Review Article

Clinical Recommendations on the Management of Seasonal & Acute Febrile Infections

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Objective : Acute fever with multisystem illness is endemic in South Asia and in cases where the cause is unknown; treatment is done with generic antipyretics and antibodies. This has led to compromised clinical decision-making, since evidence-based data on fever is unavailable in the tropical region. There is a dearth of diagnostic facilities, which acts as the precursor to delayed response or inaccurate diagnosis of the patient eventually resulting in poor patient outcome or even fatality in patients with acute fever and associated symptoms.

To overcome the gap in diagnosis and management, the objective of this review is to assess the prevalence and seasonal implications of acute febrile illness and provide evidence-based clinical practice recommendations for these conditions.

Method : The review process followed for formulating the clinical recommendations was systematic review of available evidence in the form of published literature followed by deliberations among the members of the expert panel. Where there was little or no evidence, the panel relied on logical empiricism and consensus to generate recommendations about the rational method of therapy and management of acute febrile illnesses and the role of broad spectrum antibiotics.

Conclusion : Six acute febrile illnesses with high prevalence and burden in India were identified; Typhus, Dengue, Chikungunya, Influenza, Upper Respiratory Infections (URIs) and Malaria. The authors have provided clinical practice recommendations for all the 6 febrile illnesses.

[*J Indian Med Assoc* 2020; **118(3):** 13-9]

Key words **: Fever, Chikungunya, Malaria, Respiratory tract disease, Influenza, Typhus, Dengue.**

Acute febrile illness involving multiple systems is a common characteristic of many endemic infectious diseases in South East Asia and includes diseases such as malaria, dengue, scrub typhus etc[1]. In most cases of febrile illness of unknown etiology, a generalized treatment approach using antibiotics and antipyretics is followed. Hence, it is also suggested that unavailability of epidemiological or evidence-based information on febrile illness in tropical region becomes a prominent reason for compromised clinical judgment and treatment[2].

It is the need of the hour that general physicians have easy access to clinical guidelines on the treatment and management of seasonal febrile illness of known etiology. This will help them in taking informed and improved clinical decisions.

In this paper, we discuss some of the prevalent febrile seasonal infections in India, their current management and give clinical practice recommendations for the same.

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Received on : 17/02/2020
Accepted on : 07/03/2020

Editor's Comment :

- **In scurb typhus, treatment with doxycycline should be initiated before referring the patient for assessment of complication**
- **Scrub typhus is one important cause of Acute Encephalitis Syndrome (AES).**
- **Patients with simple fever without any danger signs or complications may be managed with symptomatic approach**
- **In case of chikungunya, treatment is entirely symptomatic**
- **In case of H1N1 influenza, use of antiviral medication oseltamivir is recommended**
- **In case of URTI, except for streptococcal infections presenting with fever and sore throat, antibiotics are not recommended**
- **In all fever cases diagnosed as malaria by RDT or microscopy should promptly be given effective treatment.**
- **Dengue fever may be diagnosed on day one by NS1 test by Elisa method.**

Methodology

The present paper assesses the recent evidence on seasonal and acute febrile illnesses and their management.

In order to impart the highest possible evidence base for the management of acute febrile illness, a systematic review of literature was conducted. Existing guidelines, meta-analyses, systematic reviews, reports, white papers and key cited articles on prevalence, epidemiology, seasonal implications and management of acute febrile illnesses were reviewed and recommendations were framed.

As a result of the review, 6 acute febrile illnesses with high prevalence and burden in India were identified; Typhus, Dengue, Chikungunya, Influenza, Upper Respiratory Infections (URIs) and Malaria. Recommendations for each disease were discussed by the expert panel and where there was little or no evidence the panel relied on logical empiricism and consensus to generate recommendations about the rational method of therapy and management of acute febrile illnesses and the role of antibiotics.

Discussion

Acute febrile Illness Definition :

Fever of rapid onset & lasting less than 21 days (14 days in some definition) with no identified source.

Fever with no localising signs is called Acute Undifferentiatiated Febrile Illness (AUFI).

The febrile response is supervised and coordinated by the central nervous system through endocrine, neurological, immunological and behavioral mechanisms. Therefore, it is marked by a regulated increase in temperature accompanied by various sickness behaviors, alterations in metabolic and physiological characteristics of body systems and alterations in immune responses. Fever and the febrile response are important contributors to the pathogenesis, clinical presentation and outcome of many illnesses and diseases[3]. As a result of the literature search, 6 febrile illnesses with significant prevalence in India were selected. This review highlights their clinical manifestations, management and expert recommendations.

No antibiotics are generally recommended till reports are available in case of acute febrile illness, but if there is a compelling indication to start an empirical antibiotic, then less resistance-prone; older, broad spectral antibiotics like oral or IV doxycycline should be used. Antibiotics should be started early in immunocompromised or high-risk patients with acute febrile illness including those with associated disease conditions such as suspected sepsis, deep-seated abscess, pneumonia, meningitis, typhus encephalitis, bacterial pansinusitis, bacterial otitis media, osteomyelitis and streptococcal sore throat. In fact, doxycycline and cephalexin are the only broad-spectrum antibiotics approved by the Drug Controller General of India (DCGI) as per the Central Drugs Standard Control Organization (CDSCO). Oral or IV doxycycline (200 mg) is approved as broad-spectrum antibiotic of choice in acute undifferentiated fever with suspected typhus fever, leptospirosis, malaria, typhoid, dengue or respiratory tract infections.

Typhus

Scrub typhus is a serious public health problem in the Asia-Pacific region including, but not limited to, Korea, Japan, China, Taiwan, India, Indonesia, Thailand, Sri Lanka and the Philippines. It was observed that maximum cases of Typhus occurred in seasons with cooler temperature[4]. In India, the peak of the disease is between August and October[5].

Clinical manifestations :

Typhus is caused by mite infection. The clinical symptoms include high temperature, severe generalized headache, diffuse myalgia, presence of rash and an eschar at the site of the chigger bite in many patients. If typhus is not treated in time, it may cause encephalitis[6]. Eschar can be seen early in patients depicting local tissue necrosis at the site of chigger bite. Care should be observed while examining moist intertriginous surfaces such as axilla, scrotum or perianal region so that the clinician does not miss the eschar[6].

Management :

The disease persists for 14 to 21 days in absence of treatment. Patients treated with appropriate antibiotics

Table 1 — *Treatment of Typhus*

Drug	Dose	Duration	Treatment
Doxycycline :			
Adults	200 mg/day in two divided doses	7 days (IV or oral)	Treatment of choice
Children	4.5 mg/Kg body weight/day in two divided doses	5 days	
Pregnant women	Contraindicated		
Azithromycin :			
Adults	500 mg in a single dose	5 days	
Children	Azithromycin in the dose 10mg/kg body weight	5 days	
Pregnant women	500mg in single dose	5 days	Drug of choice
Chloramphenicol :			
	50-100 mg/Kg/day divided every 6h IV OR 500mg qid orally	7-14 days (oral)	In adults
Rifampicin :	600 to 900 mg/day		Should be used where there is poor response to doxycycline

typically become afebrile within 48 hours of starting therapy[7]. DHR-ICMR guidelines endorse the use of doxycycline 200 mg/day in two divided doses for patients above 45 Kg for a period of seven days or a single dose of azithromycin 500 mg for five days when the fever has persisted for five or more days and other febrile illnesses such as malaria, dengue and typhoid have already been ruled out. Alternative diagnosis should be considered, if clinical signs and symptoms persist even after the first line of treatment. Table 1 describes the different medicines used in the treatment of Typhus[8-10]. Even though South Asia has seen the presence of Doxycycline or chloramphenicol resistant strains, these strains have shown susceptibility towards azithromycin[11].

Expert Clinical recommendations :

If the patient presents to the primary care clinician or general physician with suspected typhus infection, it is recommended to initiate treatment with doxycycline even before the patient gets examined for presence of associated complications. If the patient shows signs of complications such as Acute respiratory distress syndrome, acute renal failure, meningoencephalitis, multi-organ dysfunction, it is recommended to prescribe doxycycline for managing typhus along with a treatment regimen for pneumonia.

Dengue

Currently prevalent in over 100 countries across the globe, dengue attributes to probably 50 million infections occurring annually. From 1998 to 2014, the highest dengue incidence was reported in Pondicherry, followed by Dadra Nagar Haveli and Delhi. Similarly, high dengue incidence, ranging between 21 and 50 per million was reported for the states of Punjab, Gujarat, Karnataka, Kerala, Tamil Nadu and Orissa[12].

Clinical manifestations :

WHO reviewed the classification of dengue cases in 2009, wherein the traditional dengue fever and dengue hemorrhagic fever or dengue shock syndrome was replaced with dengue with and without warning signs and severe dengue[13].

Management :

No therapeutic agents exist for dengue infections; the key to successful management is timely and judicious use of supportive care[14].

While treating dengue, the management strategy is dependent on the severity of condition; ranging from mild, moderate to aggressive. NVBDCP & World Health Organization (WHO) have published Indian National Guidelines for dengue management which recommends that clinical supportive and symptomatic therapy should be given to patients based on the severity of the condition. Simple approach of management should be adopted for patients with fever but without any danger signs or associated complications. In case of patients with warning signs, the management should be accompanied with close observation of the patient to check and control progression of DHF/DSS or severe bleeding. Symptomatic and supportive management is provided in dengue fever. Antipyretics may be considered for lowering body temperature. Oral fluid and electrolyte therapy are recommended for patients experiencing rigorous sweating, vomiting or low blood pressure. Continuous monitoring for a period of 24-48 hours is recommended in case of DHF in endemic areas until the patients stops getting fever without the use of antipyretic drugs and once the hematocrit values stabilize, platelet count is >50,000/mm^3 or improving. Another recommendation is for the clinician to be watchful for detecting anyred flags for signs of fluid overload as the patient is prone to developing complications in the later stages of fever or in the afebrile phase of the disease[15,16]. In a study including dengue hemorrhagic fever patients (n=231), the results suggested that doxycycline offers clinical advantages to patients who are highly susceptible to complications. It is suggested that this effect may occur via the reduction in the pro-inflammatory cytokine levels[17]. In another study, doxycycline was evaluated with regard to changing serum levels of IL-6, IL-1B, and TNF. The results showed that treatment with tetracycline or doxycycline significantly brought down cytokine levels, with doxycycline demonstrating better cytokine modulating activity and cytokine receptor/antagonist levels compared with tetracycline[18].

Expert Clinical recommendations :

We recommend that patients with simple fever without any red flags or associated complications should be simply managed by providing symptomatic treatment. Rigorous treatment should only be given to patients who have grade III and IV Dengue Hemorrhagic Fever, substantial bleeding or are experiencing multi-organ dysfunction. A simple rule of 20 may be followed in the management of dengue; "*in a patient with dengue fever; if there is acute rise in pulse by 20, acute fall in blood pressure by 20 mm Hg, pulse pressure lower than 20, rapid rise in hematocrit by 20% with rapid fall in platelet count to less than 20, 000 or more than 20 petechiae in the tourniquet test, give 20ml/Kg fluid immediately and shift the patient to the nearest medical center for observations and treatment*." It is recommended that doxycycline may be considered in Dengue Hemorrhagic Fever patients.

Chikungunya

Chikungunya fever is one of the most important public health problems in India[19].

Clinical manifestations :

When an epidemic occurs with characteristic pattern

of abrupt onset of fever accompanied with arthralgia, myalgia, with/without rash, chikungunya is suspected. Fever and arthralgia are the hallmark of chikungunya fever. As the clinical manifestations of chikungunya fever resemble those of dengue and other fevers caused by arthropod borne viruses, lab diagnosis is critical to establish the cause of diagnosis[20].

Management :

Management is mostly symptomatic for this self-limiting illness. During an epidemic, every patient clinically suspected does not need to undergo serological testing. Systemic manifestation is rare, relapse or reinfection is not seen. Co-infection with dengue and malaria can occur concurrently. No specific treatment or antiviral drug is currently available for managing chikungunya[21].

Indian guidelines on chikungunya management have suggested that the treatment should be initiated in all suspected cases of chikungunya, even before the serological or viral presence is confirmed in the diagnostic tests. All control measures including mosquito nets should be provided to all suspected fever cases. Treatment recommendations include paracetamol 1 g administered 3 to 4 times a day for the management of fever, headache and other pain; and antihistamines for itching. The recommended dose for children is 50-60 mg per Kg body weight administered in multiple doses. Lukewarm water sponging may be considered. Another important recommendation is that if paracetamol or other analgesics have already been given to the patient with no response, Nonsteroidal anti-inflammatory drugs may be considered. Topical or systemic drugs can be used for topical manifestations of the disease[22,23].

Patients who are non-responders or have obstinate joint pain or incapacitating arthritis even after treatment duration of 3 days, patients aged above 60 years or below 1 year also require immediate hospitalization. Serious complications should be treated; bleeding disorders with blood components, hypotension with fluids/inotropics, acute renal failure with dialysis, contractures and deformities with physiotherapy/surgery, cutaneous manifestations with topical or systemic drugs, neuropsychiatric problems with specialist care and drugs[22,23]. When the patient is in the recovery phase, recommend mild exercise and physiotherapy to them. If effective, cold compress may also be considered in recovering patients[22,23].

Expert Clinical recommendations :

Symptomatic approach should be followed for treatment. Initiate treatment in all suspected cases. The drug of choice is paracetamol; however other pain relieving medications or NSAIDs may be considered if the patient is not responding to paracetamol. Steroids should be avoided in the acute stage of the disease because they may be associated with side effects. Aspirin should also be avoided in these patients as it may lead to gastrointestinal side effects like Reye's syndrome.

Single dose of steroids or hydroxychloroquine 200 mg may be considered to be administered orally for duration of 4 weeks in patients who have acute fever associated with 'chikun' flexion posture due to painful arthritis or persistent inflammatory arthritis.

Influenza

There are no estimates of influenza-associated mortality existing for India and the exact burden of influenza in India is also not known[24].

Clinical manifestations :

The hallmark of influenza is the sudden, rapid onset of symptoms which include fever, chills, body aches, sore throat, non-productive cough, runny nose and headache[25].

Management :

The recommended treatment is oseltamivir. The recommended dose for treatment is provided in Table 2. Supportive therapy includes IV fluids, parenteral nutrition, oxygen therapy, antibiotics for secondary infection, vasopressors for shock, paracetamol or ibuprofen for fever, myalgia and headache. The suspected patients should be constantly monitored[25]. Patients should increase their intake of fluids. Oxygen therapy should be considered in patients experiencing symptoms of tachypnea, dyspnea, respiratory distress or less than 90 per cent oxygen saturation[26].

Expert Clinical recommendations :

We recommend considering the disease severity and progression, age of the patient, other comorbid conditions, probability of progression to severe stage of influenza and time elapsed since the onset of symptoms before initiating them on antiviral medication, oseltamivir.

Other recommendations include use of topical decongestants, saline nasal drops, throat lozenges and steam inhalation for symptomatic relief. Complete cessation

Table 2 — *Oseltamivir dose and duration for the treatment of seasonal influenza*

Oseltamivir dose and duration :			
By weight	Dose	For infants	Dose
<15 Kg	30 mg BD for 5 days	<3 months	12 mg BD for 5 days
15-23 Kg	45 mg BD for 5 days	3-5 months	20 mg BD for 5 days
24-<40 Kg	60 mg BD for 5 days	6-11 months	25 mg BD for 5 days
>40 Kg	75 mg BD for 5 days		It is also available as syrup 12 mg per mlIf required dose and duration can be changed based n clinical situation

of smoking is recommended to abort disease progression or worsening of the symptoms. Avoid aspirin in all influenza patients. It is recommended to closely monitor the patient to detect clinical or radiological signs of lower respiratory tract infection or hypoxia.

For prevention of influenza, we recommend respiratory hygiene (maintaining a distance of 3 feet from an infected person), encouraging cough etiquette (coughing on the sleeve or tissue paper) and timely annual influenza vaccination.

Upper Respiratory Infection

Acute respiratory infection (ARI) is the largest single disease category for India, accounting for about one-ninth of the national burden[27]. The incidence of acute Upper Respiratory Tract Viral Infections (URTI) is directly correlated to air temperature with most URTI occurring seasonally in cold weather[28].

Clinical manifestations :

The most common symptoms of upper respiratory tract infections include sore throat, congestion, rhinorrhea, pain & fever and cough[29].

Management :

As per the ICMR guidelines, the upper respiratory tract infections are mostly due to viral infections. Hence, role of empirical antibiotics is limited. In most immunocompetent adult patients, the URI treatment is based on providing symptomatic relief. However, in certain patients antimicrobial or antiviral treatment may be warranted depending on the symptoms and cause[28]. Table 3 discusses the treatment based on guidelines in different upper respiratory tract infections[28].

A multi-center trial including patients with infections of respiratory tract who were treated with doxycycline, the results clearly demonstrated that treatment with 200 mg doxycycline given on the first day followed by 100 mg daily resulted in effective results and rapid onset of action (in 87% of patients)[30-32]. In a survey conducted among general practitioners, a statistically significant better response was seen in acute and acute-on-chronic bronchitis patients who were given doxycycline as compared with amoxicillin[33,34].

Table 3 — *General upper respiratory infections with their diagnostic findings and treatment approach*

Condition	ICMR guidelines	AFP guidelines
Acute bronchitis and tracheitis	Viral, antibiotics not required	Symptomatic treatment; antibiotics not recommended
Acute otitis media	Amoxicillin clavulanate 1 gm oral BD for 7 days Azithromycin 500 mg OD for 5 days OR ciprofloxacin 500 mg BD for 7 days	Amoxicillin, 80 to 90 mg per Kg per day, in two divided doses: first line treatment
Acute rhinosinusitis	Amoxicillin clavulanate 1 gm oral BD for 7 days Azithromycin 500 mg OD for 5 days OR Ciprofloxacin 500 mg BD for 7 days	Observe in mild cases; Amoxicillin (80 to 90 mg per Kg per day in two divided does) as first line therapy Doxycycline as alternative therapy
Common cold	No antibiotics	Symptomatic treatment; antibiotics are not recommended
Epiglottis		Consider antibiotics A third-generation cephalosporin and an antistaphylococcal agent active against methicillin-resistant *Staphylococcus aureus*(IV) or ceftriaxone, cefotaxime or ampicillin/ sulbactam (IV).
Influenza	No antibiotics	Influenza vaccination; supportive care; initiation of antiviral therapy within 48 hours of symptom onset
Laryngitis	No antibiotics	Symptomatic treatment; antibiotics not required Treatment based on modified Centor score In patients with a score of 1 or less, no further treatment is indicated.
Pharyngitis and tonsillitis	Commonly viral, no antibiotics. If bacterial, oral Penicillin V 500 mg BD or amoxicillin 500 mg oral TDS for 7 days. In case of Penicillin allergy, azithromycin 500 mg OD for 5 days.	In those with score of 2 or 3, streptococcal rapid antigen detection testing recommended and antibiotic treatment if test results are positive. Antibiotic treatment is recommended for patients with a score of 4 or 5. The recommended first line treatment is a 10-day course of Penicillin. Erythromycin can be used in patients who are allergic to penicillin. Amoxicillin, azithromycin and first generation cephalosporins are other alternatives.

Expert Clinical recommendations :

We recommend except for streptococcal infections presenting with fever and sore throat and absent cough and cold, antibiotics are not recommended in viral infections. However, presumptive antibiotic therapy may be initiated in bacterial cases. Based on the results of trials and survey among general practitioners, doxycycline can be considered in the management of upper respiratory tract infections.

Malaria

Over the past two decades, India has made immense progress in malaria control[35]. It has been noted that malaria cases start increasing in April and peak during the monsoon period (ie, June and July) and then steadily drop from August onward[36].

Clinical manifestations :

Malaria has non-specific clinical manifestations. Fever or a history of fever forms the primary basis of clinically suspecting malaria. There are no distinguishing features of malaria; making the specific diagnosis difficult and increased chances of over treatment. In regions with endemic malaria, malaria is suspected in all patients with a history of fever or temperature ≥37.5ºC without any other prominent cause. It is suggested that in places where malaria transmission is stable, it should be suspected in children who present with palmar pallor or hemoglobin level <8gdL[37].

Management :

The treatment of malaria should be refrained till laboratory investigations have established the diagnosis. "Presumptive treatment" without a confirmed diagnosis should only be considered in extreme cases[38].

A parasitological test to confirm diagnosis is a must in all suspected malaria cases. The WHO recommendations suggest that all confirmed cases in children and adults with uncomplicated *P falciparum* malaria (excluding pregnant women in their first trimester) should be treated with any artemisinin-based combination therapies (ACT); artemether + lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, dihydroartemisinin + piperaquine, artesunate + sulfadoxine-pyrimethamine. The treatment duration for Artemisinin derivative based therapy is recommended to be 3 days. In low-transmission areas, one dose of primaquine with ACT is recommended in patients with *P. falciparum* malaria (excluding pregnant women, infants below 6 months of age and women breastfeeding infants aged <6 months) to lower the rate of disease spread. In the first trimester of pregnancy, quinine + clindamycin is recommended to treat uncomplicated cases of *P falciparum* malaria[39].

Plasmodium falciparum isolates with reduced sensitivity to quinine have been isolated from various regions of the world; hence either doxycycline or clindamycin (for instance in children and pregnant women where doxycycline is contraindicated) may be given for 7 days alongside quinine[40].

Expert Clinical recommendations :

We recommend that confirmed cases of malaria (Rapid diagnostic test or Microscopy) should be immediately started on treatment. Recommended treatment is chloroquine 25 mg/Kg in confirmed *P. vivax* cases. Primaquine 0.25 mg/Kg body weight should be given for 14 days under close observation to prevent relapse of the disease. Artemisinin combination therapy is recommended in all confirmed *P falciparum* cases. Doxycycline 100 mg/day (1.5 mg/Kg of body weight) is recommended for short-term prophylaxis and mefloquine 250 mg weekly (5 mg/Kg of body weight/week) for long-term prophylaxis. Doxycycline is note recommended in pregnant and lactating women and in children younger than 8 years.

Conclusion

Acute fever is related with multi-system dysfunction and may be viral or bacterial in nature. In this article, 6 such febrile infections were discussed and recommendations for their management have been discussed. Most of the diseases were viral infections and did not require the use of an antibiotic in the management of the disease conditions. In many cases where there is no anti-viral treatment available so far, symptomatic treatment as well as vector prevention has been recommended.

Funding : None

Conflict of Interest : The authors would like to state that there are no conflicts of interest.

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