Stepwise Guide for Diagnosis and Management of Acute Fever in Primary Care

Updated in 2023

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Message From President and Hon. Secretary-General

We, at the Indian Medical Association (IMA), a national voluntary organization of doctors within the modern scientific allopathic system of medicine, are dedicated to safeguarding the interests of medical practitioners and the well-being of the community on a larger scale.

Our primary objective revolves around fostering and advancing medical and its allied sciences, spanning across various branches. Our mission is deeply rooted in the enhancement of public health and the elevation of medical education standards in India. As we progress, IMA remains committed to pioneering recommendations that are meticulously crafted through comprehensive literature reviews and robust evidential support. These recommendations are designed to serve as a guiding light for general practitioners (GPs), enabling them to execute precise diagnoses and stepwise management protocols for acute fever cases in the Indian context.

In light of this commitment, in 2021, IMA convened a collaborative session involving GPs, pediatricians, internal medicine specialists, and chest physicians. This gathering facilitated an in-depth exploration of pivotal aspects concerning the stepwise management of acute fever.

In 2023, we take immense pride in unveiling the latest development—a supplementary chapter addressing the role of antipyretics in fever management. This progressive addition stems from an unwavering dedication to refining our understanding and approaches. It stands as a testament to our relentless pursuit of excellence in healthcare.

We extend our heartfelt gratitude to all the experts who wholeheartedly contributed to the evolution of these recommendations. Their invaluable insights and expertise have culminated in a resource that empowers GPs to effectively diagnose and manage acute fever within the intricate landscape of the Indian healthcare scenario. This shared effort embodies the collaborative spirit of the medical community and embodies our ongoing commitment to advancing the field for the greater well-being of our nation.

Dr. Sharad Agarwal
National President, 2023
Indian Medical Association

Dr. Anilkumar Nayak
Hon. Secretary-General (HSG), 2023
Indian Medical Association

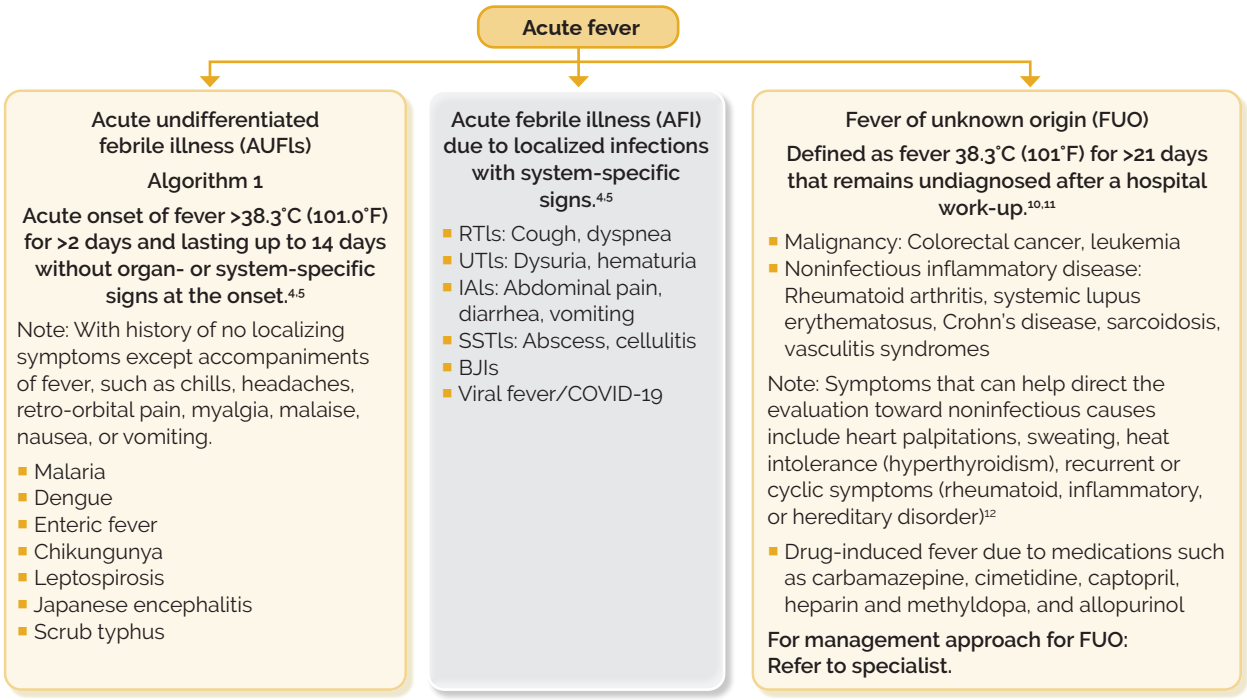
Stepwise Guide for Diagnosis and Management of Acute Fever in Primary Care

INTRODUCTION

Broad Classification of Acute Fever

Acute fever, an elevation in core body temperature above the daily range (98.6°F), is one of the most common presenting complaints to physicians in primary care and outpatient departments in India.[1–3] It has a wide spectrum of differential diagnoses from infectious to noninfectious causes. Acute undifferentiated febrile illnesses (AUFI) are characterized by fever (>38.3˚C or 101.0˚F) for greater than 2 days **(Figure 1)** and lasting up to 14 days without organ-specific symptoms at the onset.[4,5] The severity of AUFIs ranges from mild or self-limiting to life-threatening illness.[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] Studies have reported the incidence of leptospirosis that ranges from 3% to 7% in India.[6,8] A retro-prospective observational study by Mittal *et al*. evaluated the etiologies of AUFIs in adult patients (N=2547; aged greater than 18 years) presenting with acute fever (duration: 5–14 days).[9] The study revealed the heavy burden of tropical infections, such as dengue with an incidence of 37.54% followed by enteric fever (16.5%), scrub typhus (14.42%), bacterial sepsis (10.3%), malaria (6.8%), and leptospirosis (0.14%).[9] 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 work-up or 1 week of inpatient evaluation.[10,11]

Figure 1: Classification of acute fever.[4,5,10–12]



BJIs: Bone and joint infections; CAP: Community-acquired pneumonia; COVID-19: Coronavirus disease of 2019; IAI: Intra-abdominal infection; RTIs: Respiratory tract infections; SSTIs: Skin and soft tissue infections;UTIs: Urinary tract infections.

Unmet Needs in Management of Acute Fever in Primary Care

Acute fever has myriad causes. The diverse infectious etiologies often overlap and present a challenge to the treating physicians.

The majority of patients with acute fever present at clinics with nonspecific symptoms, such as low-grade fever, general malaise, headache, arthralgia, myalgia, and rash with or without a focal point of infection.[4,5,13]

The diagnosis of acute fever is not always definitive based on clinical presentation alone, and correct diagnosis is reached only with definite diagnostic tests.[3,5] The nonspecific and overlapping clinical symptoms along with nonavailability of appropriate diagnostic modalities present a challenge to the treating physicians and can make timely treatment difficult.[2,14]

A common approach to the management of acute fever relies on the use of empirical antibiotics and supportive therapy with antipyretics.[3] Given the difficulty in discriminating the etiology of fever based on clinical features alone results in the inappropriate or overuse of antibiotics/ antimalarial drugs in primary care contributing significantly to the development of antimicrobial resistance (AMR).[2,15]

PATTERNS OF FEVER AND APPROACHES TO MEASURE TEMPERATURE

Based on the pattern, fever can be classified into sustained/continuous fever, intermittent fever, and remittent fever.

- Continuous or sustained fever is termed as fever that does not fluctuate more than about 1˚C (1.5˚F) for 24 hours, but at no time touches normal (37˚C–38˚C). This pattern of fever is characteristic of lobar and Gram-negative pneumonia, typhoid, acute bacterial meningitis, and UTIs.[16]
- Intermittent fever is defined as fever present only for several hours during the day and can be seen in malaria, pyogenic infections, tuberculosis, lymphomas, and septicemia.[16]
- Remittent fever is defined as fever with daily fluctuations exceeding 2˚C but at no time touches normal and can be seen in patients with infective endocarditis and rickettsial infections.[16]

Table 1 lists the pros and cons of approaches available for measuring temperature during acute fever[17–20]

Table 1: Comparison of different methods for measuring body temperature during acute fever[17–20]

Approaches	Pros	Cons
Rectal thermometry involves temperature measurement by inserting the thermometer into the rectum via the anus. 	▪ Accurate way of core temperature measurement at steady state ▪ Most reliable for assessing exertional heat stroke	▪ Uncomfortable ▪ Rectal temperatures are slow to change in relation to changing core temperature and rectal readings are affected by the depth of the measurement, conditions affecting local blood flow, and the presence of stool ▪ May underestimate hepatic or brain hyperthermia ▪ Potential for the transmission of stool-borne pathogens ▪ Rarely traumatic injury to the rectum
Axillary thermometry involves temperature measurement by inserting the thermometer over the axillary artery for greater than 4 minutes. 	▪ Convenient to use ▪ Inexpensive ▪ Approximates core temperature in newborns	▪ Takes a longer time to reach equilibrium and is altered by various factors, such as ambient temperature, sweat, humidity, and density of hair.
Oral thermometry is performed by inserting a thermometer into the mouth under the tongue for 3–4 minutes reflecting the temperature of the lingual arteries. 	▪ Convenient to use ▪ Inexpensive	▪ Hazards of broken glass and mercury ▪ Underestimates core temperature due to air or variable probe placement

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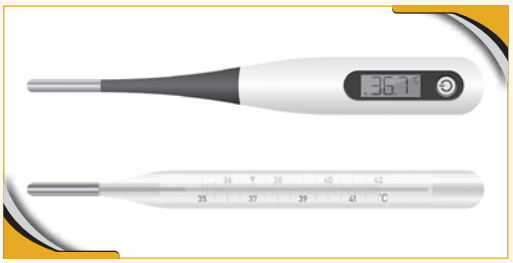
Table 1: Comparison of different methods for measuring body temperature during acute fever[17–20]

Approaches	Pros	Cons
Tympanic thermometry relies on the use of small hand-held devices with a probe that is inserted into the patient's ear canal. The sensor at the end of the probe of the tympanic device records the infrared radiation and converts it into a temperature reading. 	▪ Ease and speed of use ▪ More closely estimates core temperature than oral methods ▪ Reasonably accurate in children and adults	▪ Accuracy is limited by air or cerumen in the ear canal
Noncontact handheld infrared thermometry involves the use of a lens to focus the infrared energy onto a detector, which converts the energy to an electrical signal that can be displayed in temperature measurement after being compensated for ambient temperature variation. 	▪ Useful for mass screening at public places, such as airports and shopping malls	▪ Not reliable ▪ The accuracy of measurements depends on the subject–thermometer distance and the angle at which it is aimed at the forehead ▪ Pregnancy and menstruation might be associated with raised forehead temperature and affect measurements ▪ Intense perspiration and air conditioning can decrease the cutaneous temperature and affect the reliability of results



Mercury-free digital thermometers are recommended over traditional mercury thermometers for temperature measurement in primary care to avoid the potential hazards of broken glass and liquid mercury.[21] Digital thermometers are safe and provide faster, more accurate results as opposed to mercury thermometers.[21–23]

Note:
- Digital thermometers should not be used beyond 1 year.
- Sterilization should be performed after every use by wiping the surface with 70%–90% of alcohol to minimize the chances of cross contamination.
- Auxiliary thermometry is preferred over oral thermometry as it reduces the risk of cross-contamination.

STEPWISE APPROACH FOR DIAGNOSIS OF ACUTE FEVER IN PRIMARY CARE

Table 2 summarizes the stepwise approach for the identification of the root cause of acute fever in primary care settings.[4,5]

Table 2: Diagnostic flow of acute fever in primary care[4,5]	
Step 1: Evaluation of medical history of the patient	Consider factors: age, comorbidities, immunosuppression, and pregnancy.
Step 2: Thorough clinical examination of the patient	A complete and thorough physical examination is mandatory. ▪ A search is required for hidden foci, such as throat examination, sinus tenderness, renal or hepatic tenderness, heart murmurs, chest examination, lymph nodes, and splenomegaly. ▪ Fundus examination (if headache or bleeding tendency) and examination of the skin for eschar and petechiae or purpura must be made.
Step 3: Evaluation of clinical features and assessment of disease severity	▪ Consider key features: onset, duration, and course of fever; key rule-in and rule-out features; and characteristic pattern of organ involvement. ▪ Rule out localized infections for AUFIs. ▪ Look for localized infections in system-specific AFIs. ▪ Assess for severity and triage.
Step 4: Perform diagnostic tests	Perform first-line and, if possible, confirmatory diagnostic tests for acute fever.

AFIs: Acute febrile illnesses; AUFIs: Acute undifferentiated febrile illnesses.

Step 1: Evaluation of Medical History of Patient

This step includes an assessment of the previous medical history of the patient, such as prior fevers, infections, or known conditions predisposing to infections.[12] 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, 24–27]

Step 2: Clinical Examination of Patient

Preliminary clinical examination should involve the assessment of respiratory rate, hydration status, mental status, oropharynx, conjunctiva, skin, chest, heart, and abdomen.[5,12,28,29,30]

Review of systems should include (i) febrile seizures; (ii) headache (sinusitis, meningitis); (iii) runny nose and congestion (viral UTI); (iv) cough or wheezing (pneumonia, bronchiolitis); (v) ear pain or waking in the night with signs of discomfort (otitis media); (vi) abdominal pain (pneumonia, strep pharyngitis, gastroenteritis, abdominal abscess); (vii) back pain (pyelonephritis); (viii) and joint swelling or redness (osteomyelitis).[5,12,29,30]

Special attention should be provided to elderly patients with underlying conditions that predispose them to select infections, such as diabetes mellitus, poor swallowing or gag reflex, long-term indwelling urinary catheters, prosthetic devices (artificial joints leading to septic arthritis), altered mental status (for aspiration pneumonia), or chronic immobility.[28]

Step 3: Evaluation of Clinical Features and Assessment of Disease Severity

This step involves the evaluation of disease onset, key rule-in and rule-out clinical features, the pattern of organ involvement (if any), and red flags.[5] Figure 2 details the clinical features of tropical AUFIs and red flags (in adult and pediatric patients) indicating the need for hospitalization, referral, and urgent treatment.[24–27]

ROLE OF ANTIPYRETICS IN FEVER

An antipyretic (from anti- 'against' and pyretic 'feverish') is a class of drugs that are used to **reduce fever** by lowering body temperature. They can be further classified based on their chemical structure and mechanism of action. The most common class are **acetaminophen or paracetamol** and nonsteroidal anti-inflammatory drugs (NSAIDs) like **Nimesulide,** whereas, salicylates are less commonly used antipyretics. **Use of steroids in fever management is irrational and not recommended.**

Mechanism of action

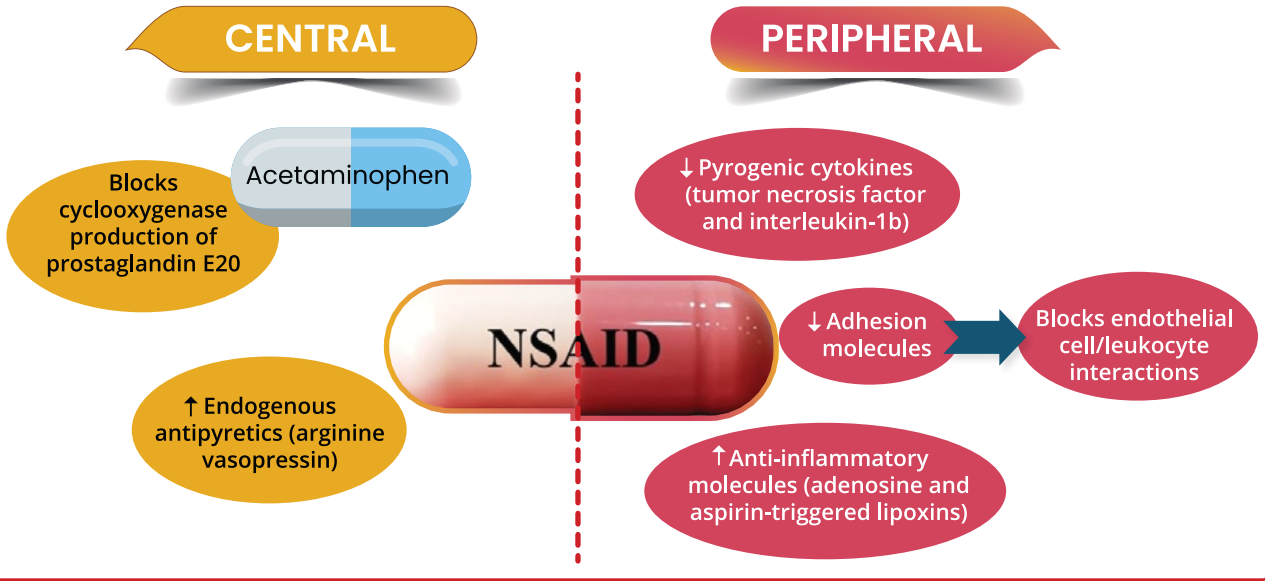
- Acts by inhibiting the inflammatory messages at both **peripheral and central sites**.[49]
- Each antipyretic has an impact at a **different location** along the febrile response pathway[50], depicted in Figure 6.
- Unique antipyretic potencies of different antipyretic medications are based on how well they interact with the various **cyclo-oxygenase (COX) variations**.[50]
- Duration of action is determined by both its concentration at the site of action and its ability to **inhibit COX** reversibly or irreversibly.[51]
- **Acetaminophen** and other NSAIDs are **reversible COX inhibitors**, and as such, their actions should be expected to differ depending on their concentration at the site of action[50].
- **Nimesulide** is a **selective COX-2 inhibtor**

Features of an ideal antipyretic

An ideal antipyretic should:

- Safely and effectively reduce fever without any influence on hemodynamics.[52]
- Give rapid result and be effective in reducing fever by at least 1˚C (1.8˚F).
- Have low rate of side effects in therapeutic doses.
- Have low incidence of interaction with other medications.
- Be cost effective.

Figure 6: Mechanism of action of antipyretics



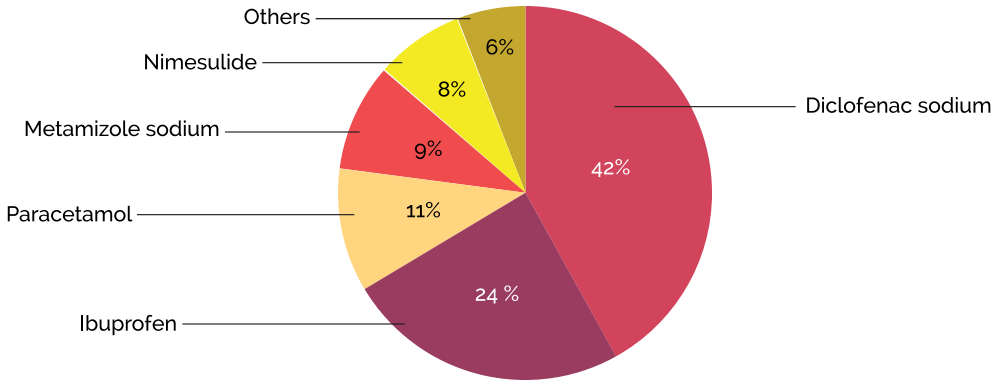
Adverse reactions caused by antipyretics

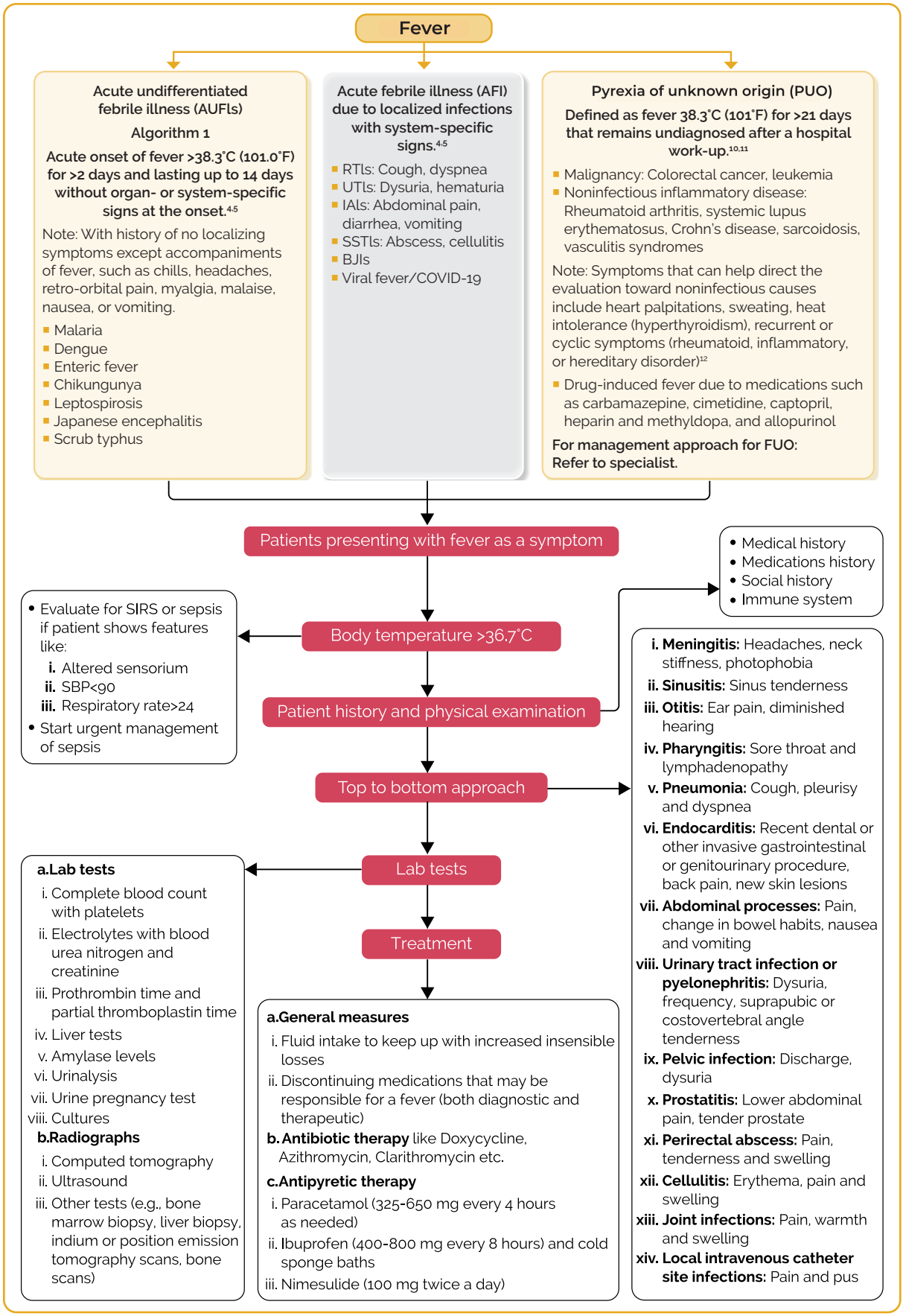
Table 11: Adverse reactions caused by antipyretics

Antipyretics	Adverse effects
Paracetamol	▪ Skin reactions ▪ Nausea and rashes occur occasionally ▪ Elevated liver transaminase ▪ Leukopenia is rare
Ibuprofen+Paracetamol	▪ Gastrointestinal disorders like abdominal pain, vomiting, diarrhoea, nausea, dyspepsia and abdominal discomfort ▪ Hyperhidrosis ▪ Rarely causes hepatobiliary Disorders ▪ Elevated alanine aminotransferase and gamma-glutamyltransferase
Nimesulide	▪ Dermatological (Rash, Pruritus) ▪ Gastrointestinal (Epigastralgia, Heart burn, Nausea, Loose motions) ▪ Rarely causes hepatic impairment ▪ Headache, somnolence and dizziness

Stepaniuk et al. examined **1460 cases** pertaining to adverse reactions (ARs) induced by the use of NSAIDs, analgesics, and antipyretics. The distribution of ARs caused by the use of NSAIDs, analgesics, and antipyretics are given in Figure 7.[53] The adverse effects associated with different antipyretics are provided in Table 11.

Figure 7: Distribution of adverse reactions caused by the use of analgesic- antipyretics and NSAIDs





SBP: Systolic blood pressure; SIRS: Systemic inflammatory response syndrome

ROLE AND EVIDENCE OF PARACETAMOL IN FEVER

History

In the **1950s**, acetaminophen, also known as paracetamol, effectively supplanted aspirin as the main fever medication **to avoid Reye's syndrome** after adequate evidence of a link between salicylates and Reye syndrome emerged.[54,55] Since then Paracetamol is the **most used** and over-prescribed over-the-counter drug because of its **easy accessibility, great tolerability** and **safer profile**.[56]

Role of Paracetamol in fever

Paracetamol is the **drug of choice** in fever management. Antipyretic effect of paracetamol begins to take action within **30 to 60 minutes**; within that period, about **80%** of youngsters will notice a moderate drop in temperature.[54] The information regarding paracetamol are presented in Table 12.

Table 12: Information regarding Paracetamol

Decline in temperature	1–2˚C
Time to onset	1 hour
Time to peak effect	3-4 hours
Duration of effect	4-6 hours
Dose	Dose depends on age and body weight, generally 10 to 15 mg/kg/dose
Maximum daily adult dose	4 g/day
Lower age limit	3 months
Use in pediatrics	Safe when used at the recommended dose
Use in pregnancy	Can be used during pregnancy if clinically needed however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency
Use while breastfeeding	Can be used during breast-feeding as long as the recommended dosage is not exceeded

Use in elderly patients	Dose adjustment not required
Use in patients with impaired hepatic function or Gilbert's syndrome	Dose must be reduced or the dosing interval prolonged
Use in patients with renal insufficiency	Dose must be reduced

Evidence of Paracetamol in fever

- Paracetamol is the **most commonly utilised** pharmacological treatment for **fever**, followed by NSAIDs according to a recent multicentre study involving children (<16 years age) of Latin America and Caribbean, Middle East, and Africa.[57]
- Widespread usage of ibuprofen and paracetamol has demonstrated benefits in reducing fever in **paediatric population**.
- Patients receiving intravenous acetaminophen had a **lower body temperature** than individuals receiving placebo without having more adverse events.[58]
- Lower mean daily peak body temperature (38.4˚C vs. 38.6˚C; P<0.001) and average body temperature (37.0˚C vs. 37.3˚C; P<0.001) observed in patients receiving paracetamol compared to placebo.[58]
- Acetaminophen and ibuprofen **equally safe and efficient** for treating fever among **children (<2 years)**.[59]

ROLE AND EVIDENCE OF NIMESULIDE IN FEVER

History

Nimesulide is a **potent antipyretic agent** which was released in Italy in **1985**. In 2012, the European Medicines Agency restricted its use in children **below the age of 12**. Nimesulide use has increased as a result of its efficacy in clinical practice. Its onset of action starts within **15 minutes** and duration of action last for **12 hours.** It can **rapidly reduce body temperature**.[60] Nimesulide should **not be** used in **children below 12 years of age**. Nimesulide in **syrup/drop form is not recommended**.

Mechanism of action

- **Selectively inhibits** the enzyme COX, preventing the synthesis of prostaglandins- involved in pain and inflammatory pathways.
- Nimesulide is a selective COX-2 inhibitor having **analgesic**, **anti-inflammatory**, and **antipyretic** properties.
- Has a **rapid onset of action** and properties other than cyclo-oxygenase inhibition that may be relevant in its antiinflammatory and analgesic effects.[61] The information regarding nimesulide are presented in Table 13.

Table 13: Information regarding Nimesulide

Decline in temperature	3.5˚C
Time to onset	<15 minutes
Time to peak effect	1-4 hours
Duration of effect	8-12 hours
Dose	100 mg twice a day (no dosage adjustment required in 12-18 years age group)
Maximum daily adult dose	200 mg/day
Lower age limit	12 years
Use in pregnancy	Contraindicated
Use while breastfeeding	No data available
Use in elderly patients	No need to reduce the daily dosage
Use in patients with impaired hepatic function	Close observation in hepatic impairment patients required
Use in patients with renal insufficiency	Can be used in mild to moderate renal imparment

Evidence of Nimesulide in Fever

- A retrospective, multicenter study conducted by Ahulraj et al. in 2021 observed nimesulide as **well-tolerated** and **efficacious** as an antipyretic for acute fever control in adults in **real-world setting**. Nimesulide significantly ($p<0.0001$) reduced mean baseline body temperature of 103.2˚F to 99.7˚F; adverse symptoms **(nausea and dyspepsia)** noted in just **2%**.[62]
- **Effective and safe as paracetamol** in the treatment of hyperpyrexia in elders. A double-blind clinical study noted that after the first day, all mean values in the nimesulide-treated group were <37˚C. No increases in mean body temperature values were found on the third day of the study, after medication was discontinued in the elderly.[63]

- Not only lowered fever but also improved oxygen saturation **within 5 days** in patients with moderate to severe COVID-19 infection. The fever subsided in 93.94% patients patients within 3 days[64]
- **More** effective than normal **diclofenac formulation** in the treatment of fever in **18-90 years** old patients. Nimesulide was found to be just as efficient as diclofenac in normalising body temperature and fever-related objective indicators (heart rate and arterial pressure), as well as significantly reducing the duration of fever when compared to placebo.[65]
- Compared to other NSAIDs, nimesulide has a comparatively **low** propensity to cause s**erious gastrointestinal** problems when used appropriately.[66]
- The European Medicines Agency and numerous recently released reports have **not identified** an increased risk of severe hepatotoxicity in contrast to other NSAIDs. The incidence of liver reactions with nimesulide is approximately **0.1 per 100** treated individuals, which is comparable to other NSAIDs widely used in clinical use.[66]
- Severe **renal and cardiovascular events** are extremely **uncommon** with nimesulide treatment.[66]
- The pharmacokinetic characteristics of nimesulide are **not altered** in patients with moderate renal impairment.[60]
- When compared to other NSAIDs, such as diclofenac, nimesulide has a **lower risk** of **myocardial infarction** and can be deemed relatively safer for usage in **cardiac patients**.[60]

Key highlights for Nimesulide

- Nimesulide is effective to treat **"high" grade fever**, **fever with body pain**, fevers which are **refractory to Paracetamol**.
- **GI safety is excellent** with Nimesulide and it should be preferred over Ibuprofen.
- Nimesulide is associated with **50% fewer GI side effects** compared with the other NSAIDs.
- Nimesulide can be used in **all types of fever except Dengue fever**.
- Nimesulide has **quick onset** of antipyretic action of 15 minutes.
- Nimesulide has **longer duration** of antipyretic action (10-12 hours) as compared to paracetamol (3-6 hours).
- Nimesulide reduces the mean temperature with **fewer number of doses** compared to paracetamol.
- **Combination of Nimesulide + Paracetamol** dispersible tablet is **irrational** and should **not be used**.
- To be used for a **shorter duration** i.e for a maximum of 10 days.
- Consuming Paracetamol and Nimesulide together increase the risk of hypothermia. If required to be taken for fever management, a gap of atleast 4 hours should be maintained between each molecule dose.

Key Points to Consider During Evaluation in Special Population:

- Normal body temperature ranges in pediatrics are higher than in adults and should be taken into attention when diagnosing fever.[12]
- Symptoms that can help direct the evaluation toward noninfectious causes in pediatric patients include: (i) heart palpitations; (ii) recurrent/cyclic symptoms (rheumatoid, inflammatory, or hereditary disorder); and (iii) sweating/heat intolerance.[12]
- Pregnancy-related immunosuppression is associated with an increased severity of falciparum malaria. Influenza, UTIs, pneumonia, tonsillitis, influenza, viral gastroenteritis, and kidney infection are other causes of fever in pregnant women and should be considered during differential diagnosis step.[5,29,30]
- Gastroenteritis, SSTI, UTI, and pneumonia are familiar issues among older adults with fever and should be considered during evaluation.[28]

Recommendations for the use of antipyretics

- Use of an antipyretic medicine should be **limited to symptomatic treatment** and preventing fever from increasing to harmful levels. It should not be taken only to reduce fever.[67]
- **In children**, antipyretics should **not be used just to suppress fever**, according to the National Institute for Health and Care Excellence (NICE) (2021), unless the child is distressed.[68]
- The practice of **combining antipyretics is not recommended** and is irrational.[49]
- Choice to prescribe antipyretic medicines must be based on clear, evidence-based rationales and on the particular needs of patients, as part of a comprehensive assessment.[68]
- Paracetamol is the **drug of choice** in management of mild to moderate fever.
- For **high grade fever** in adults, **Nimesulide can be preferred drug** till the high grade fever is reduced.
- **For fever with body pain** in adults, **Nimesulide** and/OR, combination of paracetamol & ibuprofen can be preferred

Figure 2: Evaluation of clinical features of AUFIs and assessment of disease severity.[5,12,31–33]

Malaria[31,32]

Onset:

Plasmodium falciparum (IP: 9–14 days)

Plasmodium vivax (IP: 10–14 days)

Clinical features:

- Acute onset of high-grade intermittent fever
- Paroxysm of fever, shaking chills, and sweats occur every 48 hours or 72 hours, depending on species

Manifestations of severe malaria

- Cerebral malaria, severe anemia, metabolic acidosis, and acute renal failure
- ARDS and shock

Dengue[31,32]

Onset:

IP: 3–14 days with acute onset of high-grade continuous fever (onset of symptom average 4–7 days)

Clinical features:

- 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, hypotension
- Expanded dengue syndrome: Encephalitis, myocarditis, hepatitis, renal failure, ARDS, and hemophagocytosis

Enteric fever[31,32]

Onset:

IP: 1–14 days

Clinical features:

- First week: Fever, headache, and relative bradycardia
- Second week: Abdominal pain, diarrhea, constipation, hepatosplenomegaly, and encephalopathy
- Third week: Intestinal bleeding, perforation, and MODS

Chikungunya[33]

Onset:

IP: 1–12 days (Onset of symptom: average 3–7 days)

Clinical features:

Acute onset of moderate-to-high grade continuous fever, rash, malaise, arthralgia, myalgia, and red eyes

Complications:

- Respiratory failure
- Cardiovascular decompensation
- Myocarditis
- Acute hepatitis
- Renal failure
- Hemorrhage
- Meningoencephalitis
- Acute flaccid paralysis

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Leptospirosis[31,32]

Onset:

IP: 2–26 days (onset of symptom: average 6–10 days)

Acute onset of moderate-to–high grade continuous fever

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

Scrub typhus[31,32]

Onset:

IP: 1–3 weeks

Clinical features:

- Fever, headache, and myalgia
- Breathing difficulty, delirium, vomiting, cough, and jaundice

Complications:

- Overwhelming pneumonia with ARDS-like presentation
- Hepatitis
- Aseptic meningitis
- Myocarditis and disseminated intravascular coagulation

Japanese encephalitis[31,32]

Onset:

IP: Averages 6–8 days, with a range of 4–15 days.

Clinical features:

- 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

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Red flag signs in patients with AUFIs indicating the need for hospitalization, referral, and urgent treatment.[5]

- Prostration—Unable to stand, sit, or walk without support
- Temperature—Hyperpyrexia (temperature >41.5˚C) or hypothermia (temperature <36˚C) or rigors
- Respiration—Shortness of breath, respiratory rate >22 breaths/minute, cyanosis, arterial oxygen saturation <92% on room air
- Circulation—Blood pressure <100 mmHg systolic, cold clammy extremities, capillary refill >3 seconds
- Neurological—Altered mental status (Glasgow Coma Scale <13), convulsions, positive meningeal signs (such as neck stiffness and Kernig's sign)
- Abdominal pain—Severe or persistent vomiting
- Severe conjunctival or palmar pallor
- Jaundice on examination of sclera
- Petechial or purpuric rash
- Bleeding—From nose, gums, or venipuncture sites; hematemesis, melena

Criteria for immediate attention and referral in fever in pediatric patients.[12]	
▪ Age <1 month	▪ Petechiae or purpura
▪ Lethargy, listlessness, or toxic appearance	▪ Inconsolable crying
▪ Respiratory distress	▪ Seizures, difficulty to stay awake, and stiff neck

AUFIs: Acute undifferentiated febrile illnesses; ARDS: Acute respiratory distress syndrome; IP: Incubation period; MODS: Multiple organ dysfunction syndrome.

Figure 3 summarizes the characteristic clinical features and complications associated with different types of AFIs due to localized infections.[4,32,34]

Figure 3: Evaluation of clinical features associated with different types of AFIs due to localized infections. [4,32,34]

Fever due to URTI[4]

Presenting features of URTI include sore throat, runny/blocked nose, and cough with or without systemic symptoms including fever and malaise:

- *Streptococcal pharyngitis*: Sudden onset of fever and sore throat with pain during swallowing.
- Bacterial sinusitis: Worsening of symptoms or signs includes new-onset fever, headache, or increase in nasal discharge following a typical viral URTI that lasts for 5–6 days and was initially improving (double sickening).

Fever due to LRTI[4]

CAP is 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).

Fever due to BJI[4]

Septic arthritis includes acute onset of high-grade fever with tender swollen joint.

Fever due to UTI[4]

Acute cystitis characterized by dysuria, frequency, and urgency with or without fever with chills.

Acute pyelonephritis characterized by flank pain, tenderness, or both and fever associated with dysuria, urgency, and frequency.

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Viral fever[4,32,34]

Viral pneumonia due to adenovirus, influenza A and B, human metapneumovirus, parainfluenza, rhinovirus, and cytomegalovirus. Characterized by high-grade fever, cough, sore throat, or myalgia

Note: Influenza-like illness is characterized by systemic signs, such as fever and malaise, along with the upper respiratory symptoms. The patients should be warned about symptoms, which indicate complications, such as breathing difficulty, persistent fever beyond 4–5 days, or ear pain.

COVID-19 caused by SARS-CoV-2 is characterized by low-to–moderate grade continuous fever. IP: 2–4 days (onset of symptom average: 5–7 days).

- 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

Fever due to SSTI[4]

SSTIs involve features of inflammatory response, with other manifestations, such as fever, rapid progression of lesions, and bullae.

Cellulitis is characterized by clinically rapidly intensifying pain and redness. Fever and lymphadenopathy may be present.

Fever due to IAI[4]

Invasive bacterial (inflammatory) diarrhea characterized by fever, tenesmus, and grossly bloody stool.

AFI: Acute febrile illness; ARDS: Acute respiratory distress syndrome; BJIs: Bone and joint infections; CAP: Community-acquired pneumonia; COVID-19: Coronavirus disease of 2019; IAI: Intra-abdominal infection; IP: Incubation period; LRTIs: Lower respiratory tract infections; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SSTIs: Skin and soft tissue infection; URTIs: Upper respiratory tract infections; UTI: Urinary tract infection.

Step 4: Perform Diagnostic Tests

This step involves performing first-line and confirmatory diagnostic tests depending on the day of investigation of the patient and the gravity of the fever. A complete blood count, urine analysis, and smear microscopy, and/or rapid diagnostic test (RDT) are important in patients with fever.[5] **Table 3** lists preliminary diagnostic investigations for AUFIs.[5] **Table 4** lists initial and confirmatory diagnostic tests for different AUFIs.[5,31–33,35]

Table 3: Preliminary diagnostic investigation for AUFIs[5]

Basic investigations	Diagnostic value*	Suggests severe illness*
Complete blood count	Perform in all patients	
▪ Hematocrit	—	Anemia in patients with malaria, rising hematocrit in severe dengue.
▪ Leukocytosis	Seen often in leptospirosis, enteric fever in children, and in scrub typhus. Seen in the majority of patients of hepatic amoebiasis.	Leukocytosis may occur in enteric fever in adults with onset of complications (intestinal perforation), associated with severe forms of leptospirosis, scrub typhus, malaria, and dengue fever.
▪ Leukopenia	Leukopenia occurring early in illness and in association with thrombocytopenia is suggestive of dengue. Seen later in course of typhoid fever.	Falling TLC+thrombocytopenia+rising hematocrit seen with severe dengue
▪ Lymphocytosis	May be seen in rickettsial and viral infections	—
▪ Thrombocytopenia	Thrombocytopenia may be seen in all common AUFIs, so poor discriminatory value. Thrombocytopenia+splenomegaly suggestive of malaria, Thrombocytopenia+bleeding is seen in dengue and other VHFs, but is unusual in malaria.	Dengue fever: in association with bleeding

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Table 3: Preliminary diagnostic investigation for AUFIs[5]

Basic investigations	Diagnostic value*	Suggests severe illness*
▪ Eosinophilia	Seen in filariasis, acute schistosomiasis, Loeffler's syndrome	—
Peripheral blood smear examination	Perform in all patients if facilities for microscopy available	
	Malaria, borreliosis, filariasis, and acute trypanosomiasis can be diagnosed on smear	Parasite density correlates with severity in malaria
Urine examination	Perform in severely ill patients. May be performed, especially in women and elderly, since UTIs may not have localizing symptoms	
	Proteinuria and hematuria seen in leptospirosis	Hemoglobinuria in patients with severe malaria
Biochemistry	Perform in severely ill patients to assess organ dysfunction. Hepato-renal involvement is common in leptospirosis, scrub typhus, and malaria, while pulmonary-renal syndrome is seen in scrub typhus and leptospirosis	
Liver enzymes	Raised in several AUFIs, so no discriminatory value	WHO has defined ALT or AST >1000 as suggestive of severe dengue
Bilirubin	Raised bilirubin distinguishes malaria from dengue Raised bilirubin+modest rise in transaminases (<200 IU/L)+raised CPK seen in leptospirosis	In severe leptospirosis, hyperbilirubinemia may be marked (up to 300–400 mg/L)
Renal function	AKI common in malaria, scrub typhus, leptospirosis. Non-oliguric renal failure with potassium wasting seen in leptospirosis	Correlate with prognosis especially when patient has multiorgan dysfunction syndrome
Imaging	Perform in patients with tachypnea and/or severe illness	
▪ Chest X-ray	Scrub typhus: Pneumonia is most common systemic involvement. Bilateral opacities progressing to ARDS may be seen in scrub typhus, leptospirosis, and occasionally in malaria. Pneumonia occurs occasionally in enteric fever. Pleural effusion occasional in dengue fever (sign of capillary leakage). Others: Bilateral nodular opacities or upper lobe cavitating pneumonia in melioidosis	
▪ Ultrasound scan of abdomen	May be done in severely ill patients, especially those with jaundice, shock, abdominal pain, or persistent fever without obvious cause	
	May be helpful in diagnosing infections such as hepatic amoebiasis, melioidosis (liver and splenic abscesses). Findings such as mesenteric lymphadenopathy may help in diagnosis of enteric fever	Ascites, pleural effusion, and gallbladder wall edema are associated with severe dengue infection and are signs of plasma leakage. Acute acalculous cholecystitis and acute pancreatitis have been reported in all common causes of AUFI

*Alone or in combination with other abnormalities. If confirmatory tests are not available, then the diagnosis may be 'suspected' at best, if the epidemiological and clinical features and results of basic laboratory investigations are compatible. As such, treatment may be started on clinical grounds.

ALT: Alanine aminotransferase; AKI: Acute kidney injury; ARDS: Acute respiratory distress syndrome; AST: Aspartate aminotransferase; AUFI: Acute undifferentiated febrile illness; CPK: Creatine phosphokinase; RDT: Rapid diagnostic test. TLC: Total leukocyte count; UTI: Urinary tract infections; VHF: Viral hemorrhagic fevers; WHO: World Health Organization.

Table 4: Diagnostic investigation for AUFIs[5,31–33,35]

Tests	Findings	Test performance	Advantages	Disadvantages
Malaria				
RDT for malarial antigens (ICT format): histidine-rich protein 2 (HRP-2), *Plasmodium* lactate dehydrogenase (pLDH), *Plasmodium* aldolase (pAldolase)	Parasite antigens in blood. HRP-2 antigen is unique to *P. falciparum*. pLDH can be common to genus *Plasmodium* or specific to *P. falciparum* or *P. vivax*	~95% sensitive and specific for *P. falciparum*. Acceptable as standalone test for *P. falciparum*. HRP-2 kits are the most sensitive	▪ Results in minutes, no need for laboratory, little technical skill needed. ▪ pLDH can be used to monitor treatment response.	▪ Low sensitivities for low level parasitemia (<100 parasites/µL). ▪ RDTs of different brands vary greatly in performance. ▪ Cannot quantify parasitemia. ▪ Kits deteriorate above 35˚C. ▪ In areas where HRP-2 deletion *P. falciparum* exist, only pLDH-based tests are effective.
Confirmatory test: microscopy	▪ Presence of parasites in blood. ▪ Presence of only gametocytes suggests that current illness is not malaria	▪ Detects as few as 5–10 parasites per µL of blood. ▪ Turnaround time 20–30 minutes	Current gold standard: inexpensive, quantifies parasitemia, identifies species	▪ Needs skilled staff. ▪ Asymptomatic parasitemia in hyperendemic areas can confound diagnosis
Dengue				
RDT NS1 antigen	NS1 antigen in blood collected within 6 days of onset	Pooled sensitivity: 66%, pooled specificity: 97.9%	Results in minutes, no need for laboratory, little technical skill needed	Reduced sensitivity in dengue serotype 4 infection, and in case of previous infection with any serotype
RDT IgM	Dengue-specific IgM antibody in blood. Many RDT kits test NS1 antigen and dengue IgM in same cassette.	Pooled sensitivity: 83%, pooled specificity: 86% (if taking either NS1 or IgM as proof of infection)	Results in minutes, no need for laboratory facilities, little technical skill needed	▪ IgM can persist for months and may not appear at all in secondary infections. ▪ Prior exposure to WNV, JE, or YF dampens dengue IgM response
Confirmatory test: culture	Isolation of virus from blood or tissue collected within 5 days of onset of fever	Sensitivity: ~40%, specificity: 100%	—	Turnaround time 1–2 weeks, expensive
Confirmatory test: NAA	Detection of dengue RNA in blood or tissue collected within 5 days of onset.	Sensitivity: 60%–100%, specificity: >95%	Same-day diagnosis with nearly 100% sensitivity and specificity	Expensive
Confirmatory test: serology	≥4-fold rise in titer.* Seroconversion*	Specificity: 100% for ≥4-fold increased titer or seroconversion*	Less expensive than culture or NAA	Results are retrospective and of no use in management
Enteric fever				
RDT for antibody	Detection of antibody against *Salmonella* in single serum specimens	Sensitivity: 69%–78%, specificity: 77%–90%	Turnaround time 2–4 hours	Test performance of kits has varied widely among studies. No RDT for enteric fever is accurate enough to replace reference tests.
Confirmatory test: Culture	Isolation of enteric fever *Salmonella* from blood and bone marrow	Sensitivity: 40%–87% in blood and 80% in marrow, specificity: 100%	Isolation allows drug sensitivity testing	Turnaround time 3–6 days. High level of expertise needed. Decreased sensitivity with prior therapy
Widal test†	≥4-fold rise in titer*	Sensitivity depends on local prevalence, specificity: 100%	Affordable	≥4 fold increase may not occur in partially treated patients, ≥4-fold rise can be missed if antibody level peaks before first specimen is collected.

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Table 4: Diagnostic investigation for AUFIs[5,31–33,35]

Tests	Findings	Test performance	Advantages	Disadvantages
Scrub typhus				
RDT for specific IgM (ICT format)	Detection of IgM in single specimens	Pooled sensitivity :66.0%, pooled specificity: 92.0%	Rapid	▪ IgM can remain elevated over diagnostic cut-off for 12 months post-infection. ▪ IgM may not appear in second or subsequent attacks. ▪ Higher specificity means test is more useful for ruling in a diagnosis of scrub typhus than for ruling out.
ELISA for specific IgM using recombinant antigens	≥4-fold rise in titer or seroconversion.* IgM OD reading above a predetermined cut-off in a single specimen	Sensitivity variable (91% seen in a study in northern Thailand), specificity 100% for paired sera, ≥90% for single sera	Simpler, cheaper, and more reproducible than IFA test	Same limitations as for rapid IgM tests
Confirmatory test: IFA or IPA for antibodies	≥4-fold rise in titer, seroconversion*	Specificity 100%	Current gold standard	Expensive, laborious, endpoints can be subjective
Confirmatory test: Weil-Felix test	≥4-fold rise in titer or seroconversion* for heterophile antibodies against *Proteus mirabilis* OX-K strain	Sensitivity variable, specificity high for paired specimens, low for single specimens	Inexpensive, easy to perform, turnaround time 1 day	Low sensitivity and specificity
Leptospirosis				
RDT for IgM	Specific IgM in serum	Sensitivity 13%–22% in 1st week, ~60% in 2nd week, ~80% afterward; specificity low	Short turnaround time of hours, no special expertise needed	IgM can persist for months. False-positive IgM possible in co-infection with HIV, EBV, hepatitis B or A, and *Salmonella* and *Plasmodium* spp.
IgM ELISA	Specific IgM in serum	Sensitivity 84% in acute phase and 86% overall, specificity 91% in acute phase and 90% overall	Short turnaround time, specific enough to rule in leptospirosis in presence of compatible clinical picture	IgM can persist for months after infection.
Confirmatory test: Microscopic agglutination test for antibody	≥4-fold rise in titer or seroconversion*	Sensitivity 41% in 1st week, 82% in 2nd–4th week; specificity depends on cut-off titer adopted	Highly sensitive and specific	Expensive, high technical skill needed. Need to include local serotypes in antigen pool to ensure satisfactory sensitivity
Confirmatory test: Nucleic acid amplification	Detection of *Leptospira* DNA in blood, CSF, and urine after amplification	Analytical sensitivity ~10^5 bacilli/mL sample, diagnostic sensitivity no data, specificity >95%	NAA is only test with high sensitivity in 1st week of illness	Expensive, high technical skill needed.
Confirmatory test: Culture	Isolation of *Leptospira* spp. from blood, CSF, dialysate in first 10 days, and from urine afterward	Sensitivity low, specificity 100%	Gold standard. Identifies pathogenic serovars prevalent in the locality	Expensive, very slow

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Chikungunya				
Early disease: Presence of viral RNA by RT PCR.	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 test: After first week of illness: IgM capture ELISA	-	-	-	-
Japanese encephalitis				
Initial test: IgM capture ELISA	Serum: Sensitivity: 85%–93%, specificity: 96%–98% CSF: Sensitivity 65%–80%, specificity 89%–100%	-	-	-
Confirmatory test; Detection of JE virus, antigen	Detection of JE virus, antigen in tissue/blood by immunochemistry/PCR.	-	-	-

*Fourfold or higher rise of specific antibody level in the second of two serum specimens collected 10–14 days apart compared to the first specimen. Seroconversion is the presence of antibody above a fixed level in the second of two serum specimens collected 10–14 days apart when none is detectable in the first specimen. †Performing Widal test on a single serum specimen has very poor sensitivity and specificity.

Note for dengue fever: (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.

AUFIs: Acute undifferentiated febrile illnesses; CSF: Cerebrospinal fluid; ELISA: Enzyme-linked immunosorbent assay; HIV: Human immunodeficiency virus; HRP-2 Histidine-rich protein 2; HRP-2 Histidine-rich protein 2; ICT: Immunochromatographic test; ICT: Immunochromatographic test; IFA: Immunofluorescent assay; IgG: Immunoglobulin G; IgG: Immunoglobulin G; IgM: Immunoglobulin M; IPA Immunoperoxidase assay; JE: Japanese encephalitis; NAA: Nucleic acid amplification; NS-1: Non-structural antigen 1; RDT: Rapid diagnostic test; YF: Yellow fever.

Figure 4 details the recommended diagnostic tests for different AFIs with localized infections in primary care.[4,36,37]

Figure 4: Diagnostic investigation for AFIs due to localized infection.[4,36,37]

Fever due to URTI[4,36]

- Examination findings include tonsillo-pharyngeal erythema and exudates, palatal petechiae, tender anterior cervical adenopathy, and sometimes scarlatiniform rash.
- Confirmation of diagnosis by rapid antigen test or throat swab culture is desirable.

Fever due to LRTI[36]

- X-ray PNS is done usually only if there is a chronic sinusitis to look for a fluid level.
- If duration of illness is >10 days with purulent nasal discharge, nasal obstruction, and facial pain, then a bacterial cause should be considered.

Viral fever[34]

- Laboratory findings for viral pneumonia: RT-PCR positive for the underlying virus, elevated lymphocyte counts
- Laboratory findings for COVID-19 fever: RT-PCR positive for SARS-CoV-2, lymphopenia, elevated aminotransferases, CRP, and D-dimer
- Chest CT findings for viral pneumonia: Interstitial inflammation, high-attenuation reticular patterns, localized atelectasis, or pulmonary edema
- Chest CT findings for COVID-19:
  - Early stage: GGOs
  - Progressive stage: Multiple GGOs, consolidation patches, crazy-pavement pattern
  - Advanced stage: Diffuse exudative lesions, whiteout lung

Fever due to UTI[4]

Routine urine analysis: Significant pyuria and/or dipstick leukocyte esterase test positive.

Fever due to IAI[4]

- A stool culture is indicated if the patient has symptoms lasting for more than 3–7 days or is immunosuppressed.
- Microscopic evidence containing red blood cells can provide sufficient evidence.

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Fever due to SSTI[37]

- Initial diagnosis involves morphologic features of lesion and the clinical setting. If drainage or an open wound is present, Gram stain and culture can provide a definitive diagnosis.
- In the absence of culture findings, the bacterial etiology is difficult to establish.

Fever due to BJI[4]

- Leukocytosis, high ESR, and CRP are features of septic arthritis.[1]
- Synovial fluid from the infected joint should be sent for WBC counts, Gram stain, and culture before starting antibiotics.
- Blood cultures should be obtained for all suspected cases of septic arthritis before starting antibiotics.

AFIs: Acute febrile illness; BJIs: Bone and joint infections; COVID-19: Coronavirus disease of 2019; CRP: C-reactive protein; CT: Computed tomography; ESR: Erythrocyte sedimentation rate; GGO: Ground-glass opacities; IAI: Intra-abdominal infection; LRTIs: Lower respiratory tract infections; PCR: Polymerase chain reaction; PNS: Paranasal sinus; RT: Reverse transcription; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SSTI: Skin and soft tissue infection; URTIs: Upper respiratory tract infections; UTI: Urinary tract infection.

STEPWISE APPROACH FOR TREATMENT OF ACUTE FEVER IN PRIMARY CARE

Pharmacological and nonpharmacological methods, such as tepid sponging lower temperature in patients with acute fever, are useful to relieve discomfort and constitutional symptoms of disease.[38,39] Early presumptive antibiotic therapy is important for suspected bacterial AUFIs, presenting with characteristic clinical features. These empirical therapies are necessary if diagnostic confirmatory testing is awaited or not available.[5]

Management of AUFIs

Figure 5 provides guideline-recommended empirical therapies for different AUFIs.[31–33,40–44] For patients with severe nonmalarial nonarboviral AUFI, a combination of third-generation cephalosporin plus doxycycline as empirical therapy can help 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 frequently seen in such patients.[5] Due to limited resources in the management of fever and certain compelling indications, and empirical use of broad-spectrum antibiotics like doxycycline can be considered in the management of acute febrile illness.[3]

Figure 5: List of empirical therapies for different AUFIs.[31–33,40–44]

Malaria[32,40]

Vivax malaria: Chloroquine (25 mg/kg b.w divided over three 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 body weight 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 a 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.

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Dengue[41]

Antipyretics (avoid salicylates/ibuprofen) and tepid water sponging if 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[42]

Oral amoxicillin 25 mg/kg TDS for 10–14 days.

Oral trimethoprim/sulfamethoxazole 4/20 mg/kg BD for 10–14 days.

Chikungunya[33]

Patient may 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[43]

Adults: Doxycycline 100 mg twice a day for 7 days.

Pregnant and lactating mothers should be given capsule ampicillin 500 mg every 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.

Japanese encephalitis[31,44]

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[31]

First line: Doxycycline 100 mg BD for 7 days.

Consider azithromycin or rifampicin or chloramphenicol as alternatives in children and pregnant women.

AUFIs: Acute undifferentiated febrile illnesses; b.w: body weight; BD: Twice a day; COVID-19: Coronavirus disease of 2019; NSAIDs: Nonsteroidal anti-inflammatory drugs; OD: Once a day; TDS: Thrice a day.

Management of Acute Fever in RTIs:

Table 5 lists preferred empiric antibiotic therapy and alternatives for the management of fever due to streptococcal pharyngitis and bacterial sinusitis in primary care settings.[4]

Note: Quinolones are not advised as the first-line treatment option for URTIs.

Table 5: List of medications for streptococcal pharyngitis and bacterial sinusitis[4]			
Condition	**Preferred drug**	**Alternative**	**Penicillin allergy**
Streptococcal pharyngitis	Penicillin V (not easily available in India, Penicillin G not a substitute since oral absorption is poor	Amoxicillin Benzathine penicillin single dose	Anaphylactic: Clindamycin/clarithromycin/azithromycin Non-anaphylactic: Cephalexin/cefadroxil
Bacterial sinusitis	Amoxicillin Co-amoxiclav	Ceftriaxone Cefpodoxime (adults)	Adults: Doxycycline/respiratory quinolones Children: Anaphylactic respiratory quinolones, Non-anaphylactic: Cefixime and clindamycin

Table 6 lists empiric antibiotic therapy and recommended doses for the management of CAP in adult and pediatric patients.[4] The use of empiric fluoroquinolone therapy may lead to masking and delayed diagnosis of tuberculosis (TB) and promotion of drug resistance, and therefore, fluoroquinolones are not advised for CAP patients.[4]

Note: Quinolones are not advised for CAP patients and patients with lower RTIs.

Table 6: List of empirical therapies for the management of CAP. A) in adult patients; B) in pediatric patients; C) standard dosage[4]			
A			
Type of CAP	**Preferred drug**	**Alternative**	**Comments**
Outpatients without comorbidities	Co-amoxiclav	Macrolides** Cefuroxime Cefpodoxime	Beta-lactam preferred over macrolides due to high prevalence of macrolide resistance in *S. pneumoniae* in India. Doxycycline monotherapy not recommended
Outpatients with comorbidities* or use of antimicrobial in 3 months	Co-amoxiclav and macrolide/doxycycline	Cefuroxime/cefpodoxime and macrolide/doxycycline	
Inpatient, non-ICU	Ceftriaxone with macrolide/doxycycline	Cefotaxime/amoxclav with macrolide/doxycycline	If there is hypersensitivity to beta-lactams: respiratory fluoroquinolones (exclude TB first)

B		
	Outpatient	**Inpatient**
Newborns <1 month	Cefotaxime and gentamicin, add macrolides if *Chlamydia* suspected (afebrile, staccato cough)	
Age less than 5 years	Amoxicillin Co-amoxiclav Cefuroxime	Ceftriaxone Cefotaxime Co-amoxiclav
Age more than 5 years	Amoxicillin Macrolide only if clinical features suggestive of mycoplasma	Ceftriaxone Ampicillin Co-amoxiclav with/without macrolide
Suspected MRSA: add vancomycin/teicoplanin/(linezolid only if TB ruled out)		
Suspected influenza: Add oseltamivir		

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C		
Drug	**Adult dose**	**Pediatric dose**
Penicillin V	500 mg twice daily	250 mg twice daily
Benzathine penicillin	<27 kg 6,00,000 units IM single dose ≥27 kg 1.2 million units IM single dose	
Amoxicillin	500–1000 mg thrice daily (PO or IV)	15–20 mg/kg twice daily oral 30–35 mg/kg thrice daily IV
Co-amoxiclav	1 g twice daily/625 mg thrice daily oral 1.2 g IV q8h	15–20 mg/kg of amoxicillin twice daily PO 25–30 mg/kg of amoxicillin component thrice daily IV
Azithromycin	500 mg daily (PO or IV)	10 mg/kg once daily
Clarithromycin	500 mg twice daily	7.5 mg/kg twice daily
Oseltamivir	75 mg twice daily PO	<15 kg 30 mg twice daily 16–34 kg 45 mg twice daily 35–44 kg 60 mg twice daily 45 kg and more 75 mg twice daily
Doxycycline	100 mg twice daily	1.5–2 mg/kg twice daily
Clindamycin	300 mg four times a day PO 600 mg thrice daily IV	7 mg/kg thrice daily
Cephalexin	750 mg twice daily PO	20 mg/kg twice daily PO
Cefadroxil	1 g once daily	30 mg/kg once daily
Levofloxacin	750 mg once daily PO or IV	10–15 mg/kg in one or two divided doses PO or IV
Moxifloxacin	400 mg once daily PO or IV	10 mg/kg once daily PO or IV
Cefpodoxime	200 mg twice daily	5 mg/kg twice daily
Cefuroxime	500 mg twice daily oral 1.5 g twice daily IV	10 mg/kg twice daily oral 35 mg/kg twice daily IV
Ceftriaxone	2 g once daily IV	50 mg/kg twice daily
Cefotaxime	2 g thrice daily IV	30–35 mg/kg thrice daily IV
Cefepime	2 g twice daily IV	50 mg/kg twice daily
Piperacillin tazobactam	4.5 g thrice daily	100 mg/kg piperacillin thrice daily
Cefoperazone sulbactam	3 g twice daily	50 mg/kg of cefoperazone twice daily
Imipenem	1 g thrice daily or 500 mg four times daily IV	15–25 mg/kg four times daily IV
Meropenem	1 g thrice daily IV	20–40 mg/kg thrice daily
Vancomycin	1 gm twice daily	10 mg/kg four times daily
Teicoplanin	400 mg twice daily for 3 doses and then 400 mg once daily	12 mg/kg twice daily for 3 doses and then 12 mg/kg once daily
Linezolid	600 mg twice daily PO or IV	10 mg/kg thrice daily PO or IV

*Chronic heart, liver, renal, or lung disease, diabetes mellitus, malignancies, alcoholism, or use of immunosuppressive drugs.**Azithromycin/clarithromycin.

The empiric addition of oseltamivir in patients with CAP should be considered in the setting of an influenza outbreak.
CAP: Community-acquired pneumonia; IV: Intravenous; MRSA: Methicillin-resistant *Staphylococcus aureus;* PO: Oral administration; TB: Tuberculosis.

Fever Presentation With Suspected COVID-19[32,45]

[COVID-19 clinical management: living guidance; Guidelines for the management of co-infection of COVID-19 with other seasonal epidemic prone diseases]

- 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.
- For COVID-19 patients with severe disease, it is important to collect blood cultures prior to the initiation of antimicrobial therapy.
- Consider in older people, and children <5 years of age to provide empiric antibiotic treatment for possible pneumonia.
- Consider antibiotics, such as co-amoxicillin, adequate, instead of broad-spectrum antibiotics.

Note: Quinolones are not advised for patients with respiratory tract infections

Management of Acute Fever in SSTIs

Table 7 lists the preferred empiric antibiotic therapy for the management of SSTIs.[4]

Table 7: List of empirical therapies for management of SSTIs[4]

Condition	Organism	Antibiotic	Duration	Comments
Cellulitis	*S. pyogenes* *S. aureus*	Cefazolin OR cephalexin OR Amoxicillin-clavulanate +/– clindamycin	5–7 days (longer if clinically indicated)	▪ Obtain blood/pus *S. aureus*-Consider polymicrobial pathogens in diabetics ▪ Consider risk factors for MRSA and presence of TSS before using clindamycin
Necrotizing fasciitis	*S. pyogenes* *S. aureus*, anaerobes, Gram-negative organisms (polymicrobial)	Piperacillin-tazobactam+ Clindamycin	Generally, 14 days if adequate source control achieved	▪ Early surgical debridement essential Send blood and intraoperative specimens for bacterial cultures Consider use of IVIG for streptococcal NF/TSS
Necrotizing fasciitis	*Aeromonas/V. vulnificus* (suspect when history of exposure to fresh water or salt water respectively)	Ciprofoxacin+ Doxycycline	Generally, 14 days if adequate source control achieved	
Erysipelas	*Propionibacterium acnes*/ MSSA	Amoxicillin-clavulanate	5–7 days	
Abscess	*S. pyogenes*, Oral anaerobes	Clindamycin or Ampicillin-sulbactum OR Amoxicillin-clavulanate	5–7 days	
	S. aureus, facultative Gram-negative anaerobes	Linezolid OR Vancomycin PLUS Ciprofloxacin	Generally, 14 days	

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Antibiotics	Doses, duration, and route of administration
Cefazolin	1-2 g IV q8h
Cephalexin	750 mg bd, 500 mg TID
Amoxicillin-clavulanate	Oral: 1 g bd/ IV 1.2@g TDS
Clindamycin	600-900 IV 8 hourly
Piperacillin-tazobactam+Clindamycin	IV 4.5 g 6 hourly (P-T)+IV 600 mg TDS (Clinda)
Ciprofoxacin	IV 750 mg q12h
Doxycycline	IV 200 mg stat f/b 100 mg 1-0-1
Amoxicillin-clavulanate	1 g bd

bd: Twice a day; IV: Intravenous; MSSA: Methicillin-sensitive *Staphylococcus aureus*; SSTIs: Skin and soft tissue infections; TDS: Thrice a day; TID: Three times a day.

Management of Acute Fever in IAIs

Table 8 lists preferred empiric antibiotic therapy for the management of diarrhea.[4] Adults with bloody diarrhea should be treated promptly with an antimicrobial therapy that is effective against *Shigella*; can otherwise be associated with severe complications.[4]

Table 8: List of empirical therapies for management of diarrhea[4]

Suspected cause	Antibiotic
V. Cholerae	Doxycycline (not recommended in children and pregnant women) 300 mg once Azithromycin 1 g as a single dose
Shigella	Ciprofloxacin 500 mg b.i.d. for 3 days Alternatively, ceftriaxone 2 g IV as single dose
Amoebiasis	Metronidazole 500 mg t.i.d. for 5 days
Giardiasis	Metronidazole 250 mg t.i.d. for 5 days
Campylobacter	Azithromycin 500 mg for 3days

b.i.d.: Twice a day; IV: Intravenous; t.i.d.: Three times a day.

Management of Acute Fever in BJIs

The most common bacteria causing septic arthritis are Gram-positive *Staphylococcus aureus*. **Table 9** lists the preferred empiric antibiotic therapy for the management of BJIs caused due to *Staphylococcus aureus*.[4]

Table 9: List of empirical therapies for the management of BJIs caused due to *Staphylococcus aureus*[4]

Organism	Drugs of pediatric dose	Alternative drugs	Remarks
MSSA	Cloxacillin Flucloxacillin Cefazolin	Ceftriaxone Daptomycin	Rifampicin 300–450 mg PO/day may be added in the presence of hardware Possible antagonism with beta-lactams. Best results if along with FQN (FQN use is unlikely in India due to widespread resistance)
MSSA	Vancomycin Teicoplanin	Daptomycin Linezolid	Rifampicin 300–450 mg PO/day (as above) High dose of vancomycin used 15–20 mg/kg q8–12h (max. 2 g/dose). Monitor trough levels, renal function

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Drugs of choice	Doses
Cloxacillin	2 g q4-6h
Flucloxacillin	2 g q4-6h
Cefazolin	2 g q8h
Ceftriaxone	2–4 g q2–4h
Vancomycin	1 5 mg/kg q12h
Teicoplanin	12 mg/kg q12h x 3 doses; followed by 12 mg/kg/d
Daptomycin	8–10 mg/kg/d (MRSA)
Linezolid	600 mg q12h

BJIs: Bone and joint infections; MRSA: Methicillin-resistant *Staphylococcus aureus*; MSSA: Methicillin-sensitive *Staphylococcus aureus*; PO: Oral administration;

Management of Acute Fever in UTIs

Table 10 lists preferred empiric antibiotic therapy for the management of acute cystitis and acute pyelonephritis.[4]

Table 10: List of empirical therapies for the management of acute cystitis and acute pyelonephritis[4]

Urinary syndrome	Drug of choice	Alternative choice	Comments
Acute cystitis	▪ Nitrofurantoin ▪ Fosfomycin	▪ Co-trimoxazole ▪ Ertapenem ▪ Amikacin (can be used in children as well)	▪ Dosage adjustment as per eGFR. ▪ Fosfomycin and nitrofurantoin should be avoided when there is suspicion of pyelonephritis or prostatitis/presence of systemic features of infection. ▪ Fosfomycin susceptibility to being requested for, and used only for Gram-negative MDR organisms.
Acute pyelonephritis	▪ Piperacillin–tazobactam ▪ Ertapenem	▪ Imipenem ▪ Meropenem ▪ Amikacin (recommended for children as well)	▪ Dosage adjustment as per eGFR. ▪ Treatment is for a minimum of 7 days. ▪ The total duration of treatment is 14 days in children. ▪ Same treatment regimen to be used for complicated UTI except the duration is extended (7–14 days).

Antibiotics	Doses, duration, and route of administration
Acute cystitis	
1. Nitrofurantoin	100 mg BD for 5 days
2. Nitrofurantoin	1.25–1.75 mg/kg oral 6 hourly (Dose in children)
3. Fosfomycin	3.0 g single dose
4. Co-trimoxazole	ds 1 tab bd for 3 days
5. Ertapenem	1 g IV once daily for 7 days
6. Amikacin	15 mg/kg/day once daily IV or IM for 3 days
Acute pyelonephritis	
7. Piperacillin–tazobactam	4.5 g IV 6 hrs
8. Ertapenem	1 g IV once dailyfor 7–10 days
9. Imipenem	1 g 8 hourly IV
10. Meropenem	1 g IV q8h
11. Amikacin	15 mg/kg/day once daily IV/IM for 7–14 days

BD: Twice a day: IM: Intramuscular; IV: Intravenous; UTIs: Urinary tract infections.

DOXYCYCLINE IN COMMUNITY-ONSET ACUTE UNDIFFERENTIATED FEVER IN ADULTS: ICMR GUIDELINES, 2022[69]

Adult Dose: 100 mg twice daily

Pediatric Dose: 2-4mg/kg/day divided in two doses; now considered safe for shorter duration (< 21 days)

- **Empirical treatment** with doxycycline for patients with undifferentiated fever and negative rapid diagnostic tests for malaria and dengue is an option for the clinician.
- For travelers, migrant labourers and military personnel exposed to **malaria** in highly endemic areas, doxycycline can be used for **short-term chemoprophylaxis** (less than **6 weeks).**
    - Dose: 100 mg daily in adults
      1.5 mg/kg for children more than 8 years old.
    - Drug should be started 2 days before travel and continued for 4 weeks after leaving the malarious area.
    - Contraindicated in pregnant women and children less than 8 years.
- Doxycycline is the **antimicrobial choice** for Rickettsial infections caused by *Orientia tsutsugamushi, Rickettsia conorii, R. typhi*; Duration of treatment: 7 days.
- Doxycycline can be used for Leptospirosis caused by ***Leptospira sp***. with Duration of treatment: 7 days.
- Doxycycline can be added as a **second** agent for **Falciparum in italics.**

DOXYCYCLINE AS AN ANTIVIRAL AGENT

- **A tetracycline antibiotic** that exhibits **antimicrobial** activity is found to be clinically effective in the treatment of a variety of infections caused by susceptible strains of **Gram-positive** and **Gram-negative bacteria** and certain other microorganisms like ***Clostridium*** species, ***Francisellatularensis*** and chloroquine-resistant ***falciparum*** malaria
- Has additional benefit of having **anti-inflammatory** and **anti-viral** properties against several RNA viruses.[70]
- **Downregulates proinflammatory cytokines** [like interleukin (IL)-1, IL-6, Il-8, tumor necrosis factor-alpha by macrophages] and **chemokines** (like monocyte chemotactic protein 1, macrophage inflammatory protein 1α and 1β).[71]

The antiviral activity of doxycycline was recently assessed against Dengue 2, Influenza A (H1N1), Influenza B, Human rhinovirus 17, Human Adenovirus and Human respiratory syncytial virus in an in-vitro study.

Methodology: For this, a cell infection model **(Prophylactic method and Co-culture method)** was used. Ribavirin, an established broad-spectrum antiviral agent, was used as a reference (positive control). Cytotoxicity was determined by MTT Assay.

Results:

Virus	Pharmacokinetic parameters	Prophylactic method	Co-culture method
Dengue 2	IC_{50}	135.5 µM	114.5 µM
	I_{max}	85%	87%
	Mean inhibition of CPE (Range)	6.5% to 84.9%	13.2 % to 86.7%.
Influenza A Virus (H1N1)	IC_{50}	262.3 µM	184.1 µM
	I_{max}	75%	80%
	Mean inhibition of CPE (Range)	8% to 74.8%	6.9% to 79.5%
Influenza B virus	IC_{50}	330.9 µM	286.4 µM
	I_{max}	71%	68%
	Mean inhibition of CPE (Range)	9.2% to 71.0%	13.3% to 68.2%
Human rhinovirus 17 (HRV -17)	IC_{50}	387.3 µM	325.9 µM
	I_{max}	68.3%	71.6%
	Mean inhibition of CPE (Range)	9.7% to 68.3%	8.2% to 71.6%
Human adenovirus	IC_{50}	146.5 µM	106.6 µM
	I_{max}	82.5%	83.8%
	Mean inhibition of CPE (Range)	11.0% to 82.5%	11.1% to 83.8%
Human respiratory syncytial virus	IC_{50}	225.5 µM	65.2 µM
	I_{max}	79%	81%
	Mean inhibition of CPE (Range)	12.0% to 79.3%	11.2% to 81.1%

CPE: cytopathic effects; IC_{50}: Half-maximal inhibitory concentration; I_{max}: maximum decrease in clearance relative to baseline

Conclusion: This study provides valuable insights into the **antiviral activity of doxycycline** against selected viruses. Antiviral activity of doxycycline was observed against selected viruses in both prophylactic and co-culture methods using the MTT testing. Although Doxycycline is an antibiotic and not approved as an antiviral drug, this antiviral property of Doxycycline will prove beneficial in minimizing secondary infections and complications especially when used as an adjunct.

Do's and Don'ts of Fever Management

- Antibiotics should not be prescribed during strong suspicion of viral fever.[4]
- It is important to draw two sets of blood cultures before the start of empiric antibiotic therapy.
- Start antibiotics for a presumed bacterial infection promptly, but adjust the dosage and duration, switch, or end antibiotic therapy when results do not support or justify the need to continue. Check the situation within 48 hours based on test results and patient status.[4]
- Supportive therapy with acetaminophen (650 mg every 6 hours) is advisable, accompanied by tepid sponging.[4]
- It is important to avoid indiscriminate use of antibiotic agents, nonsteroidal anti-inflammatory drugs (NSAIDs), and steroids in patients with AUFIs in primary care.
- Corticosteroids are not recommended in the treatment of AUFIs.[4]

Nutrition and Fluid Management Key Points to Consider

- Patients should be prescribed a soft bland diet loaded with immune-boosting foods, which help toughen the immune system.[46–48]
- It is important to include foods that are easily digested and absorbed, such as cereal and milk, soft fruits (banana, papaya, orange), mashed khichidi, mashed curd rice, or softly boiled veggies. Nonvegetarian foods, deep-fried foods, processed foods, alcohol, and tobacco should be avoided.[46–48]
- Adequate sleep, reduced stress, and proper exercise should be ensured for quicker recovery. Sufficient oral hydration (a minimum fluid intake of 50 mL/kg of body weight in 24 hours) should be maintained to prevent dehydration.[46–48]

SUMMARY

- Acute fever is classified into AUFIs without organ- or system-specific signs at the onset and AFIs due to localized infections with system-specific signs.
- The diagnosis of acute fever in primary care is not always possible based on the clinical presentation alone, and correct diagnosis is reached only with specific diagnostic tests.
- A stepwise evaluation considering the diagnostic possibilities in the geographical area and clinical symptoms of different acute fever types with special consideration to patient characteristics can help in the accurate diagnosis and management of patients.
- Use of this evidence-based algorithm can help guide primary care specialists to use relevant diagnostic modalities and initiate early empiric therapy based on clinical syndromes for better management of fever.
- Use of stepwise management algorithm can help healthcare professionals make wise informed decisions and reduce the irrational prescription of antibiotics and antimalarial agents.

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