Case Discussion in Medicine

Fever : A Case Based Approach for the Clinicians

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Fever is the presenting manifestation of several infective, inflammatory or neoplastic disease conditions. Acute febrile illness (duration of fever <14 days) is mainly due to infective etiologies in our country. A thorough history including the contextual history and meticulous general examination along with systemic survey will guide the clinician to localize and identify the etiology, recognize the danger signs, streamline the investigations and initiate management early. Clinicians should use rapid diagnostic tests to exclude common tropical infections such as malaria and dengue. Early identification of sepsis is also very important to reduce mortality and morbidity. It is prudent to avoid injudicious administration of antibiotics, if the duration of fever is less than 3 days in absence of any danger sign, and initial negative rapid tests. The purpose of this article is to remind the clinicians about the clinical approach to a febrile patient in day to day practice.

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Key words **: Acute febrile illness; inflammation; malaria; dengue fever; scrub typhus; leptospirosis.**

Case 1 :

A 44-year-old gentleman from Bihar presented with history of fever, non-productive cough and dyspnea for the past 3 weeks. There were neither any past history of tuberculosis or contact, nor had any chronic diseases such as diabetes, hypertension or malignancy. He was immunocompetent and denied any intake of long term medicines. On examination he was febrile with an oral temperature of 100.8°F, tachycardia (heart rate of 116 beats/min), blood pressure of 112/74 mmHg, respiratory rate of 26 /min and oxygen saturation of 98% on room air. He had a body weight of 58 kg. There was no definite history of weight loss.

Further Course in Hospital, Outcome and Follow-up :

On careful examination, jugular venous pulse was found to be raised and pulsatile along with muffled heart sounds. Laboratory investigations revealed mildly raised erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Electrocardiography (ECG) revealed sinus tachycardia with low voltage complexes. Chest X-ray showed right sided basal consolidation with pleural effusion along with increased cardio-thoracic ratio. USG-guided thoracentesis was performed fluid for acid fast staining, and PCR test for M Tuberculosis was negative. Pericardiocentesis was performed by trans-thoracic echocardiography and 600 ml of straw-colored pericardial fluid was drained. PCR test for M. tuberculosis was found positive. The patient responded well to drainage of the pericardial fluid and dyspnea subsided. He was orally started on anti-tuberculosis drugs and steroids. The patient was responding well to the treatment, with no recurrence of symptoms or any signs of deterioration in 3-months follow-up.

Editor's Comment :

- **The most important step to evaluate a febrile patient is history taking and clinical examination.**
- **Clinicians should follow the stepwise approach in management of a febrile patient.**
- **Appropriate tests to identify common infective causes should be done when suspected.**
- **Investigations in a febrile patient should be focussed and the choice of antibiotics if needed be appropriate.**

Case 2 :

A 45-year old gentleman presented with pain involving knee, hip shoulder, wrist and small joints of the hands along with unresolved fever for two weeks. He also complained of severe sore throat for the same duration. There was non-pruritic macular rash over extremities and the trunk which resolved spontaneously after two days of its appearance. On examination, he was febrile (temperature of 101.4°F). There was synovitis of the aforementioned joints, throat was mildly congested; lymphadenopathy or organomegaly was absent and other systems were unremarkable.

Further Course in Hospital, Outcome and Follow-up :

He admitted to have two similar presentations with

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six months gap over the past two years. He was diagnosed as rheumatoid arthritis and given methotrexate, but he stopped taking the medication after the pain subsided. Basic blood parameters showed leukocytosis of 21.1×10^9/L (88% neutrophils), elevated transaminases, very high CRP (244 mg/L), elevated ESR (96 mm/hr) and markedly elevated serum ferritin (14,400 ug/L). Rheumatoid factor (RF), Anti-cyclic citrullinated peptide (Anti-CCP) and antinuclear antibody (ANA) were all negative. Renal and coagulation profiles were normal. Blood and urine cultures did not reveal any evidence of infection. Computed tomographic (CT) scan of the thorax and abdomen were normal. He was diagnosed to have adult onset Still disease (AOSD) using the Yamaguchi criteria. He was started on oral analgesics and steroid (prednisolone 30 mg/day). The symptoms gradually improved and methotrexate was added after normalization of liver enzymes. During follow up, steroids were tapered off gradually and the symptoms improved.

Introduction :

Fever is one of the cardinal symptoms of many infective, inflammatory or neoplastic diseases[1, 2]. There is much debate regarding the definition of acute febrile illness. In Indian context, most of the literature has defined the duration of less than two weeks[3, 4]. There is inter-individual and circadian variation in body temperature; moreover rise of normal body temperature is seen in various physiological conditions, such as women after ovulation, after heavy meals or exercise.[2] The generally accepted definition is oral temperature >98.9ºF (evening). Acute undifferentiated fever can be defined as fever of less than two weeks duration without any localizable or organ-specific clinical features.

History Taking in a Febrile Patient :

The most important step to evaluate a febrile patient is to take a thorough and meticulous history to explore problems of the patient from different perspectives such as, the chronology of symptoms, patient's perspective and review of each system to appropriately localize the source of the fever[5, 6].

■ **Symptom analysis for fever :**

To confirm the presence of fever (whether true or factitious fever); duration of febrile illness (acute or chronic); onset (abrupt or gradual); pattern (continuous or intermittent); severity- how it affects the activity of daily living; aggravating and relieving factors; treatment received before presentation and associated symptoms suggesting any systemic illness.

■ **Pattern of temperature changes :**

Continuous fever : Temperature remains above baseline throughout the day and fluctuation is less than 1 °C in 24 hours period, eg, lobar pneumonia, urinary tract infection, enteric fever.

Intermittent fever : Fever is present only for a certain period of the day, ie, temperature returns to the baseline in between episodes of fever

Following are its types- Quotidian fever (periodicity of 24 hours) classically seen in *Plasmodium falciparum* malaria; Tertian fever (periodicity of 48 hours) classically seen P. *vivax* or *P. ovale* malaria; Quartan fever (periodicity of 72 hours) classically seen in *P. malariae* malaria.

Remittent fever : Temperature remains elevated throughout the day and fluctuation is more than 1 °C in 24 hours, *seen in* infective endocarditis.

Pel-Ebstein fever : There is much debate in the existence of it. It is used to describe the specific pattern of fever seen in Hodgkin's lymphoma, where the temperature is high for one week and normalized in the next week and so on.

■ **Chills and rigors :**

Presence of chills accompanied by rigors is mainly seen in malaria, sepsis with abscess, cholangitis and pyelonephritis.

■ **Night sweats :**

Night sweats are characteristic of lymphoma and tuberculosis.

■ **Headache and Delirium :**

Fever from any aetiology may provoke headache. Severe headache and altered sensorium in a febrile patient ay point towards more ominous causes such as, meningitis and encephalitis.

■ **Muscle pain :**

Myalgia is seen in infections such as influenza, dengue fever, malaria, leptospirosis and scrub typhus.

■ **Respiratory tract symptoms :**

(1) Sneezing, sore throat, purulent nasal discharges are suggestive of upper respiratory tract infection.

(2) Pain over the sinus and headache suggests sinusitis

(3) Cough, sputum, respiratory distress or wheezing suggests a lower respiratory tract infection.

■ **Genitourinary symptoms :**

Symptoms such as frequency of micturition, burning sensation, loin pain suggests urinary tract infection. Associated vaginal or urethral discharge indicates sexually transmitted infection (STI) or pelvic inflammatory disease(PID).

■ **Abdominal symptoms :**

Presence of diarrhea, with or without blood in the stool, significant weight loss and pain abdomen point

Fig 1 — Dew drops on rose petal appearance of Varicella

Fig 2 — Maculopapular blanching rash of dengue

Fig 3 — Morbilliform rash of measles

Fig 4 — Eschar of Scrub typhus

towards gastroenteritis, intra-abdominal infective foci, abdominal tuberculosis, inflammatory bowel disease (IBD) or malignancy.

■ **Joint symptoms :**

Pattern of joint involvement and number of joints involved are very important for diagnostic purpose. Fleeting arthritis indicates rheumatic fever. Monoarthritis always need prompt evaluation to exclude serious etiologies such as septic arthritis or gouty arthritis. Asymmetric oligoarthritis is associated with reactive arthropathy. Symmetric polyarthritis is associated with collagen vascular diseases and infective causes such a dengue and chikungunya.

■ **Constitutional symptoms:**

Weakness, anorexia, weight loss, fatigue, night sweats

■ **Contextual History:**

(1) Any medical problems such as diabetes, asthma, heart disease, tuberculosis or jaundice.

(2) Past history of surgery, intervention or transfusion.

(3) Drug history (drug fever is common in penicillin, cephalosporin, sulphonamides, phenytoin and anti tuberculous agents), use of any herbal or alternative medicine and immunization history

(4) Personal and social history regarding addiction (smoking, alcohol, intravenous drug abuse), water supply and sanitation status, exposure to animals and birds, sexual history and dietary habits.

(5) Travel history and occupational history

Essential Clinical Examination in a Febrile Patient :

Meticulous clinical examination by a physician is of paramount importance to localize the possible etiology and streamline the essential investigations.[7]

■ **General Examination :**

General examination starts with assessment of higher mental functions. In acute febrile illness, presence of altered mental function is an ominous sign and may indicate etiologies such as meningitis or encephalitis. Presence of signs of meningeal irritation with or without focal neurological deficit needs immediate admission and evaluation, Drowsiness in a patient of malaria is an ominous sign. Fever with gross emaciation suggests chronic disorders such as tuberculosis, immunosupression or malignancy.

The other important points in general examination with their common associations are:

- **Pallor :** malaria, hematological malignancy
- **Clubbing :** lung abscess, empyema , infective endocarditis
- **Cyanosis :** severe pneumonia (particularly important in patients with COVID-19)
- **Jaundice :** viral hepatitis, cholangitis, Leptospirosis, Scrub typhus
- **Alteration in pulse rate** : Normally, there is rise of pulse rate of 8-10 beats/min with each degree Celsius rise in core body temperature. Relative bradycardia is seen in infective conditions such as enteric fever (Faget Sign) and Dengue; whereas relative tachycardia is seen in rheumatic fever and myocarditis.
- **Lymphadenopathy :** Presence of

pathologically enlarged lymph nodes point towards tuberculosis, infectious mononucleosis or lymphoproliferative disorders.

- **Alteration in blood pressure:** Severe hypotension in febrile patients may indicate septic shock or acute meningococcal septicemia with adrenal involvement
- **Tachypnea:** In this present Coronavirus Pandemic, pyrexia with tachypnea and cough should be thoroughly evaluated and properly treated.

■ **Systemic Survey:** Focused examination of the respiratory, cardiovascular, neurological, lymphoreticular and musculoskeletal systems to find out underlying etiology.

Fever with Rash[8] :

- **Distribution of rash**- Central (in infectious mononucleosis, measles, dengue and adult onset Still's disease); peripheral/acral (in Chikungunya, infective endocarditis and secondary syphilis).
- **Morphology of the rash**- maculopapular rash (in measles, drug rash, rubella and initial phase of dengue fever); vesiculobullous rash (in Varicella and disseminated Herpes simplex infection); purpuric rash/ necrotic rash (meningococcemia, later stages of dengue and thrombotic thrombocytopenic purpura); nodular rash (in erythema nodosum and Sweet syndrome); confluent desquamative rash (in Kawasaki disease and scarlet fever). **Eschar** is a necrotic lesion at the site of chigger bite with a central black crust which is surrounded by a zone of erythema. It is painless usually. Presence of eschar is a pathognomonic sign of scrub typhus.
- **Day after the onset of fever-** Though there are many exceptions to this rule, but it is a very useful guide in suspecting the aetiology of the exanthematous fever (Day 1-Varicella, Day 2- Scarlet fever, Day 3- Small pox, Day 4- Measles, Day 5- Typhus, Day 6- Dengue, Day 7- enteric fever)

■ The images of rashes in chickenpox, dengue, measles and the pathognomonic eschar have been included as Figs 1-4.

Fever with Generalized Lymphadenopathy :

Although the cervical group of lymph nodes are the most commonly afflicted nodes, but careful examination of all the other areas along with detailed evaluation of lymphoreticular system is of paramount importance to find out the underlying etiology. Lymph node size of >1 cm in cervical or axillary and >1.5 cm in inguinal; any tender or matted node and lymphadenopathy of any size in supraclavicular or epitrochlear region should be considered as significant.

Tuberculosis and lymphoma are the two most common causes of generalized lymphadenopathy in our country. Localized enlargement of lymph nodes is most likely due to local infection or malignancy. However, the detailed discussion on this topic is beyond capacity of this article.

Red-flag Signs in a Febrile Patient:

- Altered sensorium
- Hypothermia or hyperthermia
- Hypotension
- Bleeding manifestation
- Persistent vomiting
- Severe anemia
- Desaturation and cyanosis

Essential investigations in a febrile patient[9, 10, 11] :

The initial investigation in a febrile patient should be complete blood count with peripheral blood smear. Both leukocytosis and leukopenia may indicate serious infections or sepsis. Complicated malaria sometimes present with hemolysis and dengue fever often presents with hemoconcentration (raised packed cell volume) and thrombocytopenia. Hematological malignancies are often diagnosed incidentally on routine hemogram. A careful examination of peripheral smear often diagnoses causative organisms such as malaria and microfilaria.

Urine analysis is also comes under the initial investigations panel as asymptomatic urinary tract infections are not very uncommon especially in pregnancy and old age. Moreover, presence of active sediments indicates toward glomerular pathology.

Liver and renal function tests are also needed because those are affected in several infectious or inflammatory pathologies and the values are often necessary to predict the toxicities of the commonly administered drugs.

In the pediatric age group, most of the febrile illnesses are often caused by respiratory tract infections and those are often caused by viruses. In the recent pandemic scenario, it is very necessary to evaluate all patients with fever and respiratory symptoms, and order the tests for COVID-19 if clinically indicated.

Most of the acute febrile illnesses in our country are caused by infections. So, etiological diagnosis of them is very important for early initiation of proper treatment. The common rapid tests performed to rule out tropical infections and their confirmatory tests are summarized in Table 1.

It is a very rational practice to send blood culture in all patients with acute febrile illness before

administration of antibiotics. Septicemia must be ruled out initially in immunocompromised, post-surgical and post-transplant patients. HIV serology should be ordered in presence of atypical infections or typical infections in atypical fashion. Appropriate imaging such as CT scan, X-rays or ultrasonogram in a febrile patient should be considered according to the localizing features elicited from the history or clinical examination. Fever with altered sensorium should be considered as a medical emergency and an urgent CSF study with brain imaging should be done. Evaluation of the auto-immune/auto-inflammatory diseases should be done when there is strong clinical suspicion and the investigations do not suggest infectious etiology of the febrile illness.

Table 1 — *Common rapid tests performed to exclude the tropical infectious etiologies*

Common tropical infections	When to suspect	Rapid tests	Confirmatory tests
Malaria	High grade fever with chills and rigor; presence of haemolysis, hepatic or renal dysfunction when complicated.	Antigen test- may be done after fever onset. Sensitivity and specificity high (95%)	Microscopy by thick and thin smear
Enteric fever	Fever in presence of prominent gastrointestinal symptoms	IgM antibody- may be done at the end of first week Sensitivity-47-98%, Specificity- 58-100%	Blood culture
Scrub typhus	Fever with presence of eschar is pathognomonic; neurological, hepatic or renal involvement when complicated.	IgM antibody (ELISA)-may be done at the end of first week, Sensitivity- Variable Specificity- 90-100%	IFA or PCR
Dengue fever	Fever with headache, bodyache, retro-orbital pain, rash and thrombocytopenia; haemorrhage or shock when complicated.	NS1- day 1-5 IgM- day 5-onwards Sensitivity- 60-80% Specificity- 80-90%	PCR
Leptospirosis	Fever with myalgia, hepatic and renal dysfunction.	IgM- may be done after 8-10 days of onset Sensitivity-80% after 2nd week Specificity- Variable	PCR/Culture

Stepwise Management in a Patient of Acute Febrile Illness :

(1) To assess the severity of symptoms and early recognition of sepsis through detailed history, examination and focussed investigations

(2) Appropriate localization and identification of complications or danger signs

(3) Use of rapid diagnostic tests to exclude common tropical infections such as malaria and dengue

(4) Use of anti-pyretics alone, if duration <3 days, no danger sign, and initial rapid tests are negative

(5) Meticulous history taking, examinations and focussed investigations and management if fever persists for longer duration with initial negative rapid tests.

(6) Search for the uncommon aetiologies and specialist opinion in case of acute undifferentiated febrile illness with negative culture which persists despite the initial empiric antibiotics

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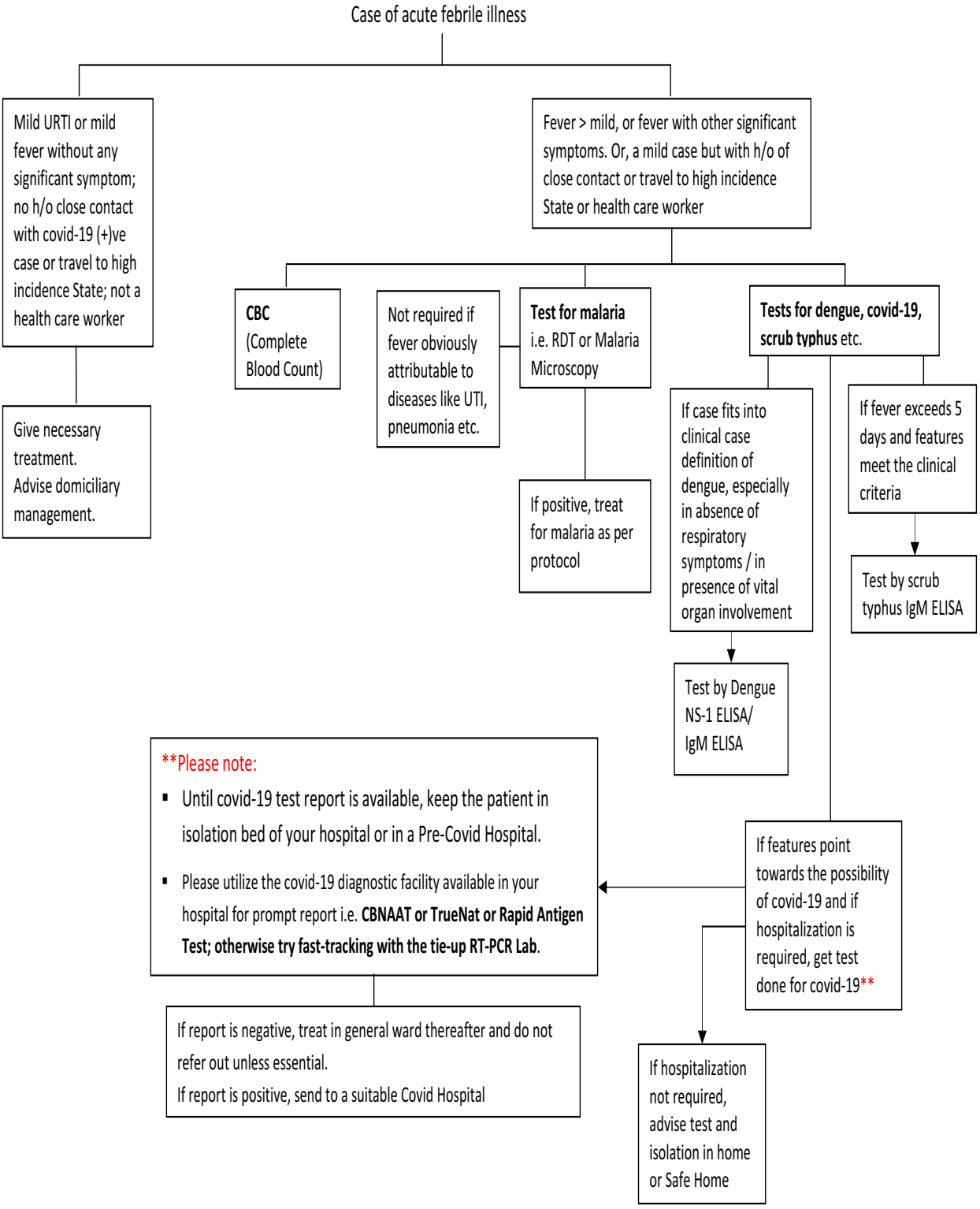
Attending a fever case in the OPD or ER, keeping covid-19 & dengue scenario in the mind



(Source : Department of Health & Family Welfare, Government of West Bengal)