CHAPTER

5

Tropical Fevers

Smarajit Banik, Sabyasachi Mukhopadhyay

INTRODUCTION

Tropical fevers are defined as infections prevalent in and unique to tropical and subtropical regions. Some of these occur throughout the year and some are seasonal. Every year different parts of India are affected by different seasonal fevers in the post monsoon period including dengue, malaria, scrub typhus, leptospirosis, typhoid fever and some other fevers leading to very high morbidity and mortality. Most of them are difficult to diagnose due to overlapping clinical presentations, and needs early empiric treatment solely on the basis of clinical evaluation during presentations. However one must remember that many common infections, such as influenza and tuberculosis, common in the tropics and may have atypical presentations confusing the clinicians.

APPROACH TO A PATIENT WITH TROPICAL FEVER SYNDROME

In approaching a acutely ill febrile patient, a detailed medical history should be aimed at eliciting the presence of any underlying conditions, associated with increased risk of infections such as diabetes, neoplastic conditions, HIV infection, splenectomy, and pregnancy. Arthropod bites, sexual exposure, occupational risks, animal contact, and immunization and drug history should be specifically taken. The history of the current illness should pay attention on the duration (acute or chronic) and pattern of fever and geographic and travel history, both within and outside the country, to any specific endemic zone of some particular disease. Absence of a classical pattern of illness should not be counted to rule out any tropical infection (Table 1).

Localizing clinical symptoms and signs are very crucial, clues like headache; altered sensorium, myalgia and arthralgia; confusional states, seizures, photophobia, conjunctivitis; skin rashes and localised dermal lesions; lymphadenopathy, hepatosplenomegaly; jaundice and anaemia (Table 3).

Knowledge of areas with recent outbreaks is very helpful in recognizing the clinical entity. The onset of illness in relation to known incubation periods and event of possible exposure can help to include or exclude various infectious diseases.

Only limited epidemiologic data is available from a few selected centres but the overall experience indicates that common tropical infections are dengue, malaria, rickettsial infections, leptospirosis, typhoid, bacterial sepsis and viral infections.

The tropical infections may be approached in the under the following syndromes.

1. Acute undifferentiated fever: patients with acute onset fever without any localizing signs and symptoms for less than 2 weeks: malaria, dengue, leptospirosis, scrub typhus, typhoid, other common viral infections.
2. Fever with rash / thrombocytopenia: Acute onset fever along with a transient skin rash or exanthems, might have thrombocytopenia (platelet count < 100,000) dengue, leptospirosis, measles, rubella, rickettsial infections, meningococcal infections, malaria (falciparum), other viral exanthems.
3. Fever with ARDS: Acute onset fever with respiratory distress such as SpO_2 <90% at room air or frank ARDS with PaO_2/FiO_2 ratio < 200 : scrub typhus, falciparum malaria, influenza (including H_1N_1), hantavirus infection, meliodosis, community acquired pneumonia.
4. Acute Febrile encephalopathy / Acute encephalitic syndrome: Fever with altered mental status within 7 days of onset of fever.

Table 1: Usual incubation periods of some common tropical fevers

Short (< 10 days)	Intermediate (1 – 4 weeks)	Long (>1 month)	Variable
1. Arbo viral diseases	1. Malaria.	1. Brucellosis.	1. Filariasis.
2. Dengue.	2. Enteric Fever.	2. Leishmaniasis.	2. Brucellosis.
3. Chikungunya.	3. Leptospirosis.	3. Viral Hepatitis (B, E, A, C)	3. Amoebiasis.
4. CCHF.	4. Brucellosis.		4. Melioidosis.
5. Plague.	5. Toxoplasmosis.		
6. SARS.			
7. Tularaemia.			

CCHF: Crimian Congo Haemorragic Fever.

Table 2

Type of exposure	Associated infections
Bites	
Mosquitoes	Malaria, dengue, viral encephalitis, yellow fever, filariasis, many arbovirus infections.
Ticks	Borreliosis (Lyme disease) rickettsioses, Crimian Congo haemorrhagic fever, Q fever, tularaemia, tick-borne encephalitis,
Biting flies	onchocerciasis, leishmaniasis
Fleas	Plague, tungiasis, murine typhus
Mites	Scrub typhus, rickettsial pox
Exposure to rodents and their excreta	Hantavirus infection, Haverhill fever, Lassa fever, leptospirosis, pasteurellosis, campylobacteriosis, yersiniosis
Ingestion	
Water (untreated)	Hepatitis A/E, cholera, noroviruses/calciviruses, salmonellosis, shigellosis, giardiasis, poliomyelitis, cryptosporidiosis, cyclosporiasis, dracunculiasis.
Dairy (unpasteurized)	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), protozoa (amoebiasis, toxoplasmosis); viruses.
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, hepatitis B/C, syphilis, herpes, disseminated gonococcal infections;

I. Encephalitis – HSV, Japanese B, enterovirus, west nile virus.

II. Meningitis- S.pneumoniae, N. meningitides, H. influenzae.

III. Scrub typhus, cerebral malaria, typhoid encephalaopthy

5. Fever with multiorgan dysfunction:

I. Bacterial sepsis, malaria, scrub typhus, leptospirosis.

II. Dengue, Hepatitis A or E with fulminant hepatic failure, Hantavirus infection.

III. Macrophage activation syndrome.

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

I: ACUTE UNDIFFERENTIATED FEVER (TABLE 4)

Fever without any specific symptoms or localising signs is a common early feature of many infections, and clinical clues to the cause of such illnesses are likely to emerge as time progresses. It is important to consider infections that require specific urgent intervention. The common diseases

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

Physical finding	Differential diagnosis
Lymphadenopathy	Plague, HIV, rickettsioses, brucellosis, leishmaniasis, dengue, infectious mononucleosis, tuberculosis,toxoplasmosis, tularaemia, anthrax, melioidosis, lymphatic filariasis
Hepatomegaly	Malaria, leishmaniasis, schistosomiasis, amoebic or pyogenic liver abscess, typhoid, hepatitis, leptospirosis, tuberculosis
Splenomegaly	Malaria, leishmaniasis, trypanosomiasis, typhoid, brucellosis, typhus, dengue, tuberculosis, toxoplasmosis, tularaemia, anthrax
Jaundice	Hepatitis, malaria, leptospirosis, relapsing fevers, enteric fever, dengue.

Table 4: Mentions the common causes of Acute undifferentiated fever

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; organomegaly less common now a days, rose spots in chest and abdomen in second week, caecal gurgling.[6]	Raised transaminases, Blood culture; bone marrow culture; urine & stool culture; leucopenia, Typhidot®, a dot enzyme immuno assay offers simplicity, speed, specificity (75%), economy, early diagnosis, sensitivity (95%) and high negative and positive predictive values.
Leptospirosis	Early (4-7 days): non-specific flu-like illness, conjunctivitis, myalgia in calf and lumbar areas. Remittent fever with headache, leucocytosis, maculopapular rash, lymphadenopathy, organomegaly is variably seen; in later immune phase, serious complications may occur eg. jaundice, hepato-renal failure, myocarditis, pulmonary haemorrhage, ARDS, Interstitial nephritis. arrythmias.	Culture and dark-field microscopy of blood not usually available; serology positive after 5-6 days of illness; prolonged PT(predictor of mortality), thrombocytopenia, elevated CPK with modest transaminase elevation. A loop mediated isothermal system (LAMP) targeting the lipL41 gene is under evaluation.
Melioidosis	Underlying disease, notably diabetes or CKD, alcohol abuse, chronic liver or lung disease; age> 40 are risk factors. Can be localized, septicaemic or chronic. Pneumonia, multiple abcesses in liver, lung, spleen, kidneys, skin and septic arthritis.	Blood, sputum, pus culture; chest x-rays; serological test available in some countries. Anemia, leucocytosis, elevated alkaline phosphatase and transaminases.
Rickettsial infections (scrub typhus)	Prevalent in foothills of Himalayas. Eschars are sometimes not detected in routine examinations; Fever with relative bradycardia, headache, apathy, lymphadenopathy and a dry cough. Maculopapular rash on trunk and extremities, may develop Interstitial pneumonia, ARDS, myocarditis, meningoencephalitis, and AKI.	Weil-Felix test is less sensitive and specific than specific serological tests; specific rickettsial IFA tests, IgM ELISA capture assay is most sensitive and should be requested.
Dengue	Headache, fever with characteristic "Saddleback pattern", malaise, poly-arthralgia, myalgia, conjunctivitis, abdominal pain,retroorbital pain and photophobia may be present. Morbilliform, blanching rash spreads centrifugally; petechiae, echymoses, purpura,bleeding from other mucosa. suspect development of Dengue shock syndrome if restlessness, prostration, hypothermia and narrow pulse pressure develops.	Leucopenia, thrombocytopenia, relative lymphocytosis,, deranged hepatic and renal function tests, prolonged PT. Non-structural protein 1 antigen detection (Rapid card test) – Sensitivity 76-93%, Specificity >98%. • IgM, IgG serology (IgG titer > 1:1280 is 90% sensitive and 98% specific).
Japanese B encephalitis	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.	CSF protein elevated, IgM capture ELISA Serum: sensitivity 85-93%, Specificity 96-98%, CSF: Sensitivity 65-80%, Specificity 89-100%. MRI brain may show involvement of thalamus, brainstem, and basal ganglia.
Malaria	Paroxysm of fever, shaking chills and sweats occur every 48 or 72 h, depending on species. Hepatosplenomegaly. Can be Manifestated as severe malaria: like • Cerebral malaria • Severe anemia • Hypoglycemia • Metabolic acidosis • AKI(serum creatinine > 3 mg/dl) • ARDS • Shock ("algid malaria") • DIC • Hemoglobinuria • Hyperparasitemia (>5%).	Microscopy: Thick smears – parasite detection; Thin smears– species identification Quantitative buffy coat test, Rapid diagnostic tests (RDTs) – histidine rich protein, lactate dehydrogenase antigen based immune-chromatography (Level IA) Sensitivity and specificity > 95%. Malaria ruled out if two negative RDTs.

Table 5: Causes of Fever and rash

Petechial Rash	Maculopapular Rash	Vesiculo-bulous Rash	Urticarial Rash	Erythematous Rash
Dengue Rubella Yellow Fever Atypical Measles. EBV Meningococcaemia Rickettsiosis.	Parvo B 19 Rubeola Enterovirus Rubella Primary HIV Typhoid Chikungunya Leptospirosis Lyme Disease Chlamydia Mycoplasma Meningococcaemia	Parvo B 19 Enterovirus HIV Staphylococcal Gonococcaemia Rickettsial Pox Varicella zoster Herpes simplex Mycoplasma	Adenovirus Enterovirus EBV HBV HIV Mycoplasma Lyme Disease	Enterovirus Streptococcal Staphylococcal Ehrlichiosis

Table 6: 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
	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 AES	Arboviral infections: West Nile, St Louis, dengue, tickborne encephalitis, and others	AME is generally mild, but a small proportion of cases progress to more severe encephalitis. older patients are often more prone to develop this.
	JE Virus.	Rapidly progressing signs and symptoms, residual motor and cognitive disability. High mortality rate observed.
	Miscellaneous infections	Include mumps, LCM, HIV, secondary syphilis, enteroviruses, mycoplasmas.
	Leptospirosis	Aseptic meningitis is typically a feature of the second phase of biphasic illness.
Encephalitis	Rabies virus	acute encephalitis, heralded by headache, anxiety, sensory changes at bite site; excitement, aerophobia and hydrophobia; delirium, paresis, coma. Death in 2-6 days.
	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.
	Herpes simplex virus	Early onset of seizures and temporal and frontal lobe localising signs.

are malaria, dengue, rickettsial infections, leptospirosis, enteric fever.

II: FEVER WITH RASH / THROMBOCYTOPENIA (TABLE 5)

Causes of fever and rash can be life threatening and the extensive differential diagnosis makes the specific diagnosis very challenging. Thrombocytopenia usually occurs due to immune destruction, bone marrow suppression, DIC and sometimes due to hypersplenism. The platelet counts can fall to as low as 5000/mm making the patient predisposed to life threatening bleeding in the central nervous system or from the GIT. Both malaria and leptospirosis can have an associated derangement of the PT and APTT, whereas dengue usually presents with thrombocytopenia only. In a Mumbai study of patients with severe falciparum malaria738% had thrombocytopenia of which 6% required platelet transfusions.

III: FEVER WITH HEPATORENAL DYSFUNCTION

Diseases that can predominantly present with hepatorenal

dysfunction are falciparum malaria, leptospirosis, scrub typhus and hepatitis E or A with fulminant hepatic failure and/or the hepatorenal syndrome. Renal failure in patients with severe malaria presents with oliguria whereas patients with leptospirosis usually have a non-oliguric renal failure with hypokalemia where tubular dysfunction plays the role. Mild jaundice may also occur and common in enteric fever which could be due to hepatitis, cholangitis, cholecystitis or haemolysis. Biochemical changes indicative of hepatitis are have frequently being reported during the acute stage of enteric fever.

IV: FEVER AND CENTRAL NERVOUS SYSTEM INVOLVEMENT

A wide spectrum of pathogens are involved in this constellation of syndromes, and certain cosmopolitan infections should always be kept as differential diagnosis regardless of the geographic location or origin of the patient, e.g. meningococci, pneumococci, Haemophilus influenzaeb, Listeria monocytogenes etc, in the case of acute purulent meningitis. Severe headache is common symptom in many infections, especially malaria, rickettsial infections, typhoid fever and influenza; likewise, feverish patients often have non-specific abnormalities of consciousness. The different patterns can be broadly divided into following CNS febrile syndromes: altered mental status without overt CNS invasion; acute meningoencephalitis or AES; haemorrhagic or eosinophilic meningitis; and encephalitis (Table 6).

TREATMENT APPROACH

The treatment approach should be aimed at achieving a definitive diagnosis as soon as possible, however, it may not always be possible. The prime objective in the emergency room is to stabilize the patient by taking care of the vitals, establishing a patent airway, maintaining oxygenation and a mean arterial pressure to have adequate tissue perfusion. This should preferably be done without any attempts of invasive monitoring as the patients with tropical infections may have associated thrombocytopenia or coagulopathy. Invasive monitoring can be reserved for the very sick and to be performed carefully after baseline laboratory data is available. Due consideration to blood or blood component therapy should be given before taking up invasive procedures. Isotonic fluid is preffered with an aim of maintaining haematocrit <33. Antipyretics and cold sponging should be used for fever control. Paracetamol in the therapeutic dose of 3 to 4 gram per day is safe but higher doses should be avoided. With the availability of antigen based rapid diagnostic kits, ruling out malaria and enteric fever is easy and should be done.Empiric chloroquine/ quinine/ artesunate is not recommended as indiscriminate use may potentiate drug resistance. It is safe to initiate doxycycline and Ceftriaxone which is recommended in indian guidelines also. They are effective in typhus, leptospirosis, enteric fever and acute pyogenic meningitis. However, the patient should be reviewed for alternative diagnosis if patient does not respond to empiric drug therapy in 48 hours.

REFERENCES

1. Singhi S, Chaudhary D, Varghese GM, Bhalla A, Karthi N, Kalantri S, et al. Tropical fevers: Management guidelines. *Indian J Crit Care Med* 2014; 18:62-9.
2. Ashish Bhalla, Mary John; Syndromic Approach to Tropical Infections. Update on Tropical Fever. Association of Physicians of India.
3. Frean J, Blumberg L. Tropical fevers part A. Viral, bacterial and fungal infections. Primer of Tropical Medicine. Ch. 5A. Brisbane:ACTM Publication; 2005. p. 1-18.
4. Rapid diagnosis of typhoid fever : *Indian J Med Res* 2006; 123:489-492.
5. S Jog, R Soman, T Singhal ; Enteric Fever in Mumbai – Clinical Profile, Sensitivity Patterns and Response to Antimicrobials. *JAPI* 2008; 56:237-240.
6. Vatsal M Kothari, Dilip R Karnad, Lata S Bichile; Tropical Infections in the ICU. Review Article. *JAPI* 2006; 54.
7. Rajneesh Joshi, SP Kalantri; Acute Undifferentiated Fever: Management Algorithm. Update on Tropical Fever. API. 1-14.
8. Singh MP, Majumdar M, Singh G, Goyal K, Preet K, Sarwal A, et al. NS1 antigen as an early diagnostic marker in dengue: Report from India. *Diagn Microbiol Infect Dis* 2010; 68:50-4.
9. Guidelines for the Treatment of Malaria. 2nd ed. Geneva: World Health Organization; 2010.