Syndromic Approach to Tropical Infections

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Tropical infections are prevalent in tropical and subtropical regions. These infections are always in consideration when ever a pyrexial episode occurs however one must remember that many common infections, such as influenza and tuberculosis, also occur in the tropics and may have atypical presentations confusing the clinician. 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. These conditions may modify the clinical presentation or accentuate the clinical condition.

Approach to a patient with tropical fever syndrome:

In approaching a febrile patient with an acute onset illness, 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 asked about.The history of the current illness should focus on the duration (acute or chronic) and any specific pattern, of fever. The clinicians should be aware of the fact that classical clinical patterns described in the books may be masked by the use of antipyretics and may be misleading. Absence of a classical pattern of illness should not be considered to rule out any tropical infection. Although history is important clinical examination to elicit signs and symptoms is equally important in suggesting possible aetiologies. Localizing clinical symptoms and signs are important clues like headache; myalgia and arthralgia; photophobia, conjunctivitis; skin rashes and localised dermal lesions; lymphadenopathy, hepatomegaly, and splenomegaly; jaundice, and anaemia. The geographic and travel history, both within and outside the country, both recent and past is of vital importance.

In a vast country like India a knowledge of areas with recent outbreaks can be very helpful in recognizing the clinical entity. The onset of illness in relation to known incubation periods and time of possible exposure can help to include or eliminate various infectious diseases. Table 1 enumerates some of the important tropical illnesses and the incubation periods.

Most of these infections are transmitted by an insect bite, which transmits the infectious agents. With India being the largest tropical region, the prevalence of these infections are increased. Some of these infections are seasonal, particularly during or after the monsoon.

These patients do present to the emergency as an "Acute undifferentiated febrile illness" defined as fever (oral temperature ≥ 101o F) for less than 14 days duration with no signs and symptoms at presentation contributing to the diagnosis.

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

A practical approach is to group the symptoms and signs in a syndromic fashion so as to enable the clinician to have a plan to treat such patients. Although it is anticipated that a syndromic approach would not be able to cover atypical presentations of commonly occurring tropical or non tropical illnesses, yet it can serve as a guide for initiating therapy in a critically ill patient presenting to the emergency.

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
    a. malaria, dengue, leptospirosis, scrub typhus, typhoid, other common viral infections)
2) Fever with rash / thrombocytopenia: Acute onset fever with a transient skin rash or exanthema, with or without thrombocytopenia (platelet count < 100,000)
    a. Dengue, rickettsial infections, meningococcal infections, malaria(falciparum), leptospirosis, measles, rubella, other viral exanthems
3) Fever with ARDS: Acute onset fever with respiratory distress in the form of SpO2 <90% at room air or frank ARDS with PaO2/FiO2 ratio <200.
    a. scrub typhus, falciparum malaria, influenza (including H1N1), hantavirus infection, meliodosis, severe community acquired pneumonia,
    b. diffuse alveolar hemorrhage secondary to tropical infections
4) Acute Febrile encephalopathy / Acute encephalitic syndrome
    a. encephalitis – HSV, Japanese B, enterovirus
    b. meningitis- S.pneumoniae, N. meningitides, H. influenza
    c. scrub typhus, cerebral malaria, typhoid encephalopathy
5) Fever with multiorgan dysfunction
    a. bacterial sepsis, malaria, scrub typhus, leptospirosis
    b. Dengue Hepatitis A or E with fulminant hepatic failure, Hantavirus infection,
    c. macrophage activation syndrome

As is evident that many infections can have an overlapping presentation, a clinician should be aware of the common etiological agents and their epidemiology in the defined geographic region to be able to make a diagnosis and initiate treatment. This would go along way in managing acutely ill patients empirically.

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

Table 2. Important modes and diseases transmitted

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
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

Laboratory investigations

Since many clinical syndrome may have an overlapping presentation, the laboratory investigations should be guided by the local epidemiology and the common infections. In case the clinician is unable to decide, the most life threatening and potentially treatable conditions should be evaluated first. Since the turn around time for laboratory investigations tends to vary and could delay the definite treatment, a conscious decision to empirically treat life threatening infections should be taken while awaiting the alb results. The laboratory tests can then help in scaling down / cutting on the drugs after a particular diagnosis has been ruled out. The details of laboratory tests needed in tropical infections has been discussed in another chapter, however, it is pertinent to mention that a clinician should remember these salient features while sending targeted investigations.

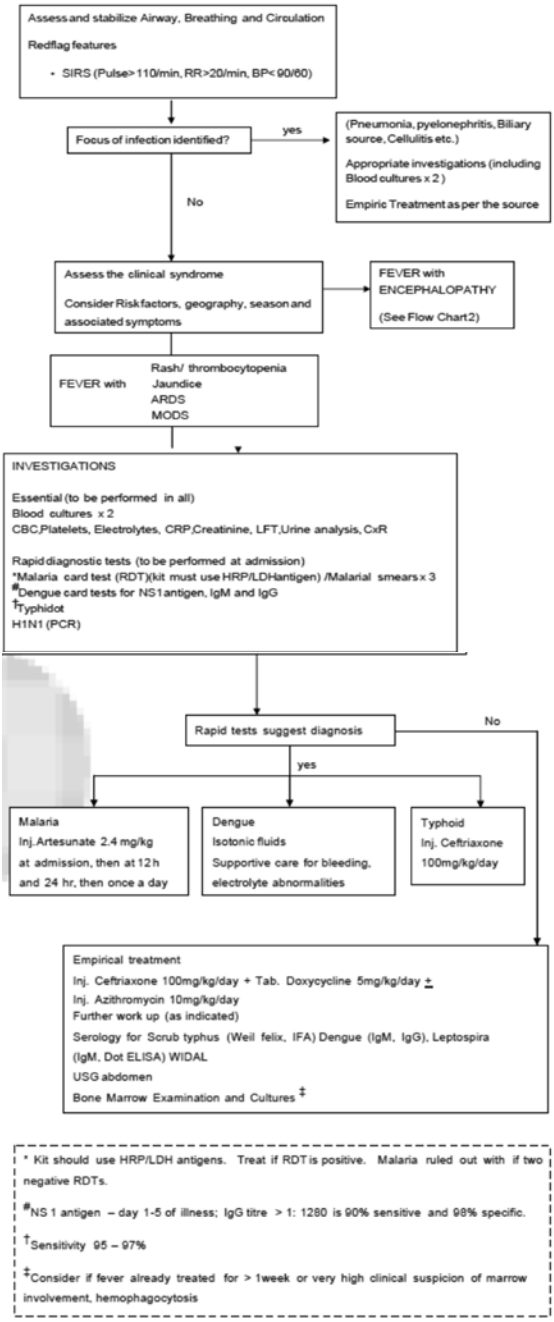
1) Date of onset of fever
    a. NS1 Ag in Dengue: 2-5 days
    b. Blood culture: 1st week in Salmonella
    c. IgM for : Scrub , Dengue , Leptospira, Typhi dot: 2nd week
2) Rapid diagnostic tests / bedside tests
    a. Malaria –Rapid diagnostic test (high negative predicative value
    b. Dengue – NS1 Antigen 9High positive predictive value)
3) Fever with hepatorenal involvement
    a. Rule out malaria; leptospirosis; scrub typhus, Enteric fever
    b. Jaundice after fever : hepatitis A-E with FHF
4) Fever with pulmonary renal involvement
    a. scrub typhus; leptospirosis;
    b. complicated malaria;
    c. Hanta virus; legionella pneumonia
5) Fever with rash
    a. Rickettsial infections, including scrub typhus;
    b. dengue; viral hemorrhagic fevers; chikungunya
    c. leptospirosis;
    d. Purpura fulminance in Meningococcal meningitis
6) Fever with ARDS: (X-ray chest and BAG to confirm the diagnsosi
    a. scrub typhus; leptospirosis, Influenza (H1N1)
    b. Complicated malaria
7) Fever with encephalopathy: NCCT / MRI brain, CSF exam, EEG
    a. Herpes simplex virus, Japanese encephalitis
    b. scrub typhus; typhoid encephalopathy
    c. cerebral malaria
8) Fever with MOD: (Sr Ferritin, LDH, Triglycerides, FDP)
    a. Infective causes: Dengue; malaria; leptospirosis; scrub typhus; Hepatitis A/E with FHF; Hanta virus;
    b. Immunological : Macrophage activation syndrome

It must also be borne in mind that the serological tests have a tendency to cross-react and these interactions should be borne in mind while interpreting the results, a single serological test could be suggestive but to make a definitive diagnosis, a four fold rise in paired / convalescent sera needs to be demonstrated. This may not have great clinical significance but is important from epidemiological purpose.

Treatment strategy

One should always aim for making a definitive diagnosis as soon as possible, however, it may not always be possible to achieve. The first aim in the emergency 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 at invasive monitoring as the patients with tropical infections may have thrombocytopenia or coagulopathy. Invasive monitoring should be reserved for the very sick and performed carefully after baseline laboratory data is available. Due consideration to supportive therapy with blood or blood component therapy should be given before taking up invasive procedures. Isotonic fluid should be advised with an aim of maintaining haematocrit <33. Antipyretics and cold sponging can be used for fever control. Paracetamol in the therapeutic dose of 3to 4 gram is safe but higher doses should be avoided so as to prevent an added drug induced liver insult. With the availability of antigen based rapid diagnostic kits, ruling out malaria is easy and should be done. There is no role of empiric chloroquine/ quinine/ artesunate as indiscriminate use may potentiate drug resistance. With the changing epidemiology of tropical infections it is safe to initiate doxycycline and Ceftriaxone in most cases as they tend to cover up most common treatable infections and have shown to be very effective. They cover typhus, leptospirosis, enteric fever and acute pyogenic meningitis. However, if the patient does not respond to empiric drug therapy in 48 hours, the patient should be reviewed for alternative diagnosis or complications. Table 4,5 and 6 describe the management approach to tropical fevers.

Table 5. Approach to the patients with tropical infections



* Kit should use HRP/LDH antigens. Treat if RDT is positive. Malaria ruled out with if two negative RDTs.

NS 1 antigen – day 1-5 of illness; IgG titre > 1: 1280 is 90% sensitive and 98% specific.

† Sensitivity 95 – 97%

‡ Consider if fever already treated for > 1week or very high clinical suspicion of marrow involvement, hemophagocytosis

Table 6. Management strategy for tropical fever syndrome

Fever with thrombocytopenia	Antipyretics for control of fever IV fluids Avoid aspirin/anticoagulants (Level IV) Watch for bleeding, dyspnea, shock Platelet transfusion if the platelet count<20,000 or clinical bleeding (Level IV) No role of steroids (Level IB) Specific therapy once the diagnosis is established
Fever with jaundice	Antipyretics for control of fever Injection ceftriaxone 2 g IV BD Tablet doxycycline 100 mg BD□ IV fluids Watch for urine output, seizures, encephalopathy, bleeding FFP/cryoprecipitate for bleeding (Level III) Specific therapy once the diagnosis is established
Fever with renal failure	Antipyretics for control of fever Injection ceftriaxone 2 g IV BD* Tablet doxycycline 100 mg BD* IV fluids according to CVP Watch for encephalopathy, bleeding, seizures, ARDS Renal replacement therapy (intermittent HD/CRRT) Specific therapy once the diagnosis is established
Fever with encephalopathy	Antipyretics for control of fever Injection ceftriaxone 2 g IV BD*□ IV acyclovir 10 mg/kg in adults (up to 20 mg/kg in children) intravenously every 8 h IV fluids IV mannitol for raised ICP Watch for seizures Specific therapy once the diagnosis is established
Fever with respiratory distress	Antipyretics for control of fever IV fluids Oxygen by Venturi mask (level IV) Injection ceftriaxone 2 g IV BD* Injection azithromycin 500 mg IV OD* Tablet oseltamivir 150 mg BD, if H1N1 is a possibility (Level IA) Watch for impending respiratory failure, shock, renal failure, alveolar hemorrhage Specific therapy on ce diagnosis is established

□Doxycycline is to be taken empty stomach/1 h before or after a meal. It is contraindicated in pregnant women and young children. *For possible typhoid, leptospirosis and scrub typhus. □For possible bacterial meningitis, typhoid and leptospirosis. FFP: Fresh frozen plasma; CVP: Central venous pressure, ARDS: Acute respiratory distress syndrome, HD: Hemodialysis, CRRT: Continuous renal replacement therapy, ICP: Intracranial pressure

Suggested reading:

1. Singhi S, Chaudhary D, Varghese GM, Bhalla A, Karthi N, Kalantri S, Peter JV, Mishra R, Bhagchandani R, Munjal M, Chugh TD, Rungta N. Tropical fevers: Management guidelines. Indian J Crit Care Med. 2014 Feb;18(2):62-9.
2. Abrahamsen SK, Haugen CN, Rupali P, Mathai D, Langeland N, Eide GE, et al. Fever in the tropics: Aetiology and case-fatality-Aprospective observational study in a tertiary care hospital in South India. BMC Infect Dis 2013;13:355.
3. Chrispal A, Boorugu H, Gopinath KG, Chandy S, Prakash JA, Thomas EM, et al. Acute undifferentiated febrile illness in adult hospitalized patients: The disease spectrum and diagnostic predictors-An experience from a tertiary care hospital in South India. Trop Doct 2010;40:230-4.
4. John TJ, Dandona L, Sharma VP, Kakkar M. Continuing challenge of infectious diseases in India. Lancet 2011;377:252-69.
5. 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. Available from: HYPERLINK "http://www. tropmed.org/primer/chapter%2005a.pdf" http://www. tropmed.org/ primer/chapter 05a.pdf. [Last accessed on 2013 Dec 23]
6. Hai Err , Viroj Wiwanitkit. "Syndromic approach" to diagnosis and treatment of critical tropical infections. Indian J Crit Care Med. Jul 2014; 18(7): 479.

Table 1, 2, 3 adapted from

7. 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.

Table 4, 5, 6 adapted from

8. Singhi S, Chaudhary D, Varghese GM, Bhalla A, Karthi N, Kalantri S, Peter JV, Mishra R, Bhagchandani R, Munjal M, Chugh TD, Rungta N. Tropical fevers: Management guidelines. Indian J Crit Care Med. 2014 Feb;18(2):62-9.