Management of acute febrile diseases in limited resource settings: a case-based approach

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SUMMARY

There is a massive burden of acute febrile diseases during the post-monsoon season in tropical countries. Despite this, there is a lack of clarity amongst the primary care physicians and travel medicine experts on how to approach such patients in a syndromic fashion. In this review, the authors summarize a case-based approach in the management of acute febrile diseases.

Keywords: Acute febrile disease, limited resourse setting.

Acute febrile diseases (AFD) are one of the important causes of morbidity and mortality in tropical countries. The most common cause of AFD in South Asia are dengue, rickettsial infections, leptospirosis and enteric fever [1]. There is a huge upsurge of patients with AFD in the post-monsoon season and they present in excessive numbers to all levels of healthcare with different manifestations. The primary aim of evaluation of these patients is to identify two important findings; first to differentiate patients requiring hospital admission from the ones who can be managed with home care and second, to identify patients who require antimicrobial therapy. However, it is easier said than done. It is usually difficult to differentiate one cause of acute febrile disease from the other based on symptoms alone. Most of the acute febrile diseases have overlapping symptoms. Patients with AFD may have mild presentations at the outset but many of them progress rapidly and end up with irreversible complications. Studies evaluating diagnostic algorithms have shown that appropriate sequential testing may help in correct identification of etiology in up to 74% of patients in India [2]. To make an etiological diagnosis, good laboratory facilities with trained personnel are required. In limited resource settings, such facilities are either not available or have high turn-around time. Use of point of care tests (POCT) may help in early diagnosis and initiation of treatment in such cases. Owing to the limited sensitivity of POCTs, some of the patients may end up without any diagnosis. In such cases where an etiological diagnosis is not made with POCTs, C-reactive protein (CRP) can be used to differentiate between patients who require antibiotics and those who do not. Although clinical features of the common etiologies are often overlapping, it is important to identify the patterns of clinical presentation. The main aim of this review is to differentiate these patterns through short representations of clinical cases which can be used as a guide for a structured approach towards making a diagnosis. We present seven different hypothetical scenarios in Table 1. The baseline patient details are common to all the scenarios and is described in the case stem.

Case stem: A 44-year-old male patient, resident of New Delhi presents in the month of October

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with fever, headache and myalgias. He is vaccinated up to date (diphtheria, pertussis, tetanus, polio, measles, mumps, rubella, varicella, influenza and hepatitis B) and does not have any known co-morbidities. He has no history of blood transfusion or any high-risk behavior. With this case stem the following differentials can be kept: malaria, dengue, chikungunya, scrub typhus, leptospirosis, enteric fever and Zika virus disease. To explain the presentation of each of this differential, following case scenarios are built on this stem and presented in a tabular format (Table 1).

In scenario 1, the patient is diagnosed with severe falciparum malaria. Patients with falciparum malaria may have severe pallor and unconjugated bilirubinemia due to hemolysis. Due to increased expression of PfEMP (*Plasmodium falciparum* erythrocyte membrane protein) on the surface of red blood cells, there is increased adhesion and sequestration in internal capillaries leading to multi-organ dysfunction, more pronounced in the central nervous system. The rapid diagnostic test (RDT) is positive for *Plasmodium falciparum*. The sensitivity of RDT depends on parasite species

Table 1 - Case scenarios of patients with acute febrile disease.

	Scenario 1	*Scenario 2*	*Scenario 3*	*Scenario 4*	*Scenario 5*	*Scenario 6*	*Scenario 7*
Fever	Fever (101 F) with chills and rigor	Fever (104 F)	Fever (104 F)	Fever (100.7 F)	Fever 100.7 F on day 1 & 102 on day 6	Fever 101 F	Fever 100.7 F for 6 days
Rash	No rash	Generalized erythematous blanchable rash (Figure 1a)	Itchy rash on day 5 (Figure 1c)	No rash	Macular rash on chest (Figure 1d)	Black necrotic eschar with surrounding erythema (Figure 1f)	Itchy rash
Vitals	BP- 110/70 mm of Hg, Heart rate- 110/min, RR-30/min	BP- 80/60 mm of Hg on day 4, Heart rate- 130/min	BP- 110/70 mm of Hg, Heart rate- 110/min	BP- 110/70 mm of Hg, Heart rate- 110/min	BP - 100/90 mm hg, Heart rate- 60/min	BP- 110/70 mm of Hg, Heart rate- 180/min	BP- 110/70 mm of Hg, Heart rate- 110/min
Positive findings	Encephalopathy	Retro-orbital pain Melena on day 5	Small joint symmetrical pain, retro-auricular lymph nodes (Figure 1b)	Conjunctival suffusion and jaundice (Figure 1e)	Diarrhea, Hepatosplenomegaly noted on day 7	Dyspnea Splenomegaly noted on D7	Arthralgia Joint swelling Conjunctivitis
CXR	B/L perihilar infiltrates	**Normal**	**Normal**	**Normal**	**Normal**	B/L perihilar infiltrates	**Normal**
Hemoglobin (gm/dL)	**8**	**13**	**11**	**12**	**12**	**12**	**11**
Haematocrit	**25**	**44**	**33**	33	33	33	33
WBC (cells/mm^3)	7K	3K	3 K	4500	4.5 K	12 K	9 K
Platelet count (cells/mm^3)	**1.5 l**	**0.5L**	**1 L**	**1.7 l**	**1.7 l**	**1.7 l**	**1.4 l**
Bilirubin (mg/dL)	3.4 (unconjugated)	1	1	3 (conjugate)	1	1	1
AST/ALT (IU/L)	38/45	134/57			54/76	40/36	40/36
Urea/ Creatinine	40/1	40/1	40/1	60/3.3	40/1	40/1	40/1

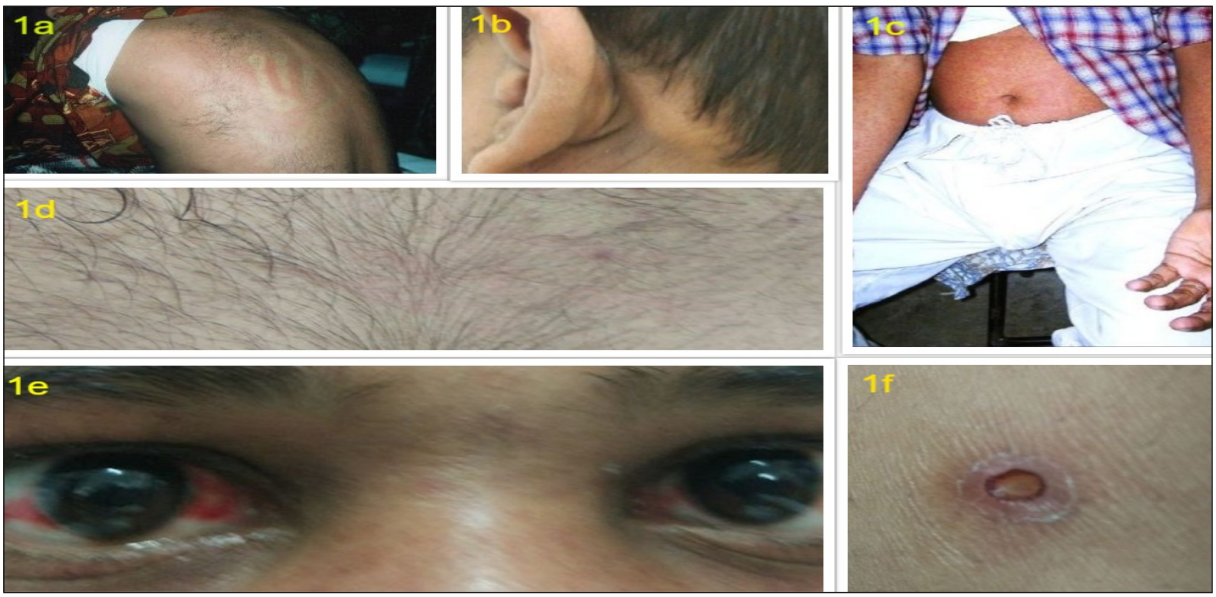

Figure 1 - Clinical images of patients presenting with acute febrile disease. 1a: diffuse blanchable rash; 1b: Retro auricular lymphnodes; 1c: Diffuse itchy rash 1d: Macular rash on chest; 1e: Conjunctival suffusion 1f: Eschar.

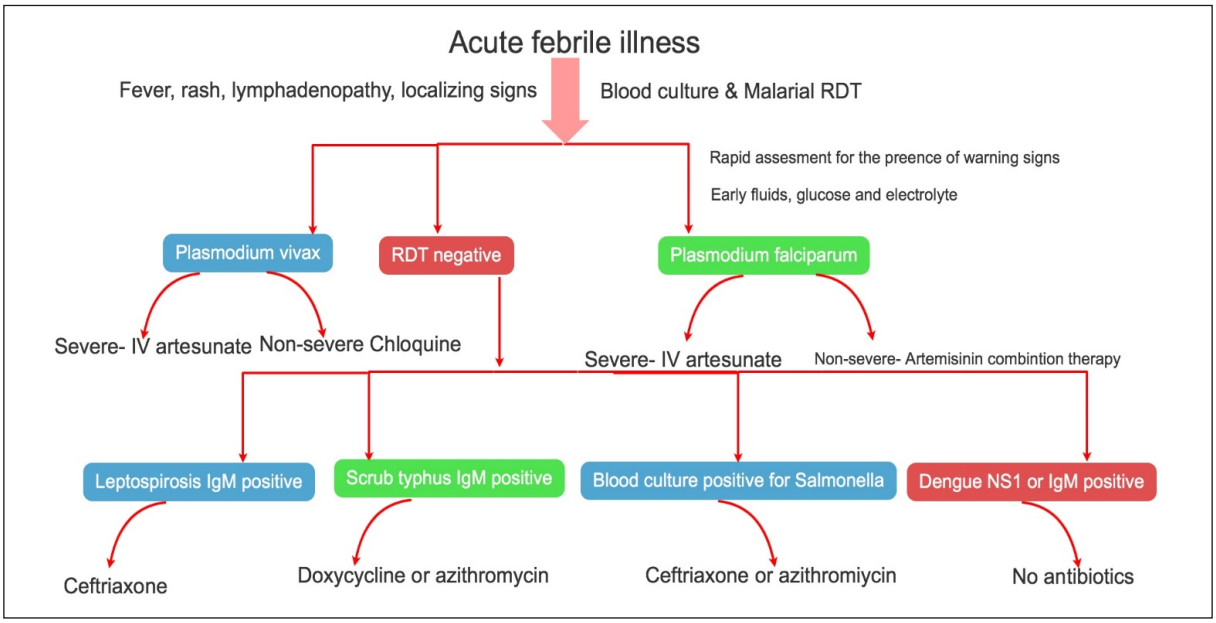

Figure 2 - Approach to acute febrile disease-diagnosis and management.

and density and the specificity is around 99.6% [3]. Other tests like peripheral smear (thin and thick smear) and quantitative buffy coat can also be used to establish the diagnosis. The patient is classified as severe malaria as he had features suggestive of encephalopathy and acute respiratory distress syndrome (ARDS). It is important to differentiate severe from uncomplicated malaria as severe malaria requires initial therapy with intravenous artesunate.

In scenario 2, the patient is diagnosed with severe dengue. Patients with dengue usually present with high grade fever, retro-orbital pain and diffuse blanching erythema (1a). In severe forms of disease, bleeding manifestations in the form of melena may be seen. This is a result of variety of reasons including quantitative reduction of platelets. Increased capillary permeability in dengue results in hemoconcentration, features of serositis and decreased intravascular volume. In this patient, RDT for malaria is negative but IgM for dengue is positive. In the first five days, NS1 antigen is the preferred investigation but after 5 days, NS1 antigen is usually negative and IgM antibodies are preferred. The sensitivity and specificity of NS1 is 38 to 71% and 76 to 80% respectively. The sensitivity and specificity of IgM dengue ELISA is 30 to 96% and 86 to 92% respectively [4]. The patient requires management with intravenous fluid and supportive care. Most studies have shown no role of prophylactic platelet transfusion.

In scenario 3, the patient is diagnosed with acute chikungunya. He has high grade fever, retro-auricular lymph nodes, itchy rash and symmetrical small joint arthritis (1b & 1c). Symmetrical small and large joint arthritis is the most common manifestation of chikungunya and it usually appears with high grade fever on day 1 itself [5]. Generalized skin rash is seen in up to 80% of cases and are usually seen between day 2 and day 5 of the disease [6]. In this patient, RDT for malaria is negative but IgM for chikungunya is positive. IgM for chikungunya is usually positive only after five days of disease. In the first five days, polymerase chain reaction assays (PCR) from whole blood can be done. The patient needs supportive care. Joint manifestations in chikungunya may remain persistent for a long time and may require prolonged therapy with non-steroidal anti-inflammatory drugs, hydroxychloroquine or steroids.

In scenario 4, the patient is diagnosed with leptospirosis. He has fever, conjunctival suffusion, jaundice and renal failure (1e). Presence of conjunctival suffusion in presence of icterus is extremely helpful in making a diagnosis of leptospirosis [7]. Weil's disease, the severe form of leptospirosis that has hepato-renal involvement along with haemorrhagic tendencies is only seen in a small percentage of patients [7]. His RDT for malaria is negative but IgM for leptospirosis is positive. The sensitivity and specificity of rapid IgM antibody test (Leptocheck) is 78-93.8% and 84.5-98% respectively [8]. IgM antibody test becomes positive only in the second week of disease. In the first week, PCR from whole blood can be done. Modified Faine' criteria that uses a set of epidemiological (contact with animal, contaminated environment, rainfall), clinical (fever, headache, jaundice, conjunctival suffusion, meningism etc.) and microbiological criteria (culture, serology or PCR) can be used to make a diagnosis [9]. A score of 26 or more has a very high specificity for making a diagnosis of leptospirosis. The patient can be managed with intravenous ceftriaxone or penicillin.

In scenario 5, the patient is diagnosed with enteric fever. He has step ladder pattern of fever along with bradycardia, macular rash on chest, diarrhea and hepatosplenomegaly (1d). Rose spots are not commonly observed in dark skinned individuals but may serve as a great specimen for culture. Patients may have diarrhea or constipation. Relative bradycardia has been classically described in enteric fever but is not commonly observed in day to day settings as antibiotic intake modifies this pattern. Untreated patients may develop intestinal perforation [10]. Tests for malaria, scrub typhus, dengue and leptospirosis are negative. Blood culture is positive for *Salmonella enterica subsp. enterica* serovar Typhi. In the second week of disease serological tests such as Widal or typhidot can be done. In a study, the sensitivity and specificity of Widal test at titres more than or equal to 1:160 was 65.38% and 89.83% respectively [11]. The sensitivity and specificity of typhidot for enteric fever is 84% and 79% respectively [12]. He needs treatment with ceftriaxone or azithromycin. It should be borne in mind that the time to defervescence with these antibiotics is often more than five days and therefore, patience is an important part of management.

In scenario 6, the patient is diagnosed with scrub typhus. He has fever, eschar, splenomegaly and features of myocarditis (1f). Eschar at the site of mite bite is pathognomonic of scrub typhus. The prevalence of eschar ranges from 7-80% in various studies [13]. It is easy to miss an eschar in a dark skinned individual as it is often hidden in clandestine locations such as axilla or groin. Myocarditis is one of the complications of scrub typhus as cardiac myocyte is one of the target cells of *Orientia tsutsugamushi*. The other common

complications are acute kidney injury and acquired respiratory distress syndrome. His RDT for malaria is negative but IgM for scrub typhus is positive. Serology becomes positive in the second week of disease. In the first week, PCR from whole blood can be done. In a study, the sensitivities of the IgM ELISA, IgM immunochromatography and PCR were found to be 97%, 87%, and 50%, respectively. All of these tests were found to be 100% specific [14]. The patient needs management with doxycycline.

In scenario 7, the patient is diagnosed with Zika virus disease. He has high grade fever, non-purulent conjunctivitis, itchy rash and joint pains. Zika virus has been found to be associated with neurological complications such as Guillain-Barré syndrome (GBS) and microcephaly in neonates. In the Indian outbreaks up until now, no cases of neurological complication has been observed [15]. In the first two weeks, PCR from whole blood or urine can be done. Serology should ideally be done after the second week of disease. Tests for malaria, scrub typhus, dengue, chikungunya, enteric fever and leptospirosis is negative. PCR of Zika virus is positive. The patient needs supportive care and careful observation for development of any neurological complications.

The approach to management of acute febrile disease is summarized in Table 2. Patients presenting with acute febrile disease should undergo a quick history and physical examination. History of co-morbidities, immunosuppression, travel and drug intake (antibiotics, steroids) should not be missed. After ascertaining the sensorium and measuring the vitals, the patient should be carefully assessed for presence of rash, lymphadenopathy, organomegaly or abnormal auscultatory findings. Hematological and biochemical parameters should be assessed for presence of hemoconcentration, anaemia, leukocytosis/leukocytopenia, thrombocytopenia, increase in transaminases or acute kidney injury. Presence of warning signs such as bleeding, altered sensorium, decreased urinary output, hypotension, respiratory distress and serositis should be clearly noted. Fluid, electrolyte and glucose management should be initiated at the earliest. After collecting the blood culture, rapid diagnostic test for malaria can be conducted as the first step. Patients with positive RDT should be treated with artesunate in case of severe malaria, artemisinin combination therapy for non-severe Falciparum malaria and chloroquine for non-severe Vivax malaria. Intravenous artesunate should always be followed by oral artemisinin combination therapy. Patient with negative RDT and less severe manifestations can be tested sequentially for respective diagnostic tests based on the pattern. In patients with negative RDT and severe manifestations, sequential testing may be time consuming and simultaneous testing for the common pathogens may be a better approach. We initiate these patients on empiric combination therapy to cover for the common pathogens such as ceftriaxone plus doxycycline or azithromycin. De-escalation to specific therapy can be done, once a diagnosis is made.

In this review, we have outlined the approach we follow in patients presenting with AFD in India. This may be helpful for primary care physicians working in India or physicians outside India who deal with travel related tropical infectious diseases. Since, the etiological agents vary with climate, season, geographical location, presence of vector and vector borne control measures etc. this approach cannot be used in its entirety in all places. But, employing a similar algorithmic approach, based on the epidemiological variables may be worthwhile in managing patients with AFD.

Conflict of interest

The authors declare that they do not have any conflicts of interest. There are no other authors to acknowledge.

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