Review Article

Approach to Tropical Infections in India

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ABSTRACT

Tropical fevers are defined as infections that are prevalent in, or are unique to tropical and subtropical regions. These infections are always in consideration whenever 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. In a vast country like India a knowledge of areas with recent outbreaks can be very helpful in recognizing the clinical entity. This article is to focus on most common infections during monsoon on the basis of available epidemiologic data from India. These included dengue hemorrhagic fever, rickettsial infections/scrub typhus, malaria (usually falciparum), typhoid, and leptospira bacterial sepsis and common viral infections like influenza.

Key words : tropical fever, India

Tropical fevers are defined as infections that are prevalent in, or are unique to tropical and subtropical regions. Some of these occur throughout the year and some especially in rainy and post-rainy season. Major Concern about them is, high prevalence and morbidity and mortality caused by these infections, and overlapping clinical presentations, difficulties in arriving at specific diagnosis and need for early empiric treatment.

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.

This article is to focus on most common infections during monsoon on the basis of available epidemiologic data from India with emphasis on appropriate diagnosis and apt management. These included dengue hemorrhagic fever, rickettsial infections / scrub typhus, malaria (usually falciparum), typhoid, and leptospira bacterial sepsis and common viral infections like influenza.

'Syndromic approach' to diagnosis and treatment of tropical infections can help in narrowing down the possibilities and simplifying the treatment. Commonly seen syndromes are undifferentiated fever, fever with rash / thrombocytopenia, fever with acute respiratory distress syndrome (ARDS), fever with encephalopathy and fever with multi organ dysfunction syndrome.

The tropical infections may be approached in the under the following syndromes[1].

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

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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. diffuses 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

These infections should be suspectedin all febrile patients as delay in the institution of specific therapy may lead to increased morbidity andmortality. Since the symptoms of many infections mayoverlap with one another and with severe bacterialsepsis, it may be very difficult to identify theseinfections at the time of presentation.

Localizing clinical symptoms and signs are important clues like headache; myalgia and arthralgia; photophobia, conjunctivitis; skin rashes and localizeddermal lesions(eschar); lymphadenopathy, hepatomegaly, and splenomegaly; jaundice, and anemia[2].

While evaluating these patients review of history (travel, occupation) will be really helpful in deciding differentials diagnosis or ruling out the etiology. The geographic and travel history, both within and outside the country, both recent and past is of vital importance. The other important tool is incubation period of the disease, few of them have very short incubation period while for others it varies up to 3-4 weeks. Based on this data differential can be narrowed down to more specific ones.

Since there is significant overlap between clinical presentation and epidemiological aspect, good clinical judgment and appropriate laboratory investigations are crucial. The turnaround 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 lab results. Things to be kept in mind while ordering labs

1. Time to positivity (NS1 - 2-5 days, blood culture for enteric-max in first week, IGM Elisa-might be negative in early infections due to low antibody levels (false negative).

2. Sensitivity of test and its specificity-sensitivity and specificity for IGM Elisa Scrub typhus □ 90%. While for weilfelix it drops down to 40% [3].

3. False positives and false negatives - 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

Incubation period of common tropical infections-

Short : = 10 days	Intermediate : 7 28 Days	Long : > 4 weeks	Variable : Weeks to years
Arbovirus infections Avian influenza Crimean-Congo Hemorrhagic Fever Chikungunya Dengue Marburg / Ebola Hemorrhagic fever	Hemorrhagic fever with renal syndrome Leptospirosis, Malaria (falciparum, ovale, vivax) Typhoid and paratyphoid fever Typhus	Leishmaniasis Malaria (malariae)	Melioidosis

results, a single serological test could be suggestive but to make a definitive diagnosis, a fourfold rise in paired / convalescent sera needs to be demonstrated. This may not have great clinical significance but is important from epidemiological purpose.

Blood culture remains gold standard for enteric fever. Despite being on prior antibiotics blood culture positivity rates can be as high as 40% if performed by BACTEC method[4].

Yet, most of the time, empiric therapy needs to be initiated at the outset. There can be no uniform guideline for empiric therapy but trends of tropical infections should guide the treating physician. In a sick patient, the idea is to hit wide and hit early with the intention to deescalate once the definitive diagnosis is established. Single patient with two different etiologies at same time is also possible owing to mode of spread and epidemiological aspect of the disease and should be kept in mind while analyzing non resolving fever.

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.

Paracetamol in the therapeutic dose of 3 to 4 gram is safe but higher doses should be avoided so as to prevent an added drug induced liver insult.

Dengue fever -

Common misconceptions about dengue management include blood transfusions and platelet transfusion.

There is no role of prophylactic platelet transfusion in uncomplicated dengue fever[5]. High dose dexamethasone regimen is not effective in achieving a higher rise in the platelet count in the acute stage of dengue fever or dengue shock syndrome[6].

Cases of Dengue fever / Dengue Haemorrhagic Fever (DF/DHF) should be observed every hour. Serial platelet and haematocrit determinations, drop in platelets and rise in hematocrits are essential for early diagnosis of DHF.

Pregnancy and dengue -

Dengue in pregnancy must be carefully differentiated from preeclampsia. An overlap of signs and symptoms, including thrombocytopenia, capillary leak, impaired liver function, ascites, and decreased urine output may make this clinically challenging. If the mother acquires infection in the peripartum period, newborns should be evaluated for dengue with serial platelet counts and serological studies.

Malarial fever -

With the availability of antigen based rapid diagnostic kits, ruling out malaria is easy. Malaria is ruled out if two RDTs are negative. The role of empiric chloroquine / quinine / artesunate in era of rapid diagnostics should be limited as indiscriminate use may potentiate drug resistance.

Anti-malarial drug resistance is a major public health problem which hinders the control of malaria. In India resistance of *Plasmodium falciparum* to chloroquine, the cheapest and the most used drug was first reported in the year 1973 from Diphu of Karbi-Anglong district in Assam state. Resistance to artemisinin compounds has been reported from Myanmar Cambodia border. Hence ACT combination therapy has become the need of hour[7].

ACT recommended by WHO for uncomplicated malaria in children and adult include -

1. artemetherlumefantrine
2. Artesunate - Mefloquine
3. Artesunate - Amodiaquine
4. Artesunate - SP
5. Dihydroartemisinin Piperaquine

In recent phase 4 trial, (AMPQPArterolane Maleate Piperaquine Phosphate) showed comparable efficacy and safety to AL in the treatment of uncomplicated P. falciparum malaria in adolescent and adult patients. AMPQP demonstrated high clinical and parasitological response rates as well as rapid parasite clearance. The drug has been available in India for the last few years[8].

Malaria and pregnancy -

Maternal mortality is approximately 50% in severe malaria, which is higher than non-pregnant adult. fetal death and premature labor are also common. The risks of infant growth restriction and infant malaria infection is maximal when maternal malaria occurs in the 12 weeks prior to delivery. Recurrent malaria is also associated with acute respiratory and diarrhea during infancy.

Artemisinin based treatments are now first line therapy for malaria in pregnancy and are superior to and less toxic than quinine. To prevent malaria in pregnant women and newborn infants, WHO recommends intermittent preventive treatment of malaria in pregnancy (IPTp) with a treatment dose of sulfadoxine-pyrimethamine to be offered at each scheduled antenatal care (ANC) visit (maximum monthly) after the first trimester

However, PREGACT Study Groupand Kakuru *et al*, present new findings to support the use of artemisinin-based combination therapy in both the prevention and the treatment of uncomplicated P. falciparum malaria in pregnancy. Artemether + lumefantrine is associated with the fewest adverse effects and with acceptable cure rates but provides the shortest post-treatment prophylaxis, whereas dihydro artemisinin piperaquine has the best efficacy and an acceptable safety profile[9,10].

Enteric fever -

There is increasing resistance for fluoroquinolonesowing to rampant use across the country. Mic (minimal inhibitory concentrations)for fluoroquinolones are also changing, and should be kept in mind while interpreting culture report. Ciprofloxacin cut-off for susceptibility using disk diffusion was raised from 21 to 31 mm and the MIC value lowered from 1 to 0.06 ìg/mLin CLSI 2012 update[11].

However, on the contrary, MDR s-typhi (resistant to chloramphenicol, amoxicillin and co-trimoxazole) prevalence is low[12]. Until now, extended-spectrum â-lactamase (ESBL) producing S. enterica ser. Typhi strains have been uncommon and have been described only in a few patients of Asian origin and in travelers returning from that region.

Ceftriaxone is an effective drug for treating typhoid, safe to use in children and antimicrobial resistance remains rare. The requirement for parenteral administration is a disadvantage, but the long half-life allows the convenience of once daily administration. Although ceftriaxone is able to penetrate intracellularly, it is slowly bactericidal in vitro against Salmonella Typhi and lacks a post-antibiotic effect (unpublished data). Symptom resolution with ceftriaxone is often slow and the optimum duration of therapy unclear. Short courses of £7 days can lead to unacceptable levels of relapse and regimens of between 10 and 14 days are often recommended.

Azithromycin is another alternative for treating mild-to-moderate enteric fever. It can be given orally, has excellent intracellular penetration and a long half-life allowing once-daily administration. Doses have varied between 10 and 20 mg/kg/day for between 5 and 7 days, and the optimum dose and duration are yet to be determined[13]. It is now widely used for treating typhoid, but there are no validated guidelines for the interpretation of in vitro antimicrobial susceptibility testing[14].

Rickettsial infections -

There is paucity of evidence based on randomized controlled trials for the management of rickettsial diseases including scrub typhus.

Without waiting for laboratory confirmation of the Rickettsial infection, antibiotic therapy should be instituted when rickettsial disease is suspected.

Doxycycline is the drug of choice and it can be used safely even in children below 8 years of age. However, pregnant women, azithromycin or chloramphenicol can be used as alternatives. There is in vitro Antagonism between Cefotaxime and Anti-Rickettsial Antibiotics against Orientiatsutsugamushi, needs further evaluation in vivo studies[15]

Levofloxacin is effective in patients with scrub typhus, but has a longer time to defervescence compared with tetracycline antibiotics. When levofloxacin is used for severe scrub typhus, higher mortality may be attributed to the longer time to defervescence.

Doxycycline and / or Chloramphenicol resistant strains have been seen in South-East Asia. These strains are sensitive to Azithromycin.

Prevention :

Dengue fever - The World Health Organization's Strategic Advisory Group of Experts on Immunization (SAGE) has recommended the use of dengue vaccine to control spread of disease. The WHO has set objectives to reduce dengue morbidity by 25 percent and mortality by 50 percent by 2020. The vaccine has been approved in four countries already, including Mexico and Brazil, which have regulatory authorities recognized by the WHO.

Enteric fever - Two typhoid vaccines are available for use : 1) a Vi capsular polysaccharide vaccine for parenteral use and 2) an oral live-attenuated vaccine. The two currently available vaccines have moderate efficacy in populations where typhoid is endemic. In a systematic review and meta-analysis, the estimated 2.53.0-year cumulative efficacy was 55% (95% confidence interval [CI] = 30%70%) for the parenteral Vi polysaccharide vaccine and 48% (CI = 34%58%) for the oral Ty21a vaccine, each based on a single trial.

Malaria - More than 30 P. falciparum malaria vaccine candidates are at either advanced preclinical or clinical stages of evaluation. 14 Approaches that use recombinant protein antigens and target different stages of the parasite lifecycle are being developed, but only the RTS, S/AS01 vaccine has completed Phase 3 evaluation and received a positive regulatory assessment.

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