FEVER GUIDELINES

A Stepwise Guide for Differential Diagnosis and Management of Acute Fever in Primary Care : An Indian Perspective

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Introduction

Acute fever is one of the most common presenting complaints addressed byphysicians in primary care and outpatient departments in India [1–3]. Acute undifferentiated febrile illnesses (AUFIs) are characterized by fever (>38.3°C or 101.0°F) for more than 2 days, lasting up to 14 days without organ-specific or system-specific symptoms at the onset [4,5]. Some of the common causes of AUFIs include malaria, dengue, enteric fever, leptospirosis, and scrub typhus, which continue to contribute significantly to the febrile disease burden in India [5]. Malaria and dengue are the most prevalent febrile illness–associated forms of fever in India [6]. India is estimated to contribute to 34% of the total global burden of dengue [7]. In a multicenter study in India, approximately 17% of AUFI cases were diagnosed as malaria, out of which 54% had *Plasmodium falciparum* [6]. Dengue was diagnosed in 16% of AUFI cases, followed by scrub typhus (10%), leptospirosis (7%), and chikungunya (6%) [6]. The incidence of scrub typhus, an underreported endemic in various parts of India, ranges from 10% to 47.5% [6,8,9]. Studies have also reported the incidence of leptospirosisin India, ranging from 3% to 7% [6,8]. Acute fever or acute febrile illness (AFI) can also arise due to localized infections, such as respiratory tract infections (RTIs), urinary tract infections (UTIs), intra-abdominal infections (IAIs), or skin and soft tissue infections (SSTIs) [4,5]. Fevers of unknown origins (FUOs) are differentiated from AUFIs or localized AFIs by a prolonged state of fever (≥38.3°C or 101.0°F for 21 days or longer) without an etiology after a hospital workup or 1 week of inpatient evaluation [10,11]. The majority of patients with acute fever present to the primary care with nonspecific symptoms, such as low-grade fever, general malaise, headache, arthralgia, myalgia, and rash with or without a focal point of infection [4,5,12]. The nonspecific and overlapping clinical symptoms, along with a scarcity of available appropriate diagnostic facilities, present a challenge to the treating physicians and can make timely treatment difficult [2,13]. The difficulty in discriminating the etiology of fever based on clinical features alone results in the irrational use of antibiotics/antimalarial drugs in primary care [2,14].A stepwise approach with a careful interpretation of local disease patterns, clinical features, risk factors, and laboratory data can help healthcare professionals (HCPs) recognize specific causes of acute fever. An enhanced understanding of the etiologies of AFI is critical for developing management algorithms for the pertinent use of antimalarials/antibiotics and essential for monitoring the impact on antimicrobial resistance in primary care. In this article, we have created a stepwise guide for differential diagnosis and management of AUFIs and AFIs due to localized infections in primary care practice based on an expert panel discussion.

Methodology

An advisory board meeting was convened on 11 July 2021, in association with Indian Medical Association (IMA) on a virtual platform to develop a "*Stepwise Guide for Management of Acute Fever in Primary Care.*"A literature review was carried out based on data from the PubMed database to identify relevant articles published between January 2001 and August 2021,using keywords such as "India,""adults,""burden,""acute undifferentiated febrile illness,""localized infections,""acute febrile illness,""antibiotics,""guidelines,""diagnosis,""management,"and "algorithm." Key articles were shortlisted and circulated among the expert panel members as prereading material before the advisory board meeting. During the advisory board meeting, in addition to the interactive discussion, a qualitative question-and-answer–based format was used to facilitate discussion. After the group discussion, key expert opinions were formulated based on the opinions and agreement of the majority.

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Stepwise Approach for Diagnosis of Acute Fever in Primary Care

Evaluation of Medical History of the Patient: This includes evaluation of the medical history of the patient, such as previous fevers, infections, or known conditions predisposing to infection (congenital heart disease, sickle cell anemia, cancer, and immunodeficiency) [4,15].Consideration of patient-related factors, such as age, immunosuppression, pregnancy, and comorbidities (diabetes, chronic kidney disease, malignancy, autoimmune disease, rheumatologic fever, or liver impairment), can help narrow the differential diagnosis and provide vital clues[5,11,16–19].

Clinical Examination of the Patient: A complete and thorough physical examination is mandatory. Initial clinical evaluation should involve assessment of respiratory rate, hydration status, mental status, oropharynx, conjunctiva, skin, chest, heart, and abdomen[4,5,15,20–22]. Symptoms that can help direct the evaluation toward noninfectious causes include (i) heart palpitations; (ii) sweating and heat intolerance (hyperthyroidism); and (iii) recurrent or cyclic symptoms (rheumatoid, inflammatory, or hereditary disorder) [15].

Key points to consider:

- The Indian Medical Association recommends mercury-free digital thermometers over traditional mercury thermometers for temperature measurement in primary care to avoid the potential hazards of broken glass and liquid mercury [23].Digital thermometers are safe and provide faster, more accurate results as opposed to mercury thermometers [24,25].In the current trying times of COVID-19, auxiliary thermometry can be preferred over oral thermometry as it reduces the risk of cross-contamination.
- Pneumonia, SSTI, UTI, and gastroenteritis are well-recognized issues among elderly patients with fever [20].
- Pregnancy-related immunosuppression is associated with increased severity of falciparum malaria. Other causes of fever in pregnancy include UTIs, influenza, pneumonia, tonsillitis, viral gastroenteritis, and pyelonephritis (kidney infection) [5,21,22].
- Review of systems should include (i) febrile seizures; (ii) runny nose and congestion (viral UTI); (iii) headache (sinusitis, meningitis); (iv) ear pain or waking in the night with signs of discomfort (otitis media); (v) cough or wheezing (pneumonia, bronchiolitis) and abdominal pain (pneumonia, streptococcal pharyngitis, gastroenteritis, abdominal abscess); and (vi) back pain (pyelonephritis) and any history of joint swelling or redness (osteomyelitis) [5,15,21,22].

*Evaluation of Clinical Features:*This step involves the evaluation of (i) onset, duration, and course of fever; (ii) key rule-in and rule-out features; (iii) characteristic pattern of organ involvement (if any); and (iv) red flags [5]. Prostration, hyperpyrexia, hypothermia, shortness of breath, altered mental status, blood pressure<100 mmHg systolic, severe or persistent vomiting, severe conjunctiva, jaundice, and bleeding are red flags in adult AUFI patients, indicating the need for hospitalization, referral, and urgent treatment [5].Criteria for immediate attention and referral in pediatric patients include (i) age <1 month; (ii) lethargy, listlessness, or toxic appearance; (iii) respiratory distress; (iv) petechiae or purpura; (v) inconsolable crying; (vi) seizures; and (vii) difficult to stay awake, and (viii) stiff neck [15].

*Perform Diagnostic Tests:*This step involves performing first-line and confirmatory diagnostic tests depending on the day of investigation of the patient by HCPs and the severity ofthe fever. A complete blood count, urine analysis, smear microscopy, and/or rapid diagnostic testsare important in patients with fever[4,5]. Biochemical tests (liver and renal function tests), imaging X-rays, and ultrasonography are valuable in patients presenting with localized symptoms and in patients with severe illness to reveal complications [5]. Table 1 lists the characteristic clinical features and complications associated with different types of AUFIs (A) and AFIs due to localized infections (B).

A) Differential Diagnosis of Acute Undifferentiated Febrile Illnesses (AUFIs)

	Analysis of clinical features	Diagnostic Evaluation
Malaria	Clinical features:[26,27] Paroxysm of fever, shaking chills, and sweats occur every 48 hours or 72 hours, depending on the species Manifestations of severe malaria: [26,27] • Cerebral malaria, severe anemia, metabolic acidosis, and acute renal failure • ARDS and shock	Initial:[5] RDT for malarial antigens (ICT format): Histidine-rich protein 2 (HRP-2), plasmodium lactate dehydrogenase (pLDH), plasmodium aldolase (pAldolase) Confirmatory:[5] Microscopy: Presence of parasites in the blood. The presence of only gametocytes suggests that the current illness is not malaria.
Dengue	Clinical features: [26,27] • Dengue fever: Headache, retro-orbital pain, myalgia, arthralgia, and rash • Dengue hemorrhagic fever: Thrombocytopenia, mucosal and gastrointestinal bleeds, rise in hematocrit • Dengue shock syndrome: Weak pulse and hypotension • Expanded dengue syndrome:Encephalitis, myocarditis, hepatitis, renal failure, ARDS, and hemophagocytosis.	Initial:[5,27] • RDT NS1 antigen: NS1 antigen in blood collected within 6 days of onset. • RDT IgM: Dengue-specific IgM antibody in blood Confirmatory:[27] Isolation of virus from blood or tissue collected within 5 days of onset of fever. Detection of dengue RNA in blood or tissue collected within 5 days of onset. Note: (i) NS1 antigen ELISA or RT-PCR: for <5 days of illness; (ii) IgM capture ELISA (MAC-ELISA) for >5 days of illness from blood/serum sample.

Enteric fever	Clinical features: [26,27] • First week:Fever, headache, and relative bradycardia • Second week:Abdominal pain, diarrhea, constipation, hepatosplenomegaly, and encephalopathy • Third week:Intestinal bleeding,perforation, and MODS	Initial: [5] RDT for antibody: Detection of antibody against salmonellae in single serum specimens Confirmatory: [5] • Isolation of enteric fever *Salmonella* from blood and bone marrow • Widal test
Chikungunya	Clinical features:[28] Acute onset of moderate-to-high–grade continuous fever, rash, malaise, arthralgia, myalgia, and red eyes. Complications:[28] • Respiratory failure • Cardiovascular decompensation • Myocarditis • Acute hepatitis • Renal failure	Initial:[27,28] Early disease: Presence of viral RNA by RT-PCR. Note: RT-PCR can also be used to quantify the viral load in the blood. CHIKV RNA can be detected during the acute phase of illness (≤8 days after symptom onset). Confirmatory: After first week of illness: IgM capture ELISA
Leptospirosis	Clinical features: [26,27] Anicteric leptospirosis: • Abrupt onset of fever, chills, headache, and myalgia • Abdominal pain, conjunctival suffusion, and transient skin rash Icteric leptospirosis: • Jaundice, proteinuria, hematuria, oliguria, and/or anuria • Pulmonary hemorrhages, ARDS, and myocarditis	Initial:[5,29] RDT for IgM: Specific IgM in serum IgM ELISA: Specific IgM in serum Confirmatory: [5,29] • Microscopic agglutination test for antibody • PCR test: Detection of *Leptospira* DNA in blood, CSF, and urine after amplification • Isolation of *Leptospira* spp. from blood, CSF, and dialysate in first 10 days, and from urine afterward
Japanese encephalitis	Clinical features: [26,27] • Prodromal period fever, headache, vomiting, and myalgia • Neurological features range from mild confusion to agitation to overt coma • Parkinson-like extrapyramidal signs are common, including tremor, rigidity, and choreoathetoid movements	Initial:[26,30] IgM capture ELISA: Confirmatory: [26,30] Detection of JE virus, antigen in tissue/blood by immunochemistry/PCR.
Scrub typhus	Clinical features: [26,27] • Fever, headache, and myalgia • Breathing difficulty, delirium, vomiting, cough, and jaundice Complications: [26,27] • Overwhelming pneumonia • Hepatitis • Aseptic meningitis • Myocarditis and disseminated intravascular coagulation	Initial:[5] ❑ RDT for specific IgM (ICT format): Detection of IgM in single specimens ❑ ELISA for specific IgM using recombinant antigens Confirmatory: [5] ❑ IFA or IPA for antibodies ❑ Confirmatory test: Weil–Felix test

B) Differential Diagnosis of Acute Febrile Illnesses (AFIs) Due to Localized Infections		
Fever due to URTI	Presenting features of URTI include sore throat, runny/blocked nose, cough with or without systemic symptoms, including fever and malaise.[4]	Examination findings include tonsillo-pharyngeal erythema and exudates, palatal petechiae, tender anterior cervical adenopathy, and sometimes scarlatiniform rash.[4,32] Confirmation of diagnosis by rapid antigen test or throat swab culture is desirable.[4,32]
Fever due to LRTI	Characterized by (i) symptoms of acute lower respiratory tract illness (cough with or without expectoration, shortness of breath, pleuritic chest pain) for less than 1 week and (ii) at least one systemic feature (temperature >37.7°C, chills, and rigors, and/or severe malaise).[4]	X-ray PNS is done to check fluid levels, only if there is chronic sinusitis.If the duration of illness is >10 days with purulent nasal discharge, nasal obstruction, and facial pain, then a bacterial cause should be considered.[4,32]
Viral fever	Viral pneumonia due to adenovirus, influenza A and B, human metapneumovirus, parainfluenza, RSV, rhinovirus, and cytomegalovirus. Characterized by high-grade fever, cough, sore throat, or myalgia.[4,27,31] COVID-19:[4,27,31] • Symptoms include cough, dyspnea, myalgia, headache, sore throat, diarrhea, rhinorrhea, tachypnea, decreased oxygen saturation, and multiorgan involvement. • Complications include ARDS, arrhythmias, acute cardiac injury shock, pulmonary embolism, and acute stroke.	Viral pneumonia: [31] RT-PCR positive for the underlying virus, elevated lymphocyte counts COVID-19 fever: [31] RT-PCR positive for SARS-CoV-2, lymphopenia, elevated aminotransferases, CRP, and D-dimer. CT in case of viral pneumonia: [31] Interstitial inflammation, high-attenuation reticular patterns, localized atelectasis, or pulmonary edema CT in case of COVID-19: [31] • Early stage: GGOs • Progressive stage: Multiple GGOs, consolidation patches, and crazy-pavement pattern • Advanced stage: Diffuse exudative lesionsand whiteout lung

Fever due to UTI	Acute cystitis characterized by dysuria, frequency, and urgency with or without fever with chills. [4] Acute pyelonephritis characterized by flank pain, tenderness, or both and fever associated with dysuria, urgency, and frequency. [4]	Routine urine analysis: Significant pyuria and/or dipstick leukocyte esterase test positive.[4]
Fever due to IAI	Invasive bacterial (inflammatory) diarrhea characterized by fever, tenesmus, and grossly bloody stool. [4]	A stool culture is indicated if the patient has symptoms lasting for morethan 3–7 days or is immunosuppressed. Microscopic evidence containing red blood cells can provide sufficient evidence. [4]
Fever due to SSTI	SSTIs involve features of an inflammatory response, with other manifestations, such as fever, rapid progression of lesions, and bullae. [4]	Initial diagnosis involves morphologic features of lesion and the clinical setting. If drainage or an open wound is present, Gram's stain and culture can provide a definitive diagnosis.[33] In the absence of culture findings, bacterial etiology is difficult to establish. [33]
Fever due to BJI	Septic arthritis includes acute onset of high-grade fever with tender swollen joints. [4]	Leukocytosis, high ESR, and CRP are features of septic arthritis. [4] Synovial fluid from the infected joint should be sent for WBC counts, Gram stain, and culture before starting antibiotics. [4] Blood cultures should be obtained for all suspected cases of septic arthritis before starting antibiotics. [4]

Table 1: Characteristic clinical features and complications associated with different types of AUFIs (A) and AFIs due to localized infections (B). AUFIs: Acute undifferentiated febrile illnesses; AFIs: Acute febrile illness; ARDS: Acute respiratory distress syndrome; MODS: Multiple organ dysfunction syndrome; RDT: Rapid diagnostic test; ICT: Immunochromatographic test; Ig: Immunoglobulin G; NS-1: Nonstructural antigen 1; ELISA: Enzyme-linked immunosorbent assay; IFA: Immunofluorescent assay; IPA: Immunoperoxidase assay; BD: Twice a day; UTI: Urinary tract infection; SSTI: Skin and soft tissue infection; IAI: Intra-abdominal infection; BJI: Bone and joint infections; COVID-19: Coronavirus disease 2019; HCPs: Healthcare professionals; OD: Once a day; PCR: Polymerase chain reaction; RT: Reverse transcription; JE: Japanese encephalitis; RNA: Ribonucleic acid; CSF: Cerebrospinal fluid; URTIs: Upper respiratory tract infections; LRTIs: Lower respiratory tract infections; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; PCR: Polymerase chain reaction; CT: Computed tomography; CRP: C-reactive protein; GGO: Ground-glass opacities; RT: Reverse transcription; IP: Incubation period; PNS: Paranasal sinus; ESR: Erythrocyte sedimentation rate; CAP: Community-acquired pneumonia; RSV: Respiratory syncytial virus; WBC: White blood cells.

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Early presumptive antibiotic therapy is important for suspected bacterial AUFIs, which present with characteristic clinical features. These empirical therapies are necessary if diagnostic confirmatory testing is awaited or not available [5]. In cases of rapidly progressive infections, such asleptospirosis, delayed prognosis leading to delayed therapy may increase disease severity and complications [5]. In severely ill patients with nonmalarial, nonarboviral AUFIs, a combination of third-generation cephalosporin plus doxycycline as empirical therapy canhelp manage rickettsioses, leptospirosis, and enteric fever[5]. Doxycycline can also serve as a companion antimalarial drug to artesunate and ceftriaxone, and address concomitant bacterial sepsis, which is frequently observedin such patients[5]. Furthermore, incase of resource-poor settings and certain compelling indications, the empirical use of broad-spectrum antibiotics such asdoxycycline can be considered forthe management of acute fever [3].Diet plays an important role in improving the treatment plan and should be carefully planned and monitored. The patient must be prescribed a soft bland diet loaded with immune-boosting foods, which help to strengthen the immune system. Table 2 details the management of different types of AUFIs (A) and AFIs due to localized infections (B).

A) Management of Acute Undifferentiated Febrile Illnesses (AUFIs)	
Malaria[27,34]	• Vivax malaria: Chloroquine (25 mg/kg b.w divided over 3 days, i.e. 10 mg/kg on day 1, 10 mg/kg on day 2, and 5 mg/kg on day 3) and primaquine (0.25 mg/kg b.w daily for 14 days). Primaquine is used to prevent relapse but is contraindicated in pregnant women and infants. • Falciparum malaria: Artesunate 4 mg/kg b.w daily for 3 days plus sulfadoxine (25 mg/kg b.w) and pyrimethamine (1.25 mg/kg b.w) on day 1. This is to be accompanied by single dose of primaquine (0.75 mg/kg b.w) preferably on day 2. Chemoprophylaxis (<6 weeks): Doxycycline: 100 mg daily in adults and 1.5 mg/kg b.w for children more than 8 years old. The drug should be started 2 days before travel and continued for 4 weeks after leaving the malarious area. Note: Doxycycline is contraindicated in pregnant and lactating women and children less than 8 years.
Dengue[35]	Antipyretics (avoid salicylates/ibuprofen) and tepid water sponging if the temperature is above 39°C. Tab paracetamol 10 mg/kg TDS. Increase fluid intake: • Children: 50 mL/kg b.w fluids during first 4–6 hours. Maintenance: 80–100 mL/kg b.w in the next 24 hours • Adults: 2.5–4 L/day
Enteric fever[36]	Oral amoxicillin 25 mg/kg TDS for 10–14 days Oral trimethoprim/sulfamethoxazole 4–20 mg/kg BD for 10–14 days

Chikungunya[28]	The patientmay be treated symptomatically with paracetamol. If the pain is intractable, then NSAIDs, such as ibuprofen (400 mg TDS), naproxen (250 mg BD), and diclofenac (50 mg BD), can be used. To minimize gastric intolerance, H2 blockers ranitidine 150 mg BD or proton pump inhibitors, such as omeprazole 20 mg OD, may be used.
Leptospirosis[29]	• Adults: Doxycycline 100 mg BD for 7 days. • Pregnant and lactating mothers should be given capsule ampicillin 500 mg 6 hourly. • Children (<8 years): Amoxicillin/ampicillin 30–50 mg/kg/day in divided doses for 7 days. Chemoprophylaxis: During the peak transmission season, doxycycline 200 mg, once a week. Note: Chemoprophylaxis should be for 6 weeks and should never be extended for more than 8 weeks.
Japanese encephalitis[26,30]	Paracetamol 15 mg/kg diluted in 50 mL saline as retention enema. Oral syrup may be diluted 1:1 with ordinary water and used. Supportive airway management, seizure control, and management of raised intracranial pressure.
Scrub typhus[5,26]	First line: Doxycycline 100 mg BD for 7 days. Azithromycin or rifampicin or chloramphenicol as alternatives in children and pregnant women.

B) Management of Acute Febrile Illnesses (AFIs) Due to Localized Infections	
Fever due to URTI[4]	• For streptococcal pharyngitis, penicillin V (not easily available in India). Penicillin G is not a substitute asoral absorption is poor. Alternatives include amoxicillin and benzathine penicillin, single dose. • For bacterial sinusitis, amoxicillin and co-amoxiclav (preferred) is to be given. Alternatives include ceftriaxone or cefpodoxime. Quinolones are not advised as a first-line treatment option for URTIs.
Fever due to LRTI[4]	Preferred options include: • Co-amoxiclav and macrolide/doxycycline • Ceftriaxone with macrolide/doxycycline Alternatives include: • Cefuroxime/cefpodoxime and macrolide/doxycycline • Cefotaxime/amoxiclav with macrolide/doxycycline Quinolones are not advised for CAP patients and patients with LRTIs.
Viral fever[4,37]	Antibiotic therapy or prophylaxis should not be used in patients with mild COVID-19. For suspected or confirmed moderate COVID-19, antibiotics should not be prescribed unless there is clinical suspicion of a bacterial infection. • Consider in older people and children <5 years of age to provide empiric antibiotic treatment for possible pneumonia. • Consider antibiotics, such as co-amoxicillin, as adequate instead of broad-spectrum antibiotics. Quinolones are not advised for patients with respiratory tract infections.
Fever due to UTI[4]	For acute cystitis, nitrofurantoin or fosfomycin.Alternatives include co-trimoxazole, ertapenem, or amikacin. For acute pyelonephritis, piperacillin–tazobactam or ertapenem. Alternatives include imipenem, meropenem, or amikacin.
Fever due to IAI[4]	Preferred options include metronidazole and azithromycin
Fever due to SSTI[4]	Preferred therapy includes cefazolin or cephalexin or amoxicillin–clavulanate±clindamycin
Fever due to BJI[4]	MSSA: Cloxacillin, flucloxacillin, or cefazolin. Alternatives include ceftriaxone or daptomycin MRSA: Vancomycin or teicoplanin. Alternatives include daptomycin or linezolid

Table 2: Management of different types of AUFIs (A) and AFIs due to localized infections (B).AUFIs: Acute undifferentiated febrile illnesses; AFIs: Acute febrile illness; BD: Twice a day; COVID-19: Coronavirus disease 2019; b.w: body weight; TDS: Thrice a day; OD: Once a day; URTIs: Upper respiratory tract infections; LRTIs: Lower respiratory tract infections; UTI: Urinary tract infection; SSTI: Skin and soft tissue infection; IAI: Intra-abdominal infection; BJI: Bone and joint infections; COVID-19: Coronavirus disease 2019; NSAIDs: Nonsteroidal anti-inflammatory drugs; MSSA: Methicillin-sensitive *Staphylococcus aureus*; MRSA: Methicillin-resistant *Staphylococcus aureus*.

Conclusion

In this article, we have created a detailed stepwise guide for differential diagnosis and management of different types of acute fever with special consideration to patient characteristics and risk factors.The use of this evidence-based diagnostic algorithm can help guide primary care specialists to choose reliable rapid diagnostic modalities and start early empirical therapy based on clinical syndromes for better management of fever. Improving the management of acute fever through stepwise diagnosis at the primary care level can uphold appropriate treatment and allow early referral (in severe illness), reducing the occurrence of a life-threatening illness or adverse outcomes. This can also reduce irrational prescription of antibiotics and antimalarial agents, consequently reducing drug pressure andthe development of antimicrobial resistance.

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