitis, muscle pain, lower back pain, prostration; there is sometimes nausea, vomiting, abdominal pain, diarrhoea. Depending on the virus involved, a skin rash appears on days 3 to 10 of illness. This is followed rapidly by easy bruising, vomiting and coughing of blood, epistaxis, haematuria, melaena, ecchymoses, and oozing from needle puncture sites. Disease progresses to hepatorenal failure, coma and death by days 5 to 14 of illness.

Table 12 provides some clinical and laboratory features of selected VHFs.

Table 11. Viral haemorrhagic fevers – epidemiology

Disease in humans	Virus (genus)	Arthropod vector	Vertebrate hosts	Geographical distribution
Lassa fever	Lassa virus (Arenavirus)		Rodents	W. Africa
S. American VHFs (SAHF)	Other arenaviruses		Rodents	S. America
Haemorrhagic fever with renal syndrome (HFRS)	Asian and European hantaviruses		Rodents	Asia and Europe
Hantavirus pulmonary syndrome (HPS)	North & South American hantaviruses		Rodents	North and South America
Rift Valley fever (RVF)	Rift Valley fever virus (Phlebovirus)	Mosquitoes	Ruminants	Africa, Madagascar, Arabian peninsular
Crimean-Congo HF (CCHF)	Crimean-Congo HF virus (Nairovirus)	Ixodid ticks	Ruminants, small mammals, ostriches	E. Europe, Asia, Africa
Yellow fever	Yellow fever virus (Flavivirus)	Mosquitoes	Humans and monkeys	S. America, E. and W. Africa
Dengue haemorrhagic fever	Dengue virus 1-4 (Flavivirus)	Mosquitoes	Humans and monkeys	Caribbean, E. and W. Africa, Asia
Omsk HF	Omsk HF virus (Flavivirus)	Ixodid ticks	Rodents	Siberia, Romania
Kyasanur forest disease (KFD)	Kyasanur forest disease virus (Flavivirus)	Ixodid ticks	Unknown	India, Pakistan
Al Kumrah disease	Al Kumrah virus (Flavivirus)	Ixodid ticks	Unknown	Middle East
Marburg disease	Marburg virus (Filovirus)		Unknown (some evidence that bats may be involved)	Africa
Ebola fever	Ebola-Zaire, Ebola-Sudan, Ebola-Ivory Coast (Filovirus)		Unknown (some evidence that bats may be involved)	Africa (Phillipines strain non-pathogenic in humans)

Table 12. Clinical and laboratory features of VHFs

Disease	IP (d)	Haemorrhage	Thrombo-cytopenia	Leukocytes	*Organ involvement	Mortality
Lassa fever	5-16	+	+	Normal or increased	R, p, t, e, D	2-15%
SAHF	7-14	+++	+++	Markedly decreased	p, T, E	15-30%
HFRS	9-35	+++	+++	Markedly increased	K, p, e	5-15%
HPS	7-28	+	++	Usually increased	k, P, e	40-50%
RVF	2-5	+++	+++	Variably increased/ decreased	J, r, e, retinitis	50%
CCHF	3-12	+++	+++	Usually decreased	J, p, e	15-30%
Yellow fever	3-6	+++	++	Normal or decreased	J, R, p, E	20-50%
Dengue HF	3-15	++	+++	Usually increased	R, j, p, e	u10-15% t <1%
Marburg, Ebola HF	3-16	++	+++	Variably increased/ decreased	R, J, p, E, d, uveitis	25-90%

***Key -** (Upper/lower case = Major/minor clinical feature): R/r, rash; J/j, jaundice; K/k, kidney disease; P/p, pulmonary disease; T/t, tremor, dysarthria; E/e, encephalopathy; D/d, deafness

Because of their highly infectious nature, VHF viruses pose a risk to medical, nursing, and laboratory staff, and to others who may come into contact with blood, tissue, or contaminated secretions (eg patients' families, mortuary staff). Often, however, VHFs are only suspected after the patient has been treated and investigated for some time. Suspected cases should be barrier nursed in strict isolation, with stringent infection control measures. Likewise laboratory tests should only be done in appropriate biosecurity level laboratories. Detailed information about medical and nursing management of VHF patients, contacts, and outbreaks is outside the scope of this brief review.

In general, treatment is mainly symptomatic: analgesia, intravenous fluids, and blood and coagulation factor replacement. Specific treatment in the form of ribavirin can be offered in cases of Lassa, Crimean-Congo, Rift Valley, and hantavirus infections. However, availability of the intravenous formulation of the drug is limited. Antiviral therapy is most effective if instituted before day 5 of illness.

7. FEVER AND CENTRAL NERVOUS SYSTEM INVOLVEMENT

A wide spectrum of pathogens is involved in this constellation of syndromes, and certain cosmopolitan infections should always be kept in mind regardless of the geographic location or origin of the patient, e.g. meningococci, pneumococci, *Haemophilus influenzae* b, *Listeria monocytogenes* etc, in the case of acute purulent meningitis. Virtually any systemic bacterial or fungal infection can localise in the CNS. Severe headache is a common symptom in many infections, especially malaria, rickettsial infections, typhoid fever and influenza; likewise, feverish patients often have non-specific abnormalities of consciousness, and young children are at risk for febrile convulsions. As before, we bias our information towards some important infections with associations with tropical areas of the world, grouped into the following febrile syndromes: altered mental status without overt CNS invasion; acute meningoencephalitis or aseptic meningitis; haemorrhagic or eosinophilic meningitis; encephalitis; focal CNS involvement; and chronic meningitis or meningoencephalitis (see Table 13). Conditions particularly associated with HIV infection are included.

Table 13. Causes of fever and central nervous system signs and symptoms

Syndrome	Pathogens or diseases	Substantiating evidence, caveats, and clinical points
Altered mental status; neuropsychiatric symptoms	Malaria	Coma is the extreme manifestation; residual neurological damage is uncommon
	Typhoid fever	Neuropsychiatric symptoms are common; may mask the diagnosis
	Typhus (louse-borne)	Delirium, stupor are typical
	Trypanosomiasis (West African form)	Initial stage may show subtle personality change; later, overt signs of chronic meningoencephalitis develop
	Legionnaires' disease	Confusion is common in elderly patients; may be related to electrolyte disturbance
	Brucellosis	Chronic fatigue, amnesia and depression are typical of chronic brucellosis, and may persist after treatment.
Acute meningo-encephalitis (AME) or aseptic meningitis	Arboviral infections: West Nile, St Louis, W. & E. equine encephalitis, Murray Valley, sandfly virus, Rift Valley, Sindbis, dengue, tick-borne encephalitis, and others	Many arbovirus infections are associated with fever and headache but not overt AME; AME is generally mild, but a small proportion of cases progress to more severe encephalitis (see below): older patients are often more prone to develop this.
	Miscellaneous infections	Include mumps, LCM, HIV, secondary syphilis, enteroviruses, mycoplasmas
	Leptospirosis	Aseptic meningitis is typically a feature of the second phase of biphasic illness
	Relapsing fever: *Borrelia duttoni* and related species	Tick-borne form of relapsing fever; also a feature of Lyme borreliosis

	Amoebic AME: *Naegleria fowleri*	Associated with diving in warm surface water; severe purulent AME with a high mortality
	Q fever	Occurs in up to 20% of cases in UK, much less (1%) elsewhere
	East African trypanosomiasis	Much more acute disease than West African form
Haemorrhagic meningitis	Anthrax, plague	Usually secondary to other forms, but occasionally primary; about 30% mortality for both diseases
Eosinophilic meningitis	Acute invasive or ectopic helminthic infections	Angiostrongyliasis, disseminated strongyloidisis, gnathostomiasis, trichinellosis, toxocariasis, ectopic schistosomes or other flukes. Other causes: drug reactions, fungal infections, leukaemia/lymphoma
Encephalitis	Rabies virus; rabies-related viruses cause a similar illness	Non-specific prodrome; acute encephalitis, heralded by headache, anxiety, sensory changes at bite site; excitement, aerophobia and hydrophobia; delirium, paresis, coma. Death in 2-6 days
	Japanese encephalitis virus	Rural; summer epidemics in temperate Asia; endemic in tropical Asia. Fever, headache, stupor, convulsions; polio-like disease in 15%; CFR up 30%, high rate of residual neurological deficit in survivors.
	Murray Valley virus	Limited to n. tropical Australia and New Guinea; similar clinical picture to Japanese encephalitis
	West Nile virus	Severe encephalitis in <1% of cases
	Nipah virus	Causes severe and often fatal febrile encephalitis; animal hosts are fruit bats, pigs; outbreaks of NiV have occurred in Malaysia and Bangladesh
	Cat-scratch disease	Uncommon complication
Focal CNS involvement	Herpes simplex virus	Early onset of seizures and temporal and frontal lobe localising signs
	Brain abscess: amoebic, bacterial, fungal	Variable presentation, depending on localisation
	Rhinocerebral mucormycosis	Typically associated with diabetic ketoacidosis
	Opportunistic CNS infections in HIV/AIDS	Includes toxoplasmosis, TB, cryptococcoma, nocardiosis; CMV retinitis
Chronic meningitis or meningo-encephalitis	*Cryptococcus neoformans, C. gattii*	Typically HIV-associated; *C. gattii* also in immunocompetent persons
	Tuberculosis	Usually primary infection in children in developing countries
	Acanthamoeba spp., *Balamuthia mandrillaris*	Both cause granulomatous amoebic encephalitis: usually associated with HIV
	Coccidioidomycosis	Eosinophilic reaction is common

8. TROPICAL FEVERS ACQUIRED OUTSIDE THE TROPICS

Occasionally, infections are acquired outside their normal geographic distribution in patients with no history of exposure. Although uncommon, these conditions are well described, not least because patients often become very ill and are very extensively investigated before the diagnosis is made. The classic example is airport malaria and its variants (baggage malaria, port malaria, taxi malaria, etc) transmitted by vector mosquitoes accidentally transported out of their normal habitat. 'Airport dengue' has also been described. Blood transfusions and injection needle exposure are other cryptic sources of tropical infections. Medical, nursing, and diagnostic laboratory staff are more obviously at occupational risk. Finally, cases of disease caused by certain pathogens under unusual circumstances may raise the possibility of bioterrorism/biowarfare (e.g. plague, anthrax).

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