

Clinical assessment on acute febrile illness – A comprehensive review

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ABSTRACT

Acute undifferentiated febrile illness (AUFI) is a prevalent medical condition in hospitals, particularly in tropical regions. If the underlying cause is not identified and treated promptly, the fever can become life-threatening. Infectious diseases significantly contribute to morbidity and mortality in these areas. Thrombocytopenia, or low platelet count, is a common issue among patients in emergency and outpatient clinics in developing countries. Infections like dengue fever, malaria, chikungunya fever, and lower respiratory tract infections (LRTIs) often cause clusters of febrile thrombocytopenia. In women, urinary tract infections (UTIs) are a frequent cause of fever, necessitating urine culture and sensitivity tests for accurate diagnosis. Similarly, prolonged fevers due to sepsis or bloodstream infections require blood culture and sensitivity tests to identify the responsible organism and guide appropriate treatment. Commonly prescribed antibiotics for patients with tropical fevers include ceftriaxone and doxycycline, with azithromycin also widely used for conditions like malaria and AUFI. Establishing a well-designed protocol for managing fever patients is critical. Before administering medications, a thorough evaluation of the fever using appropriate diagnostic criteria is essential. Administering treatment without determining the underlying diagnosis or focus of the illness can lead to persistent fever spikes and ineffective care. An effective strategy for diagnosing and treating fever-related illnesses is crucial for enhancing patient care. Precise detection of the causative infection and customized antibiotic treatment are essential elements in the successful management of febrile conditions, particularly in tropical and less-developed areas.

Keywords: Acute Febrile Illness, Sepsis, Fever, UTI, AUFI

INTRODUCTION:

Fever can be caused by a range of infectious and non-infectious causes, including malaria, dengue, scrub typhus [7], leptospirosis, enteric fever, acute viral hepatitis, and sepsis. Developing a consistent technique for determining the etiology is difficult since fever epidemiology is always changing [1]. Measuring and recording temperature every three hours is advised, with a graph created by the end of the day. The World Health Organization (WHO) emphasizes the necessity of investigating the causes of fever in various contexts, age groups, and levels of care [3]. However, a few such studies have been undertaken in the most afflicted areas. Acute undifferentiated febrile illness (AUFI) is a prevalent clinical diagnosis in many hospitals.

The fever might become life-threatening if the underlying reason is not found and treated quickly. In tropical countries, infectious illnesses account for a considerable proportion of morbidity and death [4]. AUFI is defined as a fever lasting fewer than 14 days with no identifiable organ or system etiology.

In many circumstances, determining the etiology is critical to effective therapy. In tropical climates, infectious illnesses are the leading cause of morbidity and mortality. A systematic strategy for detecting and treating AUFI is critical for improving patient outcomes and reducing the burden of infectious illnesses in these locations [4]. In this review, we primarily discussed the importance of differential diagnostic clues, clinical manifestations, treatment options, complications, and common misconceptions regarding fever-causing agents. Thrombocytopenia (low platelet count) is commonly seen in

emergency and outpatient clinics in impoverished nations [12]. Infections such as dengue fever, malaria, chikungunya fever, lower respiratory tract infections (LRTIs), and others may cause clusters of febrile thrombocytopenia episodes [2,3].

Fever can be associated with illnesses such as gastroenteritis and sepsis. Urinary tract infections (UTIs) are among the most prevalent bacterial infections in senior people and a leading cause of community-acquired bacteremia. UTIs can sometimes cause severe thrombocytopenia, which is life-threatening [32]. Identifying and comprehending these distinct etiologies is critical for the efficient treatment and management of individuals presenting with fever and thrombocytopenia [12]. Diagnosing cases of fever accompanied by thrombocytopenia can be particularly challenging for physicians, who must be acutely aware of the regional and endemic seasonal causes of this syndrome; the presence of thrombocytopenia in an acute febrile illness should immediately prompt the clinician to identify the underlying etiology and initiate prompt treatment for the patient [12]. Clinically, fever presents with a wide range of etiologies that include infectious causes such as malaria, enteric fever, dengue, scrub typhus, sepsis, leptospirosis, and acute viral hepatitis [5]; in addition to these, non-infectious causes such as connective tissue disorders, autoimmune diseases, malignancies, and various other miscellaneous factors must also be considered [13].

CLINICAL MANIFESTATIONS

Fever can be associated with a variety of clinical presentations depending on the underlying cause: Dengue: Sudden onset of high fever, severe headache, retro-orbital pain, muscle and joint pain, rash, and mild bleeding manifestations. Severe dengue can lead to hemorrhagic fever and shock [12, 21, 27]. Malaria: Cyclical fever patterns, chills, sweating, headache, nausea, vomiting, and anemia. Severe malaria can result in cerebral malaria, organ failure, and death [20,21].

Scrub Typhus: Fever, headache, myalgia, eschar at the site of the chigger bite, rash, lymphadenopathy, and potential complications like pneumonitis, myocarditis, and meningoencephalitis [6,7,]. Leptospirosis: Fever, chills, headache, muscle aches, jaundice, red eyes, abdominal pain, diarrhea, and rash. Severe cases can result in kidney damage, liver failure, meningitis, or respiratory distress [28].

CLINICAL CLUES FOR DIFFERENTIAL DIAGNOSIS

Primary investigations are essential for providing clues for the diagnosis and treatment of patients presenting with febrile illnesses. When these primary tests do not yield a provisional diagnosis, further evaluations, such as blood culture sensitivity and urine culture and sensitivity, are warranted. Often, patients may exhibit mild symptoms with a self-limited clinical course, leading to spontaneous recovery within a few days. Elevated white blood cell (WBC) counts and thrombocytopenia are critical indicators that can help establish a provisional diagnosis and guide appropriate treatment measures.

For diagnosing seasonal viral fevers, a combination of tests such as Dengue rapid tests, Widal tests, malaria card tests, and chest X-rays are employed. In females, urinary tract infections (UTIs) are the most common cause of fever, which is confirmed through urine culture and sensitivity testing [38]. Continuous fevers caused by sepsis or blood-related infections necessitate the use of blood culture and sensitivity testing to identify the causative organism and determine the appropriate treatment. These illnesses can range from mild infections to severe, life-threatening diseases with multi-organ dysfunction. The clinical manifestations observed in our patients are consistent with reports from other studies in the Indian subcontinent [14].

Fevers with identified causes are classified as diagnosed acute undifferentiated fevers (AUF), while those without a clear diagnosis are termed undiagnosed undifferentiated fevers (UUF) [15]. The pathogenesis of fever of unknown origin (FUO) involves endogenous pyrogens such as Interleukin 1 (IL-1), IL-6, and tumor necrosis factor α (TNF- α). Diagnosing and treating acute undifferentiated febrile illness remains a challenge, even for experienced physicians. Conditions like rheumatoid arthritis and systemic-onset juvenile rheumatoid arthritis (Still's disease) can present with FUO [16]. Similarly, Crohn's disease is a common gastrointestinal cause of FUO [17].

Patients with FUO due to typhoid fever or tuberculosis often exhibit a continuous fever pattern, whereas those with connective tissue disorders typically have an intermittent fever pattern [18]. In the context of malaria, the mean platelet count is notably lower in cases of falciparum malaria compared to vivax malaria and mixed infections [19]. Furthermore, bleeding tendencies are higher in falciparum malaria and mixed infections [20]. Studies by Jadhav et al. and Kochar et al. support these findings, highlighting that severe malaria accounts for approximately 8% of tropical fever admissions to intensive care units (ICUs) [21]. Current literature frequently focuses on individual infections such as dengue, malaria, or scrub typhus, rather than providing a comprehensive profile of undifferentiated febrile illnesses and their differential diagnoses.

Viral infections can manifest as febrile illnesses or specific influenza-like illnesses, characterized by symptoms such as mild sore throat and cough. When these symptoms are combined with upper respiratory involvement and systemic signs like fever and malaise, they are referred to as influenza-like illnesses. An acute onset of high fever with facial pain or nasal discharge lasting for at least 3 to 4 days is also common [30]. Scrub typhus or murine typhus may present with distinctive signs such as a skin eschar, regional lymphadenopathy, and maculopapular rash. Leptospirosis often manifests with conjunctival suffusion, muscle tenderness, and jaundice, especially following exposure to floodwater or sewage. Respiratory tract involvement, acute renal failure, vomiting, and loose motions are common symptoms associated with scrub typhus [28]. Persistent fever accompanied by gastrointestinal symptoms and splenomegaly should raise suspicion for typhoid fever. Tuberculosis must be considered in patients with prolonged undifferentiated fever, particularly if it is accompanied by weight loss[36]. Severe dengue infections can lead to hemorrhagic manifestations such as petechiae, subconjunctival hemorrhages, and ecchymoses, with a positive tourniquet test serving as an important diagnostic indicator. The comprehensive management of febrile illnesses necessitates a multifaceted approach, incorporating both primary and advanced diagnostic tests. Accurate diagnosis and effective treatment hinge on recognizing the clinical patterns and laboratory findings associated with various infectious and non-infectious causes of fever. The challenges in diagnosing and treating acute undifferentiated febrile illness underscore the importance of continued research and education to enhance the clinical acumen of healthcare providers.

SPECIAL CONSIDERATIONS FOR SPECIFIC POPULATIONS

In geriatric and immune compromised patients, respiratory tract infections are often the primary cause of fever[35]. Accurate diagnosis and treatment planning in these populations require specific diagnostic tests such as sputum analysis and chest X-rays. However, these tests can take up to three days to provide results, during which supportive care and empirical treatment are essential. Hospital-acquired pneumonia and ventilator-associated pneumonia, often indicated by fever, are critical concerns that can develop after 48 hours of intubation or mechanical ventilation[31]. These conditions require prompt and effective management to prevent serious complications. Residents of long-term care facilities (LTCFs) are particularly vulnerable to infections due to age-related changes and chronic conditions affecting immunity[39]. The clinical presentation of infections in LTCF residents may be subtle, necessitating adapted infection diagnosis standards for this population. Understanding electrolyte imbalances such as hypernatremia and hyponatremia in febrile elderly patients in LTCFs is vital. These imbalances can predict outcomes regardless of other factors such as age, gender, or initial plasma sodium levels[35]. Hypernatremia is associated with a high risk of mortality, while hyponatremia can indicate underlying conditions such as heart failure or chronic kidney disease, necessitating careful management and monitoring.

TREATMENT OPTIONS

The treatment for fever depends significantly on its underlying cause. For infectious etiologies:

Malaria: Antimalarial drugs such as chloroquine, artemisinin-based combination therapies (ACTs), or quinine are prescribed depending on the type of malaria and resistance patterns.

Dengue: Supportive care, including hydration, pain relief with paracetamol, and monitoring for complications. There is no specific antiviral treatment for dengue.

Scrub Typhus: Doxycycline or azithromycin is typically effective. Early treatment is crucial to prevent complications.

Leptospirosis: Doxycycline or penicillin is used to treat leptospirosis, with early treatment reducing the risk of severe disease.

PROPHYLACTIC TREATMENT

When encountering a patient with undifferentiated fever and negative rapid tests for malaria and dengue, clinicians often opt for empirical treatment with antibiotics like doxycycline. Ceftriaxone and doxycycline are frequently prescribed for tropical fevers, while azithromycin is commonly used for conditions such as malaria and acute undifferentiated febrile illnesses (AUI). These fevers are often accompanied by chills, prompting initial treatment with broad-spectrum antibiotics such as cefepime and ceftriaxone, along with multivitamins to support the patient's recovery [22].

Understanding the prevalence and epidemiology of the pathogens causing these fevers is crucial for developing effective empirical antibiotic protocols [23]. Proper use of antimicrobial agents is essential to prevent the emergence of antibiotic-resistant bacteria. This requires improved access to diagnostic tools for managing specific diseases, regular studies on

causative agents, and assessments of regional antimicrobial susceptibility trends [33]. The choice of medication for treating febrile illnesses can be influenced by various factors, including the mix of patient cases, the drugs available in the formulary, and the clinical practice guidelines at different institutions. Antibiotics should be reserved for situations where early administration is known to be beneficial, such as in cases of acute bacterial meningitis, severe sepsis, septic shock, community-acquired pneumonia, and necrotizing fasciitis.

Management of fever involves several strategies. Paracetamol is effective in reducing fever, ensuring doses are spaced at least six hours apart [37]. For high fevers, cold sponging can be used as an adjunctive measure. Patients should be encouraged to drink plenty of fluids, provided there are no warning signs. Education on recognizing symptoms that may indicate complications, such as breathing difficulties or persistent fever lasting more than four to five days, is also important. Empirical treatment with antibiotics like doxycycline is often justified in the initial management of undifferentiated fevers. Doxycycline is effective against a wide range of pathogens, including those responsible for rickettsial infections, leptospirosis, and scrub typhus, which are common causes of AEFI in tropical regions [24]. Ceftriaxone, a broad-spectrum cephalosporin, is also commonly used due to its efficacy against a variety of bacterial infections, including severe sepsis and bacterial meningitis.

Azithromycin is another antibiotic frequently used in the management of febrile illnesses[11]. It is particularly useful in treating conditions like malaria and other AEFIs due to its broad antimicrobial coverage and favorable pharmacokinetic properties. In the context of febrile illnesses accompanied by chills, the initial administration of broad-spectrum antibiotics such as cefepime and ceftriaxone is often warranted [22]. These antibiotics provide broad coverage against a range of potential bacterial pathogens while awaiting definitive diagnostic results. The selection of appropriate antibiotics is guided by several factors. The mix of patient cases seen in clinical practice, the availability of drugs in the institutional formulary, and adherence to existing clinical practice guidelines all play a role. Ensuring the judicious use of antibiotics is critical to minimize the risk of antibiotic resistance. This is particularly important in regions where the prevalence of multidrug-resistant organisms is high.

To develop effective empirical treatment protocols, it is essential to have a thorough understanding of the local epidemiology of febrile illnesses. Regular surveillance studies to identify the causative agents of febrile illnesses and to assess regional patterns of antimicrobial susceptibility are vital. This information informs the selection of empirical antibiotic regimens and helps to optimize treatment outcomes while minimizing the risk of resistance. Effective management of febrile illnesses also involves supportive care measures. Antipyretic therapy with paracetamol is a cornerstone of fever management. Ensuring that doses are spaced at least six hours apart helps to avoid potential toxicity. Cold sponging can be an effective adjunctive measure for managing high fevers. Encouraging adequate fluid intake is important to prevent dehydration, especially in patients with significant fever and sweating [27]. However, patients should be monitored for warning signs such as difficulty breathing, altered mental status, or persistent high fever, which may indicate a need for more intensive medical intervention.

It is also crucial to educate patients about the appropriate use of antibiotics. For example, antibiotic therapy is unnecessary for viral upper respiratory tract infections (URTIs). Patients should be informed about the typical course of viral illnesses and the expected duration of symptoms. They should also be educated about signs that may indicate a complication or secondary bacterial infection, such as worsening symptoms, difficulty breathing, or a fever that persists beyond four to five days [29].

DISCUSSION

When a patient presents with intermittent high-grade fever, it's essential to conduct primary investigations to determine the diagnosis and appropriate treatment. Fevers often come with chills and can be caused by seasonal infections such as dengue, malaria, scrub typhus, and lower respiratory tract infections (LRTIs)[30]. Additionally, conditions like gastroenteritis and sepsis may manifest with fever, complicating the diagnostic process. For patients meeting the criteria for acute undifferentiated febrile illness, I begin with a thorough history and clinical examination [25]. This comprehensive approach helps pinpoint the cause of the fever. For instance, urinary tract infections (UTIs) are a common culprit, especially in women. These are confirmed through urine culture and sensitivity tests, which guide the selection of the most effective antibiotics.

Continuous fevers due to sepsis or bloodstream infections necessitate the use of blood culture and sensitivity tests. These tests are crucial for identifying the specific pathogens responsible and determining the appropriate antimicrobial therapy. However, I recognize that in geriatric and immunocompromised patients, respiratory tract infections are often the cause of fevers. Therefore, sputum analysis and chest X-rays are included in the diagnostic process for accurate diagnosis and

treatment planning. After three days of sending the sample to the lab, the results of the special tests—blood culture and sensitivity, urine culture and sensitivity, sputum for culture and sensitivity, and CBNAAT for sputum analysis—were discovered. We found resembling studies from India and other tropical regions of the developing world suggested that scrub typhus (47.5%), malaria (17.1%), enteric fever (8%), and dengue (7%) were the most prevalent tropical fevers among adult patients.[24] While indispensable, these tests can take up to three days to provide results, requiring careful management of the patient's symptoms and condition in the interim.

Research from India and other tropical regions highlights prevalent tropical fevers among adults, including scrub typhus, malaria, enteric fever, and dengue. Studies have identified dengue, enteric fever, scrub typhus, bacterial sepsis, and malaria as primary infections in acute undifferentiated febrile illnesses. Similarly, in a large cohort of 2547 patients with acute undifferentiated febrile illnesses dengue (37.54%), enteric fever (16.5%), scrub typhus (14.42%), bacterial sepsis (10.3%), and malaria (6.8%) were the main infections identified[19]. Another study reported dengue, scrub typhus, encephalitis/meningitis, malaria, and bacterial sepsis as common causes, also another study shows Dengue (23%) was the most common followed by scrub typhus (18.2%), encephalitis/meningitis (9.6%), malaria (8.1%), and bacterial sepsis (7%)[22]. These findings help stay updated on prevalent infections and guide diagnostic considerations.

Patients able to tolerate adequate oral fluids and pass urine regularly without warning signs may avoid hospitalization. Encouraging sufficient fluid intake can significantly reduce the need for hospital admissions, benefiting both the patient and the healthcare system. However, vigilance is necessary with geriatric and immunocompromised patients, as they often require specific diagnostic tests for optimal treatment due to their increased vulnerability to respiratory infections. Hospital-acquired pneumonia and ventilator-associated pneumonia, often signaled by fever, are critical concerns that develop after 48 hours of intubation or mechanical ventilation. Effective management of these infections is crucial to prevent severe complications [31].

Residents of long-term care facilities (LTCFs) present unique challenges due to age-related changes and chronic conditions affecting immunity. A skilled nursing facility (SNF) or another long-term care facility (LTCF) is predicted to be necessary to care for more than 40% of people over the age of 65 at some point in their lifetime [34]. The clinical presentation of infections in LTCF residents can be subtle, making it crucial to adapt infection diagnosis standards for this population. Understanding these nuances is vital for accurate diagnosis and effective treatment.

Understanding electrolyte imbalances like hypernatremia and hyponatremia in febrile elderly patients in LTCFs is particularly important, as these imbalances can predict outcomes regardless of other factors like age, gender, or initial plasma sodium levels [35]. Hypernatremia is associated with a high risk of mortality, while hyponatremia can indicate underlying conditions such as heart failure or chronic kidney disease. This knowledge allows for better management and monitoring of these patients, ensuring improved outcomes. In the final analysis, treating patients with sporadic high-grade fever necessitates a careful combination of focused diagnostics, clinical evaluation, and history-taking. We strive to deliver the best possible treatment and enhance patient outcomes by being up-to-date on the latest research and recognizing the unique needs of various patient populations. This holistic approach guarantees that we consider the complexities of fever presentations, particularly in vulnerable groups like the elderly and immunocompromised patients, and tailor our diagnostic and therapeutic tactics accordingly.

CONCLUSION

Effective management of fever often involves a combination of symptomatic and supportive treatments to alleviate fever spikes. However, it's paramount to establish a meticulously designed protocol for evaluating fever patients before initiating treatment. A thorough evaluation based on appropriate criteria is imperative for ensuring optimal patient care. In regions where patients commonly present with fever alongside respiratory symptoms and hepatitis, it's crucial to consider scrub typhus as a potential differential diagnosis.

Having a well-structured protocol in place is key to navigating the complexities of managing fever patients. Without a precise diagnosis or a clear understanding of the underlying disease, conventional treatments and medications may fall short of adequately controlling fever. When it comes to choosing antibiotics, several factors must be considered, including the severity of the illness, the presence of any accompanying medical conditions, the suspected pathogen, resistance patterns, and the patient's prior antibiotic history. Clinical presentation and procalcitonin levels serve as valuable indicators to assess the appropriateness of continuing or discontinuing antibiotic therapy.

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