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Tropical Febrile Exanthems

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Abstract

Tropic is a region of the Earth surrounding the Equator. Tropical infections have a distinct place among infectious diseases because of their limited geographic location. These infections thrive in the conditions of poverty, crowding, arthropods, rains, heat and humidity in the tropics.

Tropics have mean temperatures above 18^{0}C and vegetation is lush throughout the year. During wet season the rivers overflow their banks and cause floods in tropics. Floods and rains are associated with proliferation of arthropods which transmit malaria, rickettsiosis, dengue, chikungunya, enteric fever, filariasis and floods causing transmission of leptospirosis in tropics.

Current tropical disease portfolio includes dengue, helminths, leishmaniasis, leprosy, lymphatic filariasis, malaria, onchocerciasis, African trypanosomiasis, schistosomiasis, tuberculosis. In addition, there are other tropical infections included in the neglected infections including predominantly rickettsiosis, leptospirosis, neurocysticercosis, hookworms, strongyloidiasis, and trichuriasis.

The adult population in tropics is mostly immune to tropical infections. However these infections are responsible for high childhood mortality, malnutrition and increased morbidity in tropics. Severe cases are seen mostly in children, adolescents, elderly, immunocompromized or the travelers returning from tropics.

Febrile Exanthems

In this review we have focused on the febrile exanthems seen in tropics. The skin color for most people living in tropics is dark and a faint rash is not easily discernible. However, the rash is prominent in children and tourists with fair complexion and thus helps in establishing an early diagnosis in them. The Indian society of critical care medicine, tropical fever group has enlisted few infections that cause fever with rash or thrombocytopenia in tropics: Dengue, rickettsial infections, meningococcal infection, malaria (usually *falciparum*), leptospirosis, measles, rubella and other viral exanthems [1].

Agents

Febrile exanthems in tropics are a common finding in children and are mostly viral in origin. Most of these are self limiting but sometimes become complicated secondary to malnutrition and co-infections. Diagnosis is rarely confirmed because of poor virology and overall healthcare in these countries. Prominent viruses causing febrile exanthems in tropics are measles, rubella, scarlet fever, erythema infectiosum, exanthem subitum, hand foot and mouth disease, varicella, chikungunya and dengue [2]. Among bacterial causes of febrile exanthems prominent ones are rickettsiosis, leptospirosis, Group A streptococcus and Enteric fever. Among protozoa, malaria (*Plasmodium falciparum*) and Leishmaniasis are important cause of febrile exanthema in tropics.

Transmission

Crowding helps in persistent transmission throughout the year. Children and young adults are the commonest victims of tropical febrile exanthems. The transmission agents, reservoirs, and agents for various tropical exanthems are described in Table 1.

Epidemiology

Viral exanthems are common but self-limiting in tropics without serious complications. Herpes simplex infections occur everywhere and have no seasonal variation with highest seroprevalence seen in tropics [3]. Varicella and rubella mainly affect children between 3 and 10 years of age, both being transmitted by droplet infection [4]. Human herpes virus 6 (HHV6) and Epstein–Barr virus

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Table 1: Vector, agent, and reservoirs for various tropical exanthems.

Disease	Vector	Agent	Reservoir
Malaria	Anopheles species	Plasmodium species	Man
Dengue	Aedes species	Arbovirus Group B	Man
Chikungunya	Aedes species	Arbovirus Group A	Man
Yellow fever	Culex vishnui group	Arbovirus Group B	Man/Monkeys
Cutaneous Leishmaniasis	Lutzomya species	Leishmania major	Man/mammals
Enteric fever	M. domestica	Salmonella typhi Salmonella paratyphi A & B	Man/animals
Murine typhus	Xenopsylla species	Rickettsia typhi	Rodents
Epidemic typhus	Pediculus humanus	Rickettsia prowazeki	Man
Scrub typhus	Leptotrombidium deliense	Orientia tsusugamushi	Rodents
Rickettsial pox	Allodermanyssus sanguineus	Rickettsia akari	Rodents
Leptospirosis	Soil, flood, water, urine	Leptospira species	Rodents, cow, dog, pig, other animals
Scarlet fever, erysipelas, impetigo, ecthyma, cellulitis, streptococcal toxic shock syndrome, and rheumatic fever	Sputum, saliva, close contact	Group A streptococcus	Children

Table 2: Characteristic features of Rash in febrile patients.

Feature	Types	Disease
Visible Appearance	Macular	Rickettsiae, viral fevers, dengue, chikungunya
	Maculopapular	Rickettsiae, chikungunya, leptospirosis, dengue, secondary syphilis, viral fevers,
	Urticarial	Invasive schistosomiasis
	Hemorrhagic (peticheae, purpura)	Meningococcemia, dengue, influenza
Hallmark rash	Eschar	All rickettsiae except epidemic and endemic typhus
	Erythema chronicum migrans	Lyme's disease
	Erythema marginatum	Rheumatic fever
	Ulcers on face, arms and legs	Cutaneous leishmaniasis
	Chinese letter pattern	Meningococcemia
Time of appearance	First day of fever	Measles
	Second day of fever	Scarlet fever
	Third day of fever	Rubella
	Fourth day of fever	Staphylococcal scalded skin syndrome
	Fifth day of fever	Erythema infectiosum
	Sixth day of fever	Exanthem subitum

(EBV) infections also affect young children and by the second year, almost 100% children are seropositive for HHV6 [4]. These viruses are transmitted by contaminated saliva. Enteroviruses, occur round the year in tropics, are highly contagious and are transmitted by close contact with infected individuals. Epidemics of hand foot and mouth disease (HFM) are common and are caused by Coxsackievirus A16 or Enterovirus 71 [4]. Parvovirus B19 infections cause erythema infectiosum in children between 4-10 years and occur mainly in winter and spring transmitted via respiratory droplets [4].

Group A streptococcal infection is very common in children and can cause scarlet fever, erysipelas, impetigo, ecthyma, cellulitis, streptococcal toxic shock syndrome, and rheumatic fever [5]. The larger epidemics of meningococcemia serogroups A have affected mainly the cities of northern India with a marked seasonality which is similar to Africa. Epidemics occur in winters and highest incidence is seen in children younger than 5 years with a second peak between 15 and 24 years [6].

Among the emerging and re-emerging infections causing febrile exanthema in tropics rickettsiosis, dengue, malaria, leptospirosis, leishmaniasis and chikungunya are now endemic in most parts of India and other tropical countries.

In India, rickettsial infections are reported from Maharashtra, Tamil Nadu, Karnataka, Kerala, Jammu and Kashmir, Uttaranchal, Himachal Pradesh, Rajasthan, Assam and West Bengal [7]. Similarly Dengue has now been reported from Delhi, Punjab, Haryana, Uttar Pradesh, Andhra Pradesh, Tamil Nadu, Kerala, Kolkata, Andaman and Nicobar islands, Maharashtra, Rajasthan, Bihar, Assam, Nagaland, Gujarat, Karnataka and Madhya Pradesh [8]. All 4 serotypes of dengue have been reported from Delhi, Punjab and Tamil Nadu while from other parts of India only one or two of the four serotypes have been reported [8].

Chikungunya infection was first reported from Tanzania in 1952-53 and spread subsequently to sub-Saharan Africa, South East Asia and Pacific causing large epidemics [9]. The virus exists in three genotypes, the Asian, West African and East Central South African that are responsible for outbreaks in the respective areas. The first

Table 3: Prominent clinical features suggestive of a particular infection [20,25].

Clinical or lab parameter	Most likely febrile exanthema
Arthralgia	Chikungunya, Dengue
Myalgia	Leptospirosis, Dengue, Rickettsiosis
Meningoencephalitis	Rickettsiosis, Malaria, Leptospirosis, Tuberculosis
Splenomegaly	Malaria, Enteric fever
Thrombocytopenia	Dengue, Leptospirosis, Rickettsiosis
Hyperbilirubinemia without hepatitis	Leptospirosis, Malaria
Leucopenia	Dengue, Enteric fever
Eosinophilia	Schistosomiasis
Creatinine Kinase	Leptospirosis
Acute Kidney injury	Leptospirosis, Rickettsiosis, malaria, influenza
Acute lung injury, Acute respiratory distress syndrome (ARDS)	Rickettsiosis, Leptospirosis, Tuberculosis, Influenza, Malaria

Table 4: Recommended tests for tropical exanthems.

Disease	Tests available	Interpretation
Rickettsiosis	Weil Felix test, IgM ELISA for scrub typhus, IgM ELISA for spotted fever group, PCR, Immunofluorescence assay (IFA)	Weil Felix: OXK for Scrub typhus >1:80 OX19 for Endemic typhus >1:80 OX2 for Spotted group >1:80 Gold Standard: IFA
Dengue	NS1 antigen based kits, IgM ELISA, PCR	Easy to use in field (immunochromatographic) Gold Standard:
Malaria	Malaria card tests (HRP/LDH antigen), Malaria slide test, IFA, PCR	Easy to use in field (immunochromatographic) Gold Standard: Microscopy
Leptospirosis	IgM ELISA, Faine's criteria, PCR, Microagglutination test (MAT)	No rapid tests available commercially Gold Standard: MAT
Enteric Fever	Widal Test, Typhidot, blood culture	False positive Widal result is common Gold Standard: Blood culture
Leishmaniasis	Parasite detection (bone marrow, lymph nodes, splenic aspirate), rK39 immunochromatographic test	Gold Standard: Leishmaniasis culture from aspirate
Chikungunya	IgM ELISA, PCR	Gold Standard: Virus isolation

outbreak in Asia was in Bangkok in 1958 followed by other Asian countries [9]. India experienced massive outbreaks of CHIK in the 1960s and early 70s mainly in cities. After a gap of 32 years an explosive outbreak of CHIK devastated the country affecting more than 1.4 million people in 13 states [9]. Indian states endemic for chikungunya are West Bengal, Tamil Nadu, Kerala, Andaman and Nicobar Islands, Maharashtra, Andhra Pradesh, Karnataka, Gujarat, Madhya Pradesh, Delhi, Rajasthan, Pondicherry, and Goa [9].

Leptospirosis is now endemic in all countries in the South-East Asian region. The Indian states endemic for Leptospirosis include Tamil Nadu, Kerala, Andaman and Nicobar Islands, Gujarat, Andhra Pradesh, Maharashtra, Delhi, and Goa. It has emerged recently in the Northern parts of India including Himachal and Punjab [10].

As far as malaria is concerned, 95% of Indian population lives in malaria risk prone areas. In most parts of India, 90% malaria is unstable with relatively low incidence but with a risk of increase in cases in epidemics from every 7-10 years. The factors responsible are immune status of the population, rainfall, mosquito breeding etc. In North-East India, malaria is transmitted throughout the year. Intermediate level is maintained in Andhra Pradesh, Gujarat, Jharkhand, Madhya Pradesh, Chhattisgarh, Maharashtra, Odhisha, and Rajasthan [11].

Co-infections are not uncommon in the tropics. The same mosquitoes are responsible for transmission of dengue and chikungunya i.e. *Aedes aegypti* or *Aedes albopictus*. Co-infection of dengue and leptospirosis was reported in 63 individuals from Andhra Pradesh [12]. The same person can be infected with more than one infection from leptospirosis, dengue, malaria, rickettsiosis, chikungunya.

Emerging and Re-emerging Tropical Fevers

Rickettsial infections are one of the leading re-emerging infections in tropics. Rickettsiosis is becoming increasingly recognized as causes of febrile illness in travelers also. The re-emergence has been linked to a shift in the antibiotic usage in these countries. Over past few decades, usage of fluoroquinolones and cephalosporins has made doxycycline and Chloremphenicol unpopular agents for common febrile illnesses. This has led to widespread re-emergence of rickettsial infections in India and other South-east Asian countries [13]. In South and Central America, infection with *Rickettsia rickettsii* continues to have severe consequences. Resurgence of Mediterranean spotted fever in Bulgaria highlights the threat of rickettsial infections when there is a lapse in vector and reservoir control. Similar to African tick-bite fever, *Rickettsia parkeri* is an emerging cause of eschar-associated infection in Brazil, Argentina, and Uruguay [14].

Dengue is emerging in countries with no previous reports and is re-emerging among countries where it had disappeared for > 20 years [15]. Factors that lead to increased local outbreaks of dengue include rapid urbanization, lack of vector control, basic infrastructure failures (e.g. waste disposal), and lack of hygienic household water storage [16].

Chagas disease is another important emerging disease. It is spreading beyond its endemic region i.e. Latin America and is estimated to impact 10 million people worldwide such as Europe, USA, Canada, Australia, and Japan [17].

Characteristics of Rash

Many types of rash can occur with febrile illnesses in the tropics. Most common rash is maculopapular eruptions all over the body. It is difficult to find out the exact illness causing such a rash from its appearance only. But some characteristic features of rash that may help in the diagnosis are given in Table 2.

Febrile Exanthems in Travelers

Travelers to the tropics are exposed to all types of viral and non-viral infections. Some infections are increased in incidence during wet season (monsoon and post monsoon) due to proliferation of arthropods e.g. enteroviruses, malaria, rickettsiosis, leptospirosis, dengue, chikungunya, and typhoid. Viral exanthems are in circulation amongst children all year round and can thus be transmitted to the travelers any time of the year.

Overall, 3% to 19% of travelers to the developing world will return with fever or will develop fever within weeks of their return [18]. When evaluating a traveler with fever, it is important to know the pre-travel immunizations the patient has received, the medications taken during travel, the areas visited, the likely exposures and the incubation period between travel and onset of fever. A physical examination should include a search for focal findings that may narrow the list of possible infections. Fever compatible with a common illness that occurs in the native country should always be considered e.g. infectious mononucleosis. Not all infections acquired in tropics are tropical infections. In one study, only 36% of the diagnoses were tropical infections mainly malaria, schistosomiasis, amebiasis, gastrointestinal disorders caused by intestinal nematodes, and dengue fever [19]. Among febrile exanthems acquired during stay in Indian Ocean, Africa, and Asia, the 3 main etiologies were chikungunya (35%), dengue (26%), and African tick bite fever (ATBF) (10%) [20].

Knowledge of prevalent tropical infections in various geographical regions is important to narrow down the possible infections in a returning traveler from tropics. Coastal regions in South-east Asia have Leptospirosis, Scrub typhus, and Malaria as endemic infections and transmission may occur all year round.

Clinical Features of Tropical Febrile Exanthems

It is quite challenging for the primary physicians to differentiate the cases of febrile exanthems requiring antibiotic treatment in early stages from the much commoner viral fevers, which can be managed by conservative therapy. Febrile exanthems are thus being overtreated with unnecessary use of antibiotics [21].

Whereas most tropical infections are easily treatable in early stages with proper diagnosis and treatment, but they become life threatening with a delay of 5-7 days without treatment e.g. rickettsiosis, meningococcemia, leptospirosis, falciparum malaria, influenza and typhoid, Precious 4-5 days are lost in local consultation before the patient is seen by a qualified doctor in these countries. The diagnosis becomes difficult once multi-organ dysfunction syndrome (MODS) has set in. Empirical combination treatment of locally prevalent infections is then the only choice pending the results of investigations. However, some clinical features may help in diagnosis. (Table 3) Many patients with tropical febrile exanthems present with classical clinical syndromes [22].

Classical syndromes:

- Fever and thrombocytopenia: Dengue, malaria and leptospirosis
- Coagulopathy: Leptospirosis and viral hepatitis.
- Hepatorenal syndrome: Leptospirosis, scrub typhus and falciparum malaria.
- The pulmonary renal syndrome: Falciparum malaria, leptospirosis, Hantavirus infection and scrub typhus.
- Fever with altered mental status: Tubercular or bacterial meningitis, cerebral malaria, leptospirosis, scrub typhus, typhoid encephalopathy and fulminant hepatic failure due to viral hepatitis.

Clinical Tips Helpful in Diagnosis

1. Eschar: Don't expect it to be present on exposed parts. Mostly seen in the axilla, groin, undersurface of breast, upper arms back, and lower abdomen. It is a single, blackish crusted lesion with surrounding erythema (Figure 1). It is important to know that patients are unaware of its existence because of its painless and non-pruritic nature.

2. Conjunctival suffusion and facial swelling: suggestive of rickettsial infections and leptospirosis.

3. Adherent tick: Recent history or upon physical examination at admission, if an adherent tick is found on body, think of rickettsial infection even in absence of an eschar.

4. Deep jaundice: Either malaria or leptospirosis. In both conditions, the liver enzymes are not raised more than 5 times, differentiating them from viral hepatitis.

5. Hepatorenal failure: Most prominent in leptospirosis. Other causes may be rickettsiosis and malaria.

6. Tuberculosis must always be kept as a likely possibility in tropics in all sick patients who are not responding to treatment.

7. The classical third or fourth day fever may not be present in malaria in the local population because of repeated infections, partial immunity, and use of antipyretics.

8. A person developing massive hemoptysis (> 200ml in single bout) on 3rd to 5th day of fever may be suffering from hemorrhagic form of Leptospirosis. Andaman and Nicobar Islands and Gujarat have reported cases of hemorrhagic forms of Leptospirosis. Patients usually collapse on 4th or 5th day of illness, in absence of an early treatment with penicillin or cephalosporins. We do not have any good tests to diagnose of Leptospirosis in first 3-4 days.

9. Raised creatinine kinase levels may favor Leptospirosis.

Lab Diagnosis

Diagnosis of febrile exanthems in the residents from tropics needs a different approach compared to the travelers because, the repeated infections result in persistent antibodies in them for many infections, so serology is often misleading because of cross reactivity. Research based knowledge of cut-off titres for various serological tests for local population can help in correct interpretation of the results. Various tests available for tropical exanthems are given in Table 4.

Treatment

Treatment depends upon the diagnosis but some patients

present late with MODS when classical picture may not be found. Subtle differences in features of the organ failure exist among these infections. History is often unreliable and self medication is common in tropics. Treatable life threatening illnesses need to be covered in such circumstances, which include malaria, leptospirosis, rickettsiosis, enteric fever, influenza and tuberculosis. Injectable Cephalosporins (Ceftriaxone) will take care of Leptospirosis and enteric fever. Oral Doxycycline will take care of all rickettsial infections.

A practical approach is to use a combination of injectable ceftriaxone and oral doxycycline, which covers all of the treatable tropical infections except malaria, viral fevers, and tuberculosis. Rapid diagnostic tests (RDT) are helpful in making a quick diagnosis of malaria and tuberculosis is a diagnosis of exclusion. Falciparum malaria needs treatment with Artimesinin based injectable agents.

Treatable Infections

Rickettsiosis: First line treatment is Doxycycline 100 mg BD for 7 days (Level IA): Second line treatment is azithromycin or rifampicin or chloramphenicol as alternatives in children and pregnant women. (Level IIB) [1].

Leptospirosis: First line treatment is penicillin G 1.5 MU 6 hourly for 7 days (Level IA). Alternatively, 3rd generation cephalosporins are equally effective. Oral doxycycline is effective in uncomplicated infections, if given very early [1].

Malaria: Drug of choice for complicated falciparum malaria is injectable artesunate (Level IA) 2.4mg/kg i.v. bolus at admission, 12h and 24h; followed by once a day for 7 days + Doxycycline 100mg p.o. 12 hourly. Alternatively we can give quinine 20mg/kg loading dose, followed by 10mg/kg i.v. infusion 8 hourly + doxycycline 100mg p.o. 12 hourly. Clindamycin is recommended in place of doxycycline in pregnant women and children. (Level IA) Exchange transfusion is a treatment option for parasitemia > 10%. (It is not recommended with artesunate, Level IIA) [1].

Enteric fever: First line treatment is ceftriaxone i.v. 50-75 mg/kg/day for 10-14 days (Level IA) to cover MDR S. typhi. Alternatively, azithromycin 1gm OD and ciprofloxacin may be given. Consider dexamethasone 3mg/kg followed by 1mg/kg 6 hourly for 48h in selected cases with encephalopathy, hypotension or disseminated intravascular coagulation (Level IB) [4].

In addition, a good critical care support is the key to recovery from MODS due to all types of infections. It includes fluid and nutritional support, blood products like platelets, ventilatory support for ARDS, and vasopressors.

Research for Tropical Diseases

Only about 1% of newly developed drugs are for tropical diseases, such as African sleeping sickness, dengue fever, and Leishmaniasis [23]. While patent incentives and commercial pharmaceutical houses have made Western health care the envy of the world, the commercial model only works if companies can sell enough patented products to cover their research and development (R&D) costs. The model fails in the developing world, where few patients can afford to pay patented prices for drugs. Grants and patent incentives were never designed with tropical diseases in mind [24]. An "open source," approach to drug development, called the Tropical Diseases Initiative (TDI) as a decentralized, Web-based, community-wide effort where scientists from laboratories, universities, institutes, and corporations could work together for a common cause has been suggested to increase research for tropical diseases [24].

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