Review Article

Indian Journal of Medical Science 2018 April-August;70(2):30-37

Acute febrile illness: A stepwise approach for clinicians

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Abstract

Acute febrile illness (AFI) is a common clinical problem, and can be due to various causes. AFI without localizing featuresacute undifferentiated febrile illness is a diagnostic challenge. Knowledge about common infections present in that particular area will give a clue to the probable etiology. But because of variety of causes and atypical presentations diagnosis of AFI remains to be a great challenge. In this review we are describing a stepwise approach for the diagnosis and management of AFI which will be useful for the practicing clinicians.

Keywords: acute febrile illness, acute undifferentiated febrile illness, non-malarial acute febrile illness, host biomarkers, travellers.

Introduction

Fever is a common symptom which forces the patient to seek medical attention, and is a nightmare to physician, especially when the diagnosis is not clear, fever persistsin spite of treatment and when febrile patient is developing serious complications[1]. Variety of causes, atypical, overlapping and non-specific clinical features and limited diagnostic tools make the diagnosis of acute febrile illness a real challenge. Acute febrile illness is most often due to infections etiology, but when fever is prolonged and in patients with the Fever of Unknown Origin (FUO), non-infectious causes like malignancy, connective tissue disorders, autoimmune disorders and vasculitis syndrome contribute to significant proportion of cases (40-80%) (See table 1)[2,3]. Relevant clinical history like type of fever, history of travel, h/o exposure to any particular food/infectious agent, associated symptoms like cough, expectoration, Gastrointestinal disturbance and dysuria will help to make clinical diagnosis in patients with acute febrile illness. A detailed clinical examination to look for jaundice, skin and oral lesions, conjunctival changes, lymphadenopathy, hepatomegalyand splenomegaly will point towards particular cause of fever, making further evaluation and treatment comparatively easy. Acute febrile illness with symptoms and signs pointing towards a particular cause of fever, like acute respiratory tract infection or acute urinary tract infection, are grouped into acute differentiated febrile illness (ADFI) where the diagnosis is clear and treatment is as per standard protocol. Acutefebrile illness, without any localizing signs to point towards a particular diagnosis, is common and is a challenging clinical scenario and is collectively called 'Acute undifferentiated febrile illness (AUFI)[4].

Definitions

Acute febrile illness, short febrile illness or acute fever is defined as presence of fever or temperature more than 38^0 C lasting for more than two days and less than 2 weeks with or without localizing signs. Acute febrile illness with localizing sign/symptom is called "acute differentiated febrile illness". Acute undifferentiated febrile illness (AUFI) is defined as fever or body temperature more than 38^0 C lasting for more than 2 days and subsiding before 2 weeks without any localizing features[5]. When fever extends beyond 2 weeks clinician must follow the standard protocols for the evaluation of FUO.

Approach to acute undifferentiated febrile illness

Detailed clinical history and physical examination sometimes gives clue to the underlying cause of fever. Early diagnosis of AUFI helps the clinician to avoid unnecessary investigations and empirical treatment; helps to start specific treatment, will reduce the anxiety of the patients and relatives and will reduce the economic burden of the patients. AUFI is most of the time due to infectious etiology. Malaria, enteric fever, dengue, leptospirosis and rickettisial infections are the common etiologies encountered in clinical practice(See table 2). But the disease etiology varies from place to place. Geographical area, common infection prevalent in that area, risk of exposure to particular disease or pathogen, living condition, season, occupation and recreational activities are factors which determine the etiological of AFI[6]. Special consideration should be given to high risk groups like extremes of age, pregnancy, immunosuppressed individuals and patients on immunosuppressive drugs, organ transplant recipients and in splenectomisedpatients, where atypical presentation and development of life threatening complications are more likely[7]. In all acute febrile illness frequent clinical examination of patient is helpful to identify evolving new features, which will help to identify and diagnoselifethreatening complications at the earliest (See table 3). Development of disproportionate tachycardia or bradycardia,

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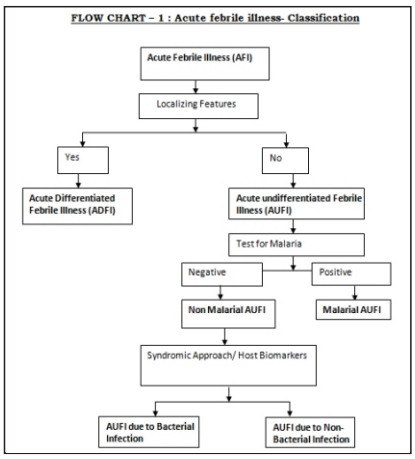

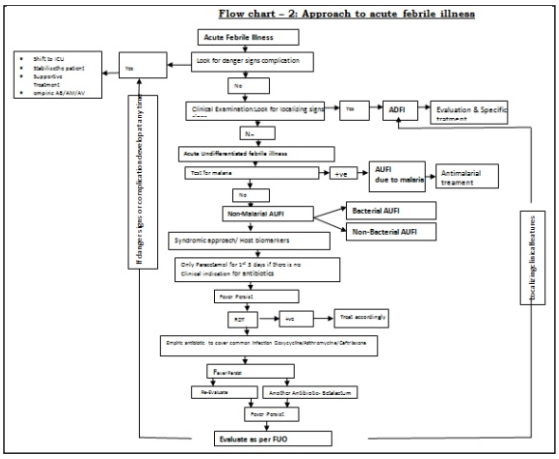

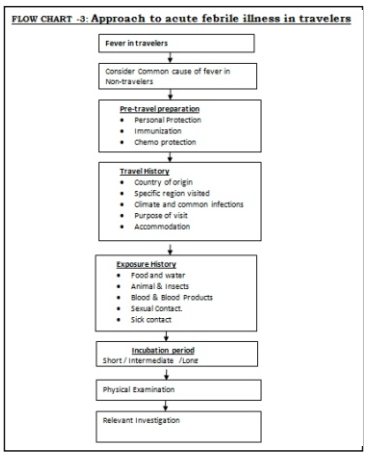

hypoxia, tachypnea, hypotension, shock, confusion, altered level of consciousness, seizure and severe dehydration indicate that the patient is having serious illness and require intensive care treatment in a well-equipped center (See table 4). Identification of AUFI due to malaria from Non-Malarial AUFI is important to start specific treatment and to reduce morbidity and mortality associated with delay in treatment [8,9]. In endemic areas it is a common practice to start anti-material drugs empirically in patients with acute febrile illness. But various studies showed that even in endemic areas, 80% of the acute febrileillness is not due to malaria[10-12]. So in acute febrile illness, where malaria is endemic, peripheral smear for malarial parasite examination/rapid malarial test (RDT) should be performed and treated with anti-malarial drugs only if found to be positive. But if found to be negative, it should be repeated every 6-8 hourly for 12-24 hours, if clinical suspicion is high[13]. All RDT positive cases have to be confirmed with peripheral smear examination. All positive cases (Both PS positive and Rapid Malarial test Positive) must be treated with antimalarial agents as per standard recommendation. In non-malarial AUFI, it is a common practice to start empirical antibiotics thinking that it is due to bacterial infection. But majority of the cases of non-malarial AUFI is due to non-bacterial etiology, where antibiotic treatment is unnecessary and may be harmful sometimes[14]. This common practice not only adds to the cost of therapy, but contributes to the global crisis of antibiotic resistance. The practical problem is that there is no reliable and easy way to differentiate NM-AUFI due to bacterial infection from that due to non-bacterial infection clinically (add flowchart 1). A syndrome based approach will help to narrow down differential diagnostic possibilities in clinical practice and is very useful in managing patients with AUFI [15]. The common acute febrile syndromesinclude fever with thrombocytopenia, fever with arthritis, fever with jaundice, fever with pulmonary involvement, fever with renal involvement and fever with CNS involvement (See Table 5). In patients with AUFI differentiation into bacterial or non- bacterial infection is difficult and can have overlapping clinical

Table 1: Common cause of acute febrile illness
• Acute Respiratory tract infection
• Acute Urinary tract infection
• Acute Gastroenteritis
• Influenza
• Malaria
• Dengue
• Typhoid
• Leptospirosis
• Rickettsial Disease/ scrub typhus
• Others: Hepatitis, Japanese Encephalitis

Table-2 : Common cause of Acute undifferentiated febrile illness
• Malaria
• Dengue
• Enteric fever
• RickettsialDisease/ scrub typhus
• Influenza
• Leptospirosis
• Japanese Encephalitis

Table-3 : Danger signs in patients with acute fever:
• Central Cyanosis
• Respiratory distress
• Circulatory Failure
• Extreme weakness
• Unconsciousness
• Inability to stand
• Neck Stiffness
• Convulsion
• Hypotension
• Tachycardia
• Tachypnea

Table-4 : Common complications of Febrile illness
• Sepsis
• Multiple Organ Dysfunctions
• ARDS
• Myocarditis
• Precipitation of Acute coronary events
• Cardiac failure
• Cardiac Arrhythmias
• Seizure
• Gullain-Barre Syndrome
• Post-Infectious Demyelination
• Thrombocytopenia and Dangerous bleeding manifestations
• Acute Kidney Injury
• Acute fulminant Hepatic failure
• Hypoglycemia
• Electrolyte imbalance
• Acute pulmonary edema

features as in dengue fever and leptospirosis, where fever and myalgia/ arthralgia is the early clinical feature[16,17]. So in areas where dengue and leptospirosis is common, early initiation of antibiotics is lifesaving. It is always worth remembering that infection can present with atypical features simulating acute differentiated febrile illness. Dengue fever can present with features of upper airway infection and leptospirosis with abdominal discomfort and diarrhea. Warningsigns of dengue fever like abdominal pain, vomiting with presence of abdominal tenderness may mislead the clinician to an alternate diagnosis of acute surgical abdomen, if dengue with warning sign is not considered as a strong possibility. Patients with acute falciparum malaria can present with gastro-intestinal symptom like vomiting, diarrhea can result in delay of diagnosis. It is not unusual to find multiple infections in same patient especially in endemic areas where dengue, malaria, enteric fever, leptospirosis and rickettisial infection can co-exist in same patient, in different combination, making diagnosis much more confusing and challenging [1,18]. Thesyndromic approach will help the clinician to narrow down diagnostic possibilities in patients with acute undifferentiated febrile illness and initiate diagnostic workup in a more focused manner. But overlapping clinical features and atypical presentations make clinical diagnosis difficult even with syndromic approach[19]. In a non–malarial AUFI even after proper clinical examination and applying principles of syndromic approach, we will not be able to differentiate bacterial infection from non-bacterial infection in most of the cases. There are lots of laboratory markers which help to differentiate these two.

Table- 5 : Acute febrile syndromes

FEVER WITH JAUNDICE
Viral infection
Hepatotropic viruses (A, B, C, D, E), Yellow fever, Dengue, Chickenpox, Cytomegalovirus, Epstein barr virus
Bacterial infection
Typhoid fever, Leptospirosis, Brucellosis, Ricketssia, Tuberculosis, Whipple's disease
Fungal Infections
Candida, Blastomyces, Cocciodies, Histoplasmosis, Cryptococcus
Parasitic Infections
Ascaris, Clonorchis, Schistosomiasis, Echinococcus, Amebiasis, Malaria Babesiosis,Toxoplasmosis, Leishmaniasis
FEVER WITH THROMBOCYTOPENIA
Malaria (usually falciparum but also vivax),Dengue fever,Leptospirosis, Rickettsial infections, Viral fevers
FEVER ARTHRALGIA
Viral infection
Human parvovirus (especially B19), Entero virus, Adenovirus,Epstein-Barr, Coxsackie virus (A9, B2, B3, B4, B6),Cytomegalovirus,Rubella,Mumps, Hepatitis B,Varicella-zoster virus (human herpes virus 3), Human immunodeficiency virus
Bacterial infection
Indirect bacterial infection (reactive arthritis)
Neisseria gonorrhoeae (gonorrhea), Bacterial endocarditis, Campylobacter species Chlamydia species, Salmonella species, Shigella species, Yersinia species, Tropherymawhippelii (Whipple's disease), Group A streptococci (rheumatic fever)
Direct bacterial infection:
N. Gonorrhoeae, Staphylococcus aureus, Gram-negative bacilli, Bacterial endocarditis,
Other infections:
Borreliaburgdorferi (Lyme disease),Mycobacterium tuberculosis (tuberculosis), Fungi
FEVER WITH RENAL INVOLVEMENT
Viruses
Viral hemorrhagic fevers, Epstein-Barr virus, Cytomegalovirus, human immunodeficiency virus
Bacteria
Leptospirosis, Streptococcus species, Legionella species
Parasitic infection
Malaria
Fungi
Candidiasis, Histoplasmosis
FEVER WITH HEPATORENAL DYSFUNCTION
Falciparum malaria, Leptospirosis, Scrub typhus, Hepatitis E or A with fulminant hepatic failure and the hepatorenal syndrome
FEVER WITH PULMONARY RENAL SYNDROME
Falciparum malaria, Leptospirosis, Hantavirus infection, Scrub typhus, Severe pneumonia due to Legionella and the pneumococcus
FEVER WITH ALTERED SENSORIUM
Cerebral malaria, Encephalitis, Meningitis, Typhoid fever, Brain abscess, Septic encephalopathy, Elderly patients with UTI or pneumonia

Investigations in acute febrile illness

Complete blood examination, urine microscopy, blood culture (if suspecting bacteremia)and chest X-ray (if patient is looking sick)are the usual initial investigations done in patients with acute febrile illness. High WBC count, especially polymorphonuclear leukocytosis usually reflects bacterial infection, but leucopenia with relative lymphocytesis is common in patients with enteric fever. Eosinophilia usually indicates invasive parasitic infection, drug reaction or fungal infection. Following investigations are helpful to differentiate AFI due to bacterial infection from non-bacterial infection.

Total WBC count

A very high WBC count usually indicates bacterial infection especially when there is predominant polymorphonuclearleukocytosis. But leucopenia is common in enteric fever[20].

Erythrocyte Sedimentations Rate(ESR)

ESR will be high in any infection or inflammation. ESR will be more in bacterial infection compared to non-bacterial infection [20,21].

C - reactive protein (CRP)

CRP is an acute phase reactant, which is increased in infection and inflammation. In patients with acute febrile illness a CRP of 20-40 mg/L can be due to bacterial and non–bacterial infections. But a CRP of >40mg/L detect around 80% of bacterial infection with 90% specificity [22]. ACRP value of >100mg/L usually shows sepsis or impending complications [20-23]. Various studies showed that CRP is a better indicator to differentiate bacterial infections than total WBC counts, especially in patients having malignancy, hematological disorders or neutropenia, where normal WBC response to infection may be impaired [24-26].

Procalcitonin

Procalcitonin is a promising biomarker in patients with acute febrile illness, helping to differentiate bacterial infection from non-bacterial infection, to assess the need for initiation of empiric antibiotic therapy, its effectiveness and time to stop antibiotic therapy [27,28]. It is an important prognostic marker, especially in patients with community acquired pneumonia and critically ill patients with sepsis [29,30]. Procalcitonin is markedly elevated (upto 5,000 fold) within 2-4 hours of bacterial infection and circulating PCT level halves daily when the infection is controlled[31]. There are lots of other host markers which help to differentiate between bacterial and no-bacterial infection, most of which are still under investigation and not available for routine clinical use. The host markers can be biochemical markers like organic or inorganic molecules, markers of cellular activity or genetic markers [32]. In future we can expect that availability of these host biomarkers in routine clinical practice make differentiation of non-malarial AUFI due to bacterial infection from non-bacterial infection easier[33]. The different host biomarkers under investigation are given in table (see table 6). Red cell distribution width and platelet distribution width are two other investigations which are reported to be high in patients with serious infection. RDW is classically more in patients with malaria, especially in falciparum malaria owing to infection of RBCs with the malarialparasites [34]. Platelet size is also found to be high in patients having severe infections, because of metabolically activeplatelet with large granules [35-37].

Specific lab findings in common infections

Progressive anemia and thrombocytopenia

Table-6 : Host biomarkers
Blood cellsandhematologicmarkers
Polymorphonuclearleukocyte(PMN) count, Neutrophil count, WBC count, ESR, Redblood cell(RBC)
Count, Lymphocyte count, Haptoglobin
inflammatory markers
CRP, Procalcitonin(PCT), Calprotectin, Angiopoietin1 receptor (sTie-1), Solubleangiopoietin 2receptor(sTie-2), Club(Clara)cellprotein16 (CC16)
Cytokines
Interleukins: IL-6,IL-8, :IL-4, IL-6,IL-8, IL-5, IL-12, IL-13, IL-9, IFN gamma-inducible protein 10(IP-10; CXCmotifchemokine 10-CXC10), Platelet factor 4 (PF-4), Eotaxin, TNF-related apoptosis-inducing ligand(TRAIL), Granulocyte-macrophage colony-stimulating factor (GM-CSF), Angiopoietin (Ang), Granulocyte colony-stimulating factor (G-CSF); Interferon (IFN), Monocyte chemoattractant protein 1 (MCP-1), Macrophage inflammatory protein 1 (MIP-1), Regulated on activation, normal T cell expressed and secreted(RANTES)/Chemokine ligand 5(CCL5), Tumor necrosis factor (TNF), Vascular endothelial growth factor 1 (VEGF) /FMS-like tyrosine kinase 1(Flt1)
Cell surface markers
Cluster of differentiation (CD)64, CD35, CD32, CD88, CD14, CD46, CD55, and CD59
Galectin (Gal)-9, Major histocompatibility complex class 1(MHC1), Human leukocyte antigen DR protein complex (HLA-DR), Toll-like receptor (TLR)
Metabolic activity markers
Glucose-CSF, Lactate-CSF, Protein-CSF, Angiopoietin-like protein (Anglpt)-3, Reactive oxygen species (ROS), Apolipoprotein E (apoE), Cortisol, Urea, Urea nitrogen
Other host biomarkers
Chloride-CSF, Heparin-binding protein (HBP), Lipopolysaccharide-binding protein(LBP), Serum-iron, Lactoferrin, Glial fibrillary acidic protein (GFAP), Prostaglandin- H2 (PGH2) D-isomerase, Soluble amyloid precursor protein (sAPP)a& b, D-Lactate-CSF, Soluble vascular endothelial growth factorreceptor (sVEGFR-2),Fibrinogen beta, Fibulin-1, Fibronectin (FN), Ferritin, Hepcidin, D-dimer, Complement component 5a (C5a), Fibroblast growthfactor (FGF), Gamma-glutamyltranspeptidase (Gamma-GT), Platelet-derived growth factor homodimer BB (PDGF-BB), Soluble cluster of differentiation protein 14 (sCD14), Serum glutamic-oxaloacetic transaminase (SGOT), Serum glutamic-pyruvic transaminase (SGPT), Surfactant protein D (SP-D),
Host transcription signatures

are common in patients with malaria, but there can be either leukocytosis or leucopenia [34,38-41]. Peripheral smear examination is gold standard in the diagnosis of Malaria, but being a time consuming procedure and because it requires experienced staff, it is not universally available. It can be false negative because of low parasitemia or due to sequestration even when the malarial parasite load is high. Rapid diagnostic test (RDT) for malaria is now widely available, which has got comparable sensitivity with thin peripheral smear examination [42,43]. In patients with suspected malaria, even if initial peripheral smear is negative, it should be repeated every 8-12 hours for few days.In RDT for malaria HRP-II (Histidine Rich Protein II)based test is performed for diagnosis of plasmodium falciparum and pLDH (Lactate Dehydrogenase) based test is done for plasmodium vivax [43]. In patients with dengue fever usually there is leucopenia and thrombocytopenia along with increase in hematocrit value. NS1antigen based rapid test is usually done in 1st five days, and RDT for Ig M antibody a done after 5th day of fever [44]. In patients with typhoid fever, leucopenia with reactive lymphocytosis is common and the organism can be demonstrated from culture of blood, stool, urine, bone marrow and duodenalaspirates within the 1st week of illness. Blood WIDAL become usually positive after 2nd week of illness, but lacksdiagnostic accuracy[45,46].

Step by Step approach to acute febrile illness[18]

Step-1: Relevant clinical examination to access severity and look for danger signs or complications

For all patients having acute febrile illness presenting with unstable vitals, hypoxia, or other danger signs,stabilize immediatelyand start supportive treatment.Depending upon the clinical features, prevalent infection pattern in that geographical area, with probable differential diagnosis start broad spectrum antibacterial agent/anti-malarialagent/antiviral agent in all patients with danger signs [18,47]. (See flow chart word file)

Table- 7 : Type of exposure and incubation period of common disease				
Exposure	Short incubation period (≤ 10 days)	Intermediate incubation period (7-28 days)	Long incubation period (≥ 4 weeks)	Variable incubation period (Weeks to years)
Contaminated food/ water	Cholera, bacillary dysentry	Typhoid, hepatitis A, polio, brucellosis	Brucellosis	Ameobiasis, Brucellosis
Animals	Plague, tularamia	Brucellosis, Q fever, toxoplasmosis	Brucellosis	Rabies, Brucellosis
Sexual contacts	Chancroid	Acute seroconversion illness in HIV	Hepatitis B, Syphilis	HIV
Mosquitos	Dengue, Yellow fever, Chickengunya	Malaria	Malaria, Leishmania	
Ticks	Relapsing fever, Lyme disease, Kyasanur Forest Disease, Crimean-Congo Hemorrhagic Fever	Ehrlichiosis, Lyme disease, Rocky Mountain spotted fever		
Sick contacts	Respiratory tract infections, Influenza, IMN			

Step-2: History and physical examination to localize the infection

Fever with localization that is,acute differentiated febrile illness, like respiratory tract infection, urinary tract infection should be evaluated and managed accordingly.

Step-3: Do rapid diagnostic test for malaria and dengue in patients with acute undifferentiated febrile illness.

In patients with AUFI, were clinical suspicion of malaria is high; repeat peripheral smear and or rapid diagnostic test for malaria every 8-12 hourly for several days, if initial reports are negative [13,18]. If positive for malaria by RDT, start specific treatment for malaria and confirm the result with peripheral smear examination. NS1 antigen based RDT for dengue is widely available, and if found positive, standard care as per dengue treatment protocol is required with proper monitoring to see development of danger signs [44,48]. Studies show that up to 80% of acute febrile illness even in malaria endemic area is not caused by malaria, questioning the common practice of empirical anti-malarial therapy in AFI, which delay the correct diagnosis and treatment and add to the issues of anti-malarial resistance[8,18,49].

Step-4: Treat with antipyretic agent, (paracetamol) alone if fever is of less than 3 days duration, RDT for malaria is negative and there is no clinical indication to start antibiotics.

Start antipyretic agents like paracetamolsos and avoid aspirin, NSAIDs and steroids in patients with acute febrile illness. Most clinician have a misconceptionthat non-malarial AUFI is due to bacterial infection, leading to indiscriminate use of antibiotic agents, contributing to global antimicrobial resistance crisis and exposingthe patients for unnecessary treatment adding to the financial burden [18,50,51]. But in some situation clinician may be forced to start antibiotics early. For example, in areas where both dengue infection and leptospirosis is common, fever with myalgia/arthralgia can be early feature of both dengue and leptospirosis and differentiation is extremely difficult in early days of fever and early initiation of antibiotic therapy is lifesaving in leptospirosis. So it is a common practice to start doxycycline in endemic areas in

patients with fever with myalgia/arthralgia, empirically in early days[52,53].

Step-5: In AUFI if fever persists and initial RDI is negative, start empirical antibiotics.

Re-examine the patient and look for any localizing features at frequent intervals and if present evaluate and manage as per guideline for ADFI. Also look for danger signs or evidence of impending complication. If fever is still persisting and there is no localizing features and RDT sare negative consider common infection in that area and the possible infections in that particular patient. Usually bacterial infection due to enteric fever, leptospirosis and scrub typhus are common causes of fever in endemic area, so that we should start empirical antibiotic treatment covering these organisms[52-55]. Doxycycline, Azithromycin or ceftriaxone covers common infectious agents. Doxycycline is usually started as 100 mg twice daily, whereasazithromycinis given 1000mg on day one, followed by 500 mg daily for next 5 days. Most of the clinicians prefer to take sample for blood culture before starting empirical antibiotics [18,56].

Step-6: If fever persists in AUFS evenafter initial empiric antibiotic treatment, re-evaluate and consider need for changingantibiotics

Experts in the field havedifferent opinion at this stage. Some prefer to stop further antibiotic and re-evaluate the patient with investigations like routine blood and urine examination, liver function test, blood culture and imaging, whereas some others initiate another 3-5 days of empiric antibiotic therapy with a different agent like Beta lactam antibiotic (if not used earlier) along withfurther investigations.

Step-7: If fever persists even after empiric antibiotics, all the investigations are negative and the duration of fever extends almost two weeks, consider further workup as perguideline for evaluation of FUO.

If the subsequent evaluation give specific diagnosis manage as per the diagnosis, but if all the evaluation in negative and still fever persist, evaluate as a case of FUO [18,57]. It is alarming to note that, various studies showed that the proportion of undiagnosed AUF ranges from 8% to 80% even after relevant investigations[4,58]. But the good thing about acute undifferentiated febrile illness is that more than 95% of cases resolve and only less than 5% progress to FUO. We wish to mention that the algorithm we prepared is based on common causes, which can vary according to geographical area and it will not cover atypical presentation. So the algorithm is not a substitute for clinical judgment, but supplement in physicians' decision making.

Approach to fever in travelers

With easy availability and affordability of various mode of transportation, the whole world has become a "global village" and acute febrile illness in travelers is a common clinical problem[59]. Fever in travelers can be due to various causes, but always consider cause of fever that is common in non–travelers, as etiology in travelers also. Respiratory tract infection, urinary tract infection and acute gastroenteritis are common cause of fever in travelers[60]. The cause of fever that needs special consideration in travelersincludes malaria, enteric fever, dengue fever, viral hepatitis, rickettisial infections etc [61]. In addition to the routine clinical examination in patients with AFI, details regarding immunization status, chemoprophylaxis, travel history, exposure history and idea about incubation period of common infectionswill help in diagnosis of fever in travelers (flow chart).

Immunization status

Vaccination against hepatitis A, hepatitis B and yellow fever offers protection against these and effectively rules out these infections, whereas vaccination against typhoid fever offers only 70% protection and hence it should be considered as a possibility even in immunized individuals[62,63].

Chemoprophylaxis

It is a common practice to take chemoprophylaxisagainst malaria in travelersvisiting endemic area which effectively reduce the risk of malaria. But it is not completely protective and various studies reported poor adherence to anti-malarial regimen in travelers, indicating the need to consider malaria as a diagnostic possibility even in those who took chemoprophylaxis [62]. It is also reported that the development of clinical symptoms of malaria is also delayed in those who took anti-malarial chemoprophylaxis [64].

Travel History

A detailed travel history regarding exact place of visit, season of the place visited, purpose of visit and occupational or recreational activities involved, and the place and type of accommodation provided will give clue to diagnosis. Clinician should be aware of specific infection that is common in that particular area [13,65-69].Centerfor disease control (CDC) publishes updated health information for international travel and details of specific infection in different locations andis available in the CDC websitehttps://wwwnc.cdc.gov/travel /www.cdc.gov/travel, which will be very useful for clinicians.

Exposure History

Exposure to various types of food, drinking water, insect bite, animals, sexual exposure, illness among fellow travellers and exposure to sick contacts give clue to the cause of fever [70,71].(see table 7)

Incubation period

The date of travel/exposure and date of onset of first symptom, in travelers will give us an idea about the incubation period of that particular illness, which will help us to narrow down our differential diagnosis (See table 7). An incubation period of less than 2 weeks usually rule out diseases with long incubation period like amoebic liver disease, filariasisetc, where as an incubation period of >3 weeks rules out the disease with short incubation period like Bacillary dysentery, dengue, chickunguniya etc. The incubation period of plasmodium falciparum ranges from 8 days to 40 days, but can be lengthened if patient has taken antimalarial chemoprophylaxis [64]. But in plasmodiumvivax, plasmodiumovale and plasmodiummalariae infection, incubation period can be prolonged for several months to years. Similarly infection like strongyloidesandschistosomiasis can manifest many months or years after exposure.Most case of plasmodium falciparum present withinone month of exposure, where plasmodium vivax present after one month.

Health status of the patient before travel

Health status of the patient before travel like cardio pulmonary disorder, malignancy,

immuno suppression and asplenia gives clues to the probable caus of fever.

Conclusion

Acute febrile illness is a common clinical problem and the diagnosis is challenging. A stepwise evaluation considering the diagnostic possibilities in that geographical area with special consideration to patient characteristics will help to tackle most of the cases. Fever in travelers can be due to common causes seen in non-travelers or can be infection specifically related to travelling. In addition to usual history and physical examination, a detail regarding immunization, chemoprophylaxis, travel history, history of various exposures and knowledge about incubation period help in clinical diagnosis of cause of fever in travelers.

References

1. Susilawati TN, McBride WJ. Acute undifferentiated fever in Asia: a review of the literature. The Southeast Asian journal of tropical medicine and public health 2014;45:719-26.

2. Varghese GM, Trowbridge P, Doherty T. Investigating and managing pyrexia of unknown origin in adults. BMJ 2010;341:C5470.

3. Hayakawa K, Ramasamy B, Chandrasekar PH. Fever of unknown origin: an evidence-based review. Am J Med Sci. 2012;344:307-16.

4. Susilawati TN, McBride WJ. Undiagnosed undifferentiated fever in Far North Queensland, Australia: a retrospective study. International journal of infectious diseases 2014;27:59-64.

5. Phuong HL, de Vries PJ, Nagelkerke N, Giao PT, Hung le Q, Binh TQ, et al. Acute undifferentiated fever in Binh Thuan province, Vietnam: imprecise clinical diagnosis and irrational pharmaco-therapy. TM & IH 2006;11:869-79.

6. Hamilton JL, John SP. Evaluation of fever in infants and young children. American family physician. 2013;87:254–60. PMID:23418797.

7. Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, etal. Global trends in emerging infectious diseases. Nature 2008;451:990–3. doi:10.1038/nature06536PMID:18288193.

8. Joshi R, Colford JM, Jr., Reingold AL, Kalantri S. Non-malarial acute undifferentiated fever in a rural hospital in central India: diagnostic uncertainty and overtreatment with antimalarial agents. The American journal of tropical medicine and hygiene 2008;78:393-9.

9. Punjabi NH, Taylor WR, Murphy GS, Purwaningsih S, Picarima H, Sisson J, et al. Etiology of acute, non-malaria, febrile illnesses in Jayapura, northeastern Papua, Indonesia. The American journal of tropical medicine and hygiene 2012;86:46-51.

10. Chappuis F, Alirol E, d'Acremont V, Bottieau E, Yansouni CP. Rapid diagnostic tests for non-malarial febrile illness in the tropics. Clin Microbiol Infect 2013;19:422–31. doi:10.1111/1469-0691.12154 PMID:23413992.

11. Crump JA, Morrissey AB, Nicholson WL, Massung RF, Stoddard RA, Galloway RL, etal. Etiology of severe non-malaria febrile illness in Northern Tanzania: a prospective cohort study. PLoS Negl Trop Dis 2013;7: e2324. doi:10.1371/ journal.pntd. 0002324 PMID:23875053; Pub Med Central PMCID: PMCPMC3715424.

12. D'Acremont V, Kahama-Maro J, Swai N, Mtasiwa D, Genton B, Lengeler C. Reduction of anti-malarial consumption after rapid diagnostic tests implementation in Dares Salaam: a before-after and cluster randomized controlled study. Malar J 2011;10:107.doi:10.1186/1475-2875-10-107 PMID:21529365; Pub Med Central PMCID: PMCPMC3108934.

13. Humar A, Keystone J. Evaluating fever in travellers returning from tropical countries. BMJ 1996;312:953-6

14. Dupuy A M, Philippart F, Pean Y, Lasocki S, Charles P E, Chalumeau M, etal. Role of biomarkers in the management of antibiotic therapy: an expert panel review: currently available biomarkers for clinical use in acute infections. Ann Intensive Care. 2013;3(1):22.doi:10.1186/2110-5820-3-22PMID: 23837559; Pub Med Central PMCID:PMC3708786.

15. Hai Err ,Viroj Wiwanitkit. "Syndromic approach" to diagnosis and treatment of critical tropical infections. Indian J Crit Care Med 2014; 18: 479.

16. Pappachan MJ, Mathew S, Aravindan KP, Khader A, Bharghavan P V, Kareem MMA, et al. Risk factors for mortality in patients with leptospirosis during an epidemic in northern Kerala. Natl Med J India 2004;17:240–2.

17. Izurieta R, Galwankar S, Clem A. Leptospirosis: The"mysterious"mimic. Journal of emergencies, trauma, and shock 2008;1:21–33. doi:10.4103/0974-2700.40573 PMID:19561939; Pub Med Central PMCID:PMC2700559.

18. Rajneesh Joshi, SP Kalantri. Acute Undifferentiated Fever: Management Algorithm. In Ashish Bhalla, editor. Update on Tropical Fever : Association of Physicians of India and Indian College of Physicians; 2015. p. 1-14. http://www.apiindia.org/pdf/monograph_2015_update_on_tropical_fever/001_acute_undifferentiated_fever.pdf

19. John TJ, Dandona L, Sharma VP, Kakkar M. Continuing challenge of infectious diseases in India. Lancet 2011;377:252-69.

20. Nuutila J, Jalava-Karvinen P, Hohenthal U, Kotilainen P, Pelliniemi T T, Nikoskelainen J, etal. A rapid flow cytometric method for distinguishing between febrile bacterial and viral infections. Journal of microbiological methods 2013;92:64–72. Epub2012/11/17. doi:10.1016/ j.mimet.2012.11.005 PMID: 23154042.

21. Nuutila J, Jalava-Karvinen P, Hohenthal U, Kotilainen P, Pelliniemi TT, Nikoskelainen J, etal. Use of complement regulators, CD35, CD46, CD55, and CD59, on leukocytes as markers for

diagnosis of viral and bacterial infections. Human immunology 2013;74:522–30.

22. Putto A, Ruuskanen O, Meurman O, et al. C reactive protein in the evaluation of febrile illness. Arch Dis Child 1986;61:24–9.

23. Haran JP, Beaudoin FL, Suner S, LuS. C-reactive protein as predictor of bacterial infection among patients with an influenza-like illness. The American journal of emergency medicine 2013;31:137–44.

24. Chaudhary N, Kosaraju K, Bhat K, BairyI, Borker A. Significance of interleukin-6(IL-6) and C-reactive protein (CRP) in children and young adults with febrile neutropenia during chemotherapy for cancer: a prospective study. Journal of pediatric hematology/oncology 2012;34:617–23.

25. Gozzard D, Yin J, Delamore I. The clinical usefulness of C-reactive protein measurements. Br J Haematol 1986; 63:411–4.

26. Grutzmeier S, von Schenck H. C-reactive protein during chemotherapy for acute leukemia with special reference to non-infective causes of fever. Med Oncol Tumor Pharmacother 1986;3:71–5.

27. Brodska H, Malickova K, Adamkova V, Benakova H, Stastna MM, Zima T. Significantly higher procalcitonin levels could differentiate Gram-negative sepsis from Gram-positive and fungal sepsis. Clinical and experimental medicine 2013;13:165–70..

28. Koya J, Nannya Y, Ichikawa M, Kurokawa M. The clinical role of procalcitonin in hematopoietic SCT. Bone marrow transplantation 2012;47:1326–31. Epub2012/02/22.doi:10.1038/bmt.2012.18 PMID:22343672.

29. Schuetz P, Briel M, Christ-Crain M, et al. Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. Clin Infect Dis 2012;55:651-662.

30. Matthaiou DK, Ntani G, Kontogiorgi M, Poulakou G, Armaganidis A, Dimopoulos G. An ESICM systematic review and meta-analysis of procalcitonin guided antibiotic therapy algorithms in adult critically ill patients. Intensive Care Med 2012;38:940-9.

31. Gilbert DN. Use of plasma procalcitonin levels as an adjunct to clinical microbiology. J ClinMicrobiol 2010;48:2325-9.

32. Mc Culloh R. Biomarkers in Sepsis and Severe Infection: Where Immunology Meets Diagnostics. J Immunodefic Disor 2012;1:1.

33. Kapasi AJ, Dittrich S, González IJ, Rodwell TC. Host Biomarkers for Distinguishing Bacterial from Non-Bacterial Causes of Acute Febrile Illness: A Comprehensive Review. PLoSONE 2016;11(8): e0160278.doi:10.1371/journal.pone.0160278

34. Lathia TB, Joshi R. Can hematological parameters discriminate malaria from non-malarious acute febrile illness in the tropics? Indian J Med Sci 2004; 58:239-44.

35. Gao Y, Li Y, Yu X, Guo S, Ji X, Sun T, Lan C, Lavergne V, Ghannoum M, Li L. The impact of various platelet indices as prognostic markers of septic shock. PLOS ONE 2014;9:e103761.

36. Varol E. Platelet indices in assessment of in hospital mortality in intensive care unit patients. J Crit Care 2014;29:864.

37. Guclu E, Durmaz Y, Karabay O. Effect of severe sepsis on platelet count and their indices. Afr Health Sci 2013;13:333–8.

38. Chrispal A, Boorugu H, Gopinath KG, Chandy S, Prakash JA, Thomas EM, et al. Acute undifferentiated febrile illness in adult hospitalized patients: the disease spectrum and diagnostic predictors - an experience from a tertiary care hospital in South India. Trop Doct 2010; 40:230-34.

39. Pasvol G. Management of severe malaria: interventions and controversies. Infect Dis Clin North Am 2005; 19: 211-40.

40. McKenzie FE, Prudhomme WA, Magill AJ, Forney JR, Permpanich B, Lucas C, et al. White blood cell counts and malaria. J Infect Dis 2005 Jul;192:323-30.

41. Zeeba Shamim Jairajpuri, Safia Rana, Mohd Jaseem Hassan, Farhat Nabi, Sujata Jetley. An Analysis of Hematological Parameters as a Diagnostic test for Malaria in Patients with Acute Febrile Illness: An Institutional Experience. Oman Medical Journal 2014;29:12-7. No. 1:12-17 DOI 10. 5001/omj.2014.04

42. Abba K, Deeks JJ, Olliaro P, Naing CM, Jackson SM, Takwoingi Y, et al. Rapid diagnostic tests for diagnosing uncomplicated P. falciparum malaria in endemic countries. The Cochrane database of systematic reviews. 2011;7:CD008122

43. Meena M, Joshi D, Joshi R, Sridhar S, Waghdhare S, Gangane N, et al. Accuracy of a multispecies rapid diagnostic test kit for detection of malarial parasite at the point of care in a low endemicity region. Transactions of the Royal Society of Tropical Medicine and Hygiene 2009;103:1237-44.

44. lacksell SD, Jarman RG, Bailey MS, Tanganuchitcharnchai A, Jenjaroen K, Gibbons RV, et al. Evaluation of six commercial point-of-care tests for diagnosis of acute dengue infections: the need for combining NS1 antigen and IgM/IgG antibody detection to achieve acceptable levels of accuracy. Clinical and vaccine immunology 2011;18:2095-101

45. Fadeel M. A., J. A. Crump, F. J. Mahoney, I. A. Nakhla, A. M. Mansour, B. Reyad, et al. Rapid diagnosis of typhoid fever by enzyme-linked immunosorbent assay detection of Salmonella serotype Typhi antigens in urine. Am. J. Trop. Med. Hyg 2004.70:323–8

46. Gilman, R. H., M. Terminel, M. M. Levine, P. Hernandez-Mendoza, and R. B. Hornick. Relative efficacy of blood, urine, rectal swab, bone- marrow, and rose-spot cultures for recovery of Salmonella typhi in typhoid fever. Lancet 1975. i:1211–3

47. Rigau-Perez JG, Laufer MK. Dengue-related deaths in Puerto Rico, 1992-1996: diagnosis and clinical alarm signals. Clinical infectious diseases 2006;42:1241-6.

48. Capending MR, Chua MN, Hadinegoro SR, Hussain II, Nallusamy R, Pitisuttithum P, et al. Dengue and other common

causes of acute febrile illness in Asia: An active surveillance study in children. PLoSNegl Trop 2013; 7:52-3

49. Leelarasamee A, Chupaprawan C, ChenchittikulM, Udompanthurat S. Etiologies ofacute undifferentiated febrile illness inThailand. J Med Assoc Thai 2004; 87: 464-72

50. Danno K, Cognet-Dementhon B, Thevenard G, Duru G, Allaert FA, Bordet MF. Effectiveness of homeopathic medicine associated with allopathic medicine in the outpatient management of influenza-like illnesses or ear, nose, and throat disorders by pharmacists. JMCP. 2013;19:631-41.

51. Batwala V, Magnussen P, Nuwaha F. Antibiotic use among patients with febrile illness in a low malaria endemicity setting in Uganda. Malaria Journal 2011 10:377-85.

52. Phimda K, Hoontrakul S, Suttinont C, Chareonwat S, Losuwanaluk K, Chueasuwanchai S, et al. Doxycycline versus azithromycin for treatment of leptospirosis and scrub typhus. Antimicrobial agents and chemotherapy 2007;51:3259-63.

53. Suttinont C, Losuwanaluk K, Niwatayakul K, Hoontrakul S, Intaranongpai W, Silpasakorn S, et al. Causes of acute, undifferentiated, febrile illness in rural Thailand: results of a prospective observational study. Annals of tropical medicine and parasitology 2006;100:363-70.

54. Mayxay M, Castonguay-Vanier J, Chansamouth V, Dubot-Peres A, Paris DH, Phetsouvanh R, et al. Causes of non-malarial fever in Laos: a prospective study. The Lancet Global health 2013;1:e46-54.

55. Charan J, Saxena D, Mulla S, Yadav P. Antibiotics for the treatment of leptospirosis: systematic review and meta-analysis of controlled trials. International journal of preventive medicine 2013;4:501-10.

56. Bhan MK, Bahl R, Bhatnagar S. Typhoid and paratyphoid fever. Lancet 2005;366:749-62.

57. Tabak F, Mert A, CelikAD,Ozaras R, Altiparmak MR, Ozturk R, Aktuglu Y. Fever of unknown origin in Turkey. Infection 2003;31: 417–20

58. Kasper MR, Blair PJ, Touch S, et al. Infectious etiologies of acute febrile illness among patients seeking health care in south-central Cambodia. Am J Trop Med Hyg 2012; 86:246-53.

59. Bruni M, Steffen R. Impact of travel-related health impairments. J Travel Med 1997;4:61-4.

60. O'Brien D, Tobin S, Brown GV, Torresi J. Fever in returned travelers: review of hospital admissions for a 3-year period. Clin Infect Dis 2001;33:603-9.

61. Doherty JF, Grant AD, Bryceson AD. Fever as the presenting complaint of travellers returning from the tropics. QJM 1995;88:277-81.

62. Strickland GT. Fever in the returned traveler. Med Clin North Am 1992;76:1375-92

63. Suh KN, Kozarsky PE, Keystone JS. Evaluation of fever in the returned traveler. Med Clin North Am 1999;83:997-1017.

64. Reyburn H, Behrens RH, Warhurst D, Bradley D. The effect of chemoprophylaxis on the timing of onset of falciparum malaria. Trop Med Int Health 1998;3:281-5.

65. Spira AM. Assessment of travellers who returnhome ill. Lancet 2003;361:1459-69.

66. Centers for Disease Control and Prevention. Brunette GW, Kozarsky PE, Cohen NJ, Gershman MD, Magill AJ, Ostroff SM, Ryan ET, Shlim DR, Weinberg M, Wilson ME. CDC Health Information for International Travel 2016. New York, NY: Oxford University Press; 2016.

67. Felton JM, Bryceson AD. Fever in the returning traveller. Br J Hosp Med 1996;55:705-11.

68. Saxe SE, Gardner P. The returning traveler with fever. Infect Dis Clin North Am 1992;6:427-39.

69. Ryan ET, Wilson ME, Kain KC. Illness after international travel. N Engl J Med 2002;347:505-16.

70. Magill AJ. Fever in the returned traveler. Infect DisClin North Am 1998;12:445-69.

71. Matteelli A, Carosi G. Sexually transmitted diseases in travelers. Clin Infect Dis 2001;32:1063-7.

Conflict of Interest: Nil
Source of Support: Nil

How to Cite this Article

Raveendran A V. Acute febrile illness: A stepwise approach for clinicians. Indian J Med Sci 2018 April-Aug;70 (2):30-37.