REUE | Training for residents

Training for Emergency Medicine Residents: Assessment of the Febrile Adult

Formación para residentes de Medicina de Urgencias y Emergencias: evaluación del adulto febril

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Case report

You begin your shift on a cold winter afternoon and review the list of patients you need to receive from your outgoing colleague. The first is an 85-year-old man with a temperature of 38°C, heart rate of 110 bpm, respiratory rate of 25 bpm, oxygen saturation of 98 % on room air, blood pressure of 130/85 mmHg, with no complaints other than fever and myalgias for the past 15 days. Patient #2 is a 35-year-old woman, 3 weeks postpartum, with a temperature of 39.3°C, heart rate of 145 bpm, respiratory rate of 30 bpm, oxygen saturation of 90 % on room air, and blood pressure of 70/45 mmHg, who reports pelvic pain, foul-smelling discharge, and a 2-day history of general deterioration. The last patient is a 25-year-old man with a temperature of 38.5°C, heart rate of 120 bpm, respiratory rate of 22 bpm, oxygen saturation of 98 %, and blood pressure of 120/70 mmHg, who reports cough and odynophagia since today, as does his partner who developed the same symptoms 2 days ago.

In these 3 cases we are faced with elevated temperatures, but clearly the risks and likely etiologies differ. Who should be hospitalized? Should I treat the fever? What etiologies are responsible for these presentations? These questions will be addressed in this article.

Introduction

Fever is one of the most frequent reasons for consultation in the emergency department (ED). It is estimated that 5 % of adult consultations are due to fever, reaching up to 15 % in older adults.[1]

Although it is essential to suspect infectious pathology when faced with this symptom, it is important to remember that there are other causes of fever. In intensive care units (ICU), 70 % of patients will have fever, but only 53 % will be of infectious origin.[2]

Fever has evolved as an adaptive response over more than 4 million years and has been documented in vertebrates, arthropods, and annelids.[2] It plays a fundamental role in our response to infections, as observed in the recent coronavirus pandemic, where the absence of fever was associated with higher mortality.[3]

Physiopathology

Fever is part of the acute-phase response along with leukocyte mobilization, production of protective proteins, decreased blood levels of iron, zinc, and manganese, reduced erythrocyte production, anorexia, destruction of muscle and fat tissue, body pain, lethargy, asthenia, and adynamia.[4]

The role of fever has been demonstrated in both *in vivo* and *in vitro* experiments, improving immune cell mobility, phagocytosis, and the production of reactive oxygen species.[4] Fever results from a change in the set point of body temperature in the hypothalamus. This change is driven by molecules called pyrogens, which may be exogenous (originating from microorganisms) or endogenous (originating from host cells).[1] Pyrogens promote cytokine release and initiate the inflammatory cascade that produces prostaglandin E2 in peripheral tissues, which then reaches the hypothalamus to produce cyclic adenosine monophosphate (cAMP), raising the thermoregulatory set point. This occurs independently of the origin of the pyrogen.[1]

The acute-phase response involves the use of limited body resources and may sometimes harm the host. For every 2°C increase in body temperature, approximately 20 % more energy is used compared to normal temperature. This may explain behavioral changes as an energy-saving strategy, although it has also been hypothesized that it may deprive pathogens of the resources necessary for survival.[4]

Risk groups

Immunocompromised patients

Immunocompromise encompasses a

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Table 1. Etiology of fever in the transplant patient according to time of presentation[5]

First month
Donor-derived pathogens
Healthcare-associated pathogens
Surgical site infection
Clostridium difficile colitis
1–6 months
Herpes virus reactivation
Hepatitis B and C
Tuberculosis
Nocardia
Listeria
Fungi: *Pneumocystis*, Cryptococcosis, *Aspergillus*, endemic fungi
> 6 months
Community-acquired infections in patients receiving corticosteroids or other immunosuppressants: cytomegalovirus
Endemic fungi

wide variety of patients, including untreated HIV patients, solid organ or bone marrow transplant recipients, and those using immunomodulators for various conditions. Each group carries different risks depending on the underlying disease.

Untreated HIV patients still most commonly require hospitalization due to pneumonia and cellulitis, but three major presentations must always be considered: pulmonary, neurological, and other febrile presentations (such as diarrhea or esophagitis). Based on history and physical examination findings, appropriate diagnostic evaluation should be performed.

Currently, an increasing number of patients with solid organ transplants are seen in emergency settings. These patients may present with fewer symptoms and signs due to immunosuppressive therapy. Additionally, non-infectious causes of fever, such as graft rejection or drug-induced fever, should be considered. Antibiotic therapy must also be adjusted to avoid interactions with immunosuppressive drugs. Table 1 summarizes infections associated with transplantation according to timing.

In neutropenic patients, common infection sources include the GI tract, lungs, paranasal sinuses, skin, and hematologic system. The use of invasive devices (e.g., central venous catheters) must also be considered as potential sources. The timing between fever onset and catheter use may help identify the cause.[5]

Pregnant woman

Febrile pregnant women face risks affecting both mother and fetus. Studies have shown an increased risk of neural tube defects, congenital heart defects, and cleft palate.[6] However, a recent cohort study from Denmark suggested that fever in the first trimester may not be associated with congenital malformations,[7] and further research is needed.

Another important aspect is the infection focus and its relationship with preterm birth, as seen in listeriosis, chorioamnionitis, and group A *Streptococcus* infections.

From the maternal perspective, pregnant women tend to have lower mortality than the general population, as they are typically younger and pathogens are more responsive to antibiotics.[6]

Table 2. Causes of fever in the pregnant woman[7]

Obstetric causes	Non-obstetric causes
Genital tract	Acquired immunodeficiency syndrome with opportunistic disease
Chorioamnionitis	Pneumonia
Postpartum endometritis	Tuberculosis
Septic abortion	Malaria
Surgical wound infection	Viral infections (influenza, varicella)
Necrotizing fasciitis	
Non-genital	
Pyelonephritis	
Mastitis	
Puerperal thrombophlebitis of the ovarian vein	

Table 2 summarizes causes of sepsis during pregnancy, both obstetric and non-obstetric.

Older adult

Older adults often present with atypical and delayed signs of disease due to a weakened immune response. It is estimated that 10 % of older patients presenting to the ED will have fever, with hospitalization rates reaching up to 90 %, and 10 % mortality within the first month. The most common infection sites are pulmonary, urinary, and soft tissue.

Given the high rate of bacterial infections in febrile older adults (up to 85 %), hospitalization is recommended to complete diagnostic evaluation.[8]

Diagnosis

Approaching fever as a symptom requires a detailed history, considering the patient's prior medical history, recent hospitalizations, current drug use, recent antibiotic use, and habits. This should be followed by a thorough physical examination.[1] The objective is to identify whether we are dealing with a patient with fever or hyperthermia and, once patients with fever have been identified, we must search for the possible cause to guide clinical management (Table 3). Figure 1 illustrates a practical algorithm for the ED.

The method of temperature measurement matters; currently, noninvasive methods do not achieve sensitivity > 90 % if 38°C is considered the definition of fever, but if we lower the definition to 37.5°C, tympanic thermometry would achieve a sensitivity and specificity of 90 %.[9]

The presence of chills is a highly specific finding for bacteremia, with an RR, 12.11 (95 % CI, 4.06 to 36.16), but low sensitivity [0.37 (0.29–0.45)].[10] The importance of this lies in the fact that chills favor timely blood culture collection and early antibiotic administration. In any case, their absence does not rule out the presence of bacteremia.

A relevant clinical sign is Faget sign, which consists of fever not being accompanied by an increase in heart rate. This occurs in patients with neoplasms, drug-associated fever, concomitant use of beta-blockers, or the presence of intracellular microorganisms.[11] Of note, the absence of fe-

Table 3. Differentials of fever[1,8]

Infectious	Non-infectious
Bacterial	Malignancy
Urinary tract infection	Autoimmune
Tubo-ovarian abscess	Drug reaction
Prostatitis	Allergy
Meningitis	Metabolic consequences
Cavernous sinus thrombosis	Intoxication (anticholinergics, sympathomimetics)
Brain abscess	Seizures
Cholangitis	Environmental
Appendicitis	Heat stroke
Cholecystitis	Excess exercise
Diverticulitis	Hyperthyroidism
Cellulitis	Thyroid storm
Necrotizing fasciitis	Neurological
Osteomyelitis	Intracranial hemorrhage
Pneumonia	Embolic – thrombosis – infarction
Retropharyngeal abscess	Myocardial infarction
Otitis media	Renal infarction
Sinusitis	Pulmonary thromboembolism
Endocarditis	Transfusion reaction
Pericarditis	Factitious
Myocarditis	Munchausen
Peritonitis	Munchausen by proxy
Viral	Malignant hyperthermia
Pharyngitis	Neurologic syndrome
Gastroenteritis	Serotonin syndrome
Aseptic meningitis	Hyperpyrexia (T° ≥ 41.5°C)
Human immunodeficiency virus	Sepsis
Influenza	Heat exposure
Pericarditis	Heat stroke
Parasitic	Neuroleptic malignant syndrome
Malaria	Malignant hyperthermia
Toxoplasmosis	Serotonin syndrome
Giardiasis	Intracranial hemorrhage
Arthropods	Thyroid storm
Lyme disease	Anticholinergic toxidrome
Rocky Mountain spotted fever	Sympathomimetic toxidrome
Babesiosis	
Fungal	
Candidiasis	
Blastomycosis	
Histoplasmosis	

ver does not mean that the patient is not septic, since between 20 % and 30 % of older adult patients will remain afebrile. The absence of fever is associated with higher 30-day mortality, and lack of early recognition is an important poor prognostic factor.[1]

To evaluate these patients, we have a broad array of laboratory tests: complete blood count, urinalysis, chest radiography, C-reactive protein (CRP), procalcitonin (PCT), viral antigens, and blood cultures. The decision to request these tests will depend on the information obtained from the history and physical examination, without excluding other specific tests such as cerebrospinal fluid, pleural fluid, ascitic fluid, thick smear, etc.

Table 3 presents the different causes of hyperthermia and fever, both infectious and noninfectious. Infections continue to lead the causes of fever, although nowadays autoimmune, inflammatory, and neoplastic causes are increasingly common.[12]

Laboratory

CRP is an acute-phase reactant that rises 4–6 hours after the stimulus and doubles every 8 hours, with a peak at 45–60 hours. Unfortunately, it rises in several conditions such as cancer, obstructive sleep apnea, and chronic vascular disease, conditions that do not require antibiotics,[13] which causes it to lose specificity.[1] It has a good correlation with bacterial infections when its values are very high, and its use may help reduce antibiotic use in some patients. Unfortunately, there is no established cutoff point, and CRP may also rise to high values in other conditions that do not require antibiotics.[13]

PCT is a 116-amino-acid peptide that usually rises more in bacterial than viral infections, and its use in respiratory illnesses has led to a reduction in antibiotic use without affecting mortality.[1] It may have prognostic value in both septic and nonseptic patients: a 30 % decrease in the first 24 hours after the start of antibiotic treatment is associated with better clinical outcomes. Despite this, its utility in the ED remains unclear, especially in febrile nonseptic patients.[14]

Neither CRP nor PCT is useful on its own to rule out or confirm the presence of an infection,[1] so history and physical examination remain fundamental in guiding us toward the possible cause.

Blood cultures are not recommended routinely in patients who are presumably going to be discharged, who have uncomplicated infections, or in clinical situations in which the result would not change management. They should be considered in septic or immunocompromised patients or when a bacteriological diagnosis is necessary.

Noninfectious causes of fever

Among the noninfectious causes of fever are pulmonary thromboembolism (PTE), intracranial hemorrhage, neuroleptic malignant syndrome, serotonin syndrome, certain toxins such as anticholinergics or sympathomimetics, thyroid storm, and heat stroke, among others. A temperature ≥ 41.5°C is considered hyperthermia, and the above diagnoses must be considered in the differential diagnosis. This is relevant because hyperthermia is not due to pyrogens and does not respond to antipyretics; moreover, in most cases immediate and aggressive cooling of the patient is an absolute priority.[1,15,16]

In the case of PTE, fever is usually low-grade (≥ 37.7°C), with an incidence rate of only 14 %, and its presence is not related to pulmonary infarction or hemorrhage. In 6 % of cases, the temperature exceeds 38.3°C and may be explained by bacterial superinfection or diffuse infarctions.[17]

Drug-related fever occurs in 2 % to 10 % of adverse reactions, with highly variable incidence in the literature. There is no exact definition of this entity, but there is agreement that to suspect it, the fever must resolve after withdrawal of the drug, not recur, and have no other explanation. In Japan, it is estimated to have a prevalence between 1.8 % and 5.7 % in patients admitted with fever and may account for up to 10 % of fever in hospitalized patients.[18]

Temperature elevation is also the main symptom in severe drug-associated reactions, such as serotonin syndrome and neuroleptic malignant syndrome.[19,20]

In serotonin syndrome, fever appears within 24 hours after drug administration. Fever may range between 38.3°C and 43.5°C and is present in 61% of fatal cases.[19] In neuroleptic malignant syndrome, fever is accompanied by altered mental status, rigidity, and dysautonomia. The temperature may exceed 40°C and usually develops 4 days after administration of the causative drug.[20]

Another frequent cause of fever is cancer, accounting for up to 20 % of causes of fever of unknown origin. It is important to consider that 67 % of patients with cancer and fever will have an infection and only 27 % will have a neoplastic cause.[11]

Heat stroke is a life-threatening condition in which there may be neurologic, hepatic, renal, and coagulation damage, as well as musculoskeletal and cardiac involvement. Core body temperature is directly related to mortality and morbidity in these cases. Early identification and initiation of cooling measures are essential for a good prognosis.[15,16]

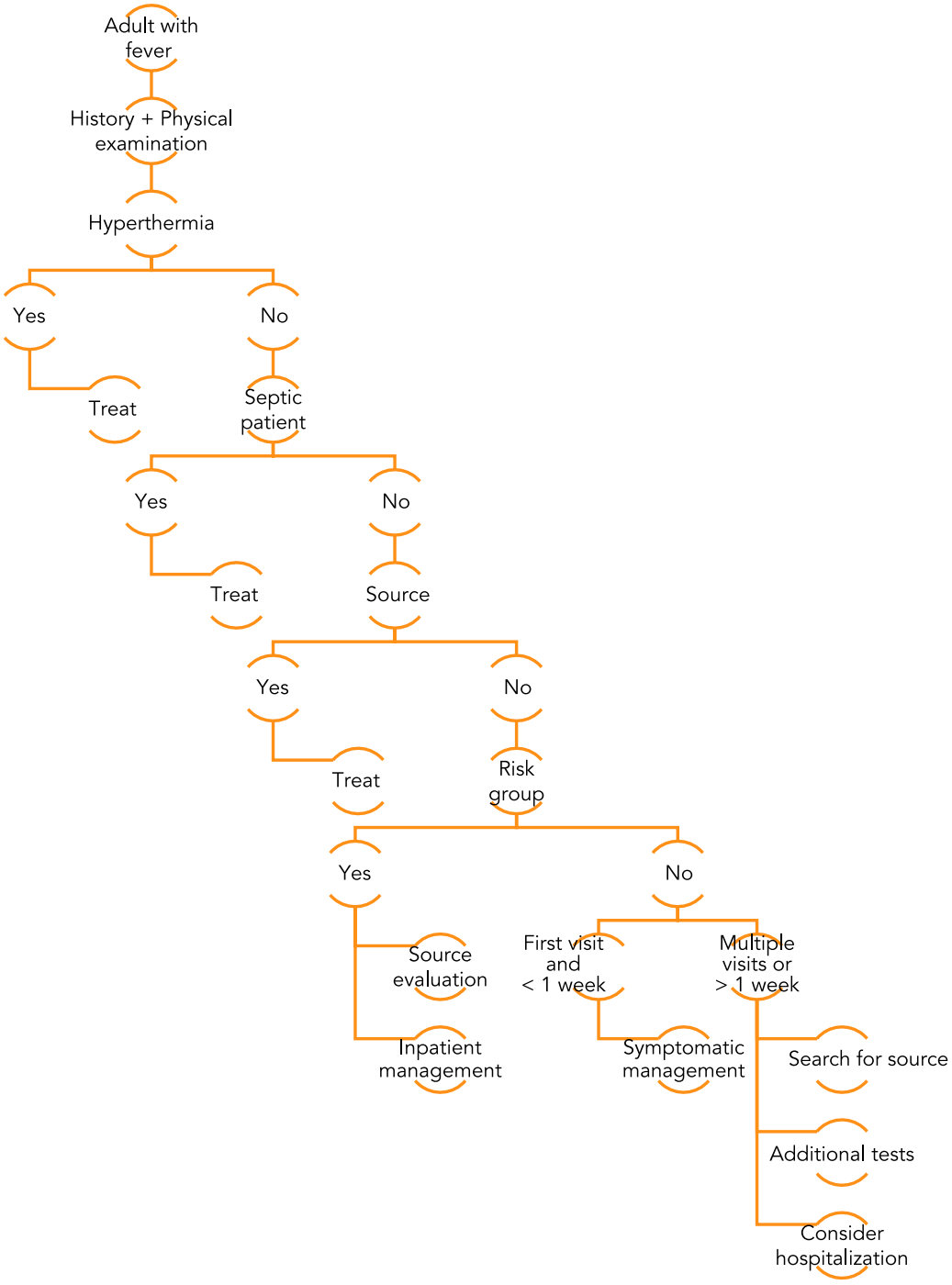

Figure 1. Algorithm.

Clinical management

There is currently some controversy regarding fever management, especially in critically ill patients. Culturally, fever is regarded as something unfavorable, and patients take antipyretics to manage symptoms associated with fever and out of fear that fever is harmful.[4] Various studies have shown adverse effects from pharmacologic fever management in pediatric patients with varicella, malaria, and pneumonia.[21-23]

Two studies of sepsis and severe infection in Sweden and Denmark, each with more than 2,000 patients, showed that the presence of fever was associated with lower mortality and that higher temperature was associated with greater survival.[24,25]

The study by Herniksen *et al.* showed that in the ICU, hypothermic patients had a mortality of 37.5 %, normothermic patients 18.3 %, and febrile patients 11 %.[24] In the study by Sundén-Cullberg *et al.* it was observed that in patients with severe sepsis or septic shock, there was an inverse relationship between body temperature in the ED and hospital stay and mortality.[25]

Although the above addresses the presence of fever at the initial assessment of the patient or during hospital stay, it is important to know whether fever management is associated with complications. To date, different studies have shown that pharmacologically lowering temperature is not associated with a greater number of complications, nor with benefits in mortality or hospital stay.[26-28]

Of note, there is no range in which it can be determined whether fever remains an adaptive response or whether it should be managed considering the energy expenditure it represents for the patient. In a retrospective study, temperatures above 39.5°C were associated with higher all-cause 30-day mortality, ICU admission, and acute kidney injury vs lower temperature ranges (38–38.1°C). However, the range between 39.2 and 39.5°C was the one with the lowest mortality.[29] This study did not assess whether reducing temperature had any benefit, but it suggested that there may be a threshold at which fever begins to become maladaptive.

Regarding the method used to lower temperature, the drug with the best efficacy is acetaminophen at a dose of 1 g or 500 mg combined with ibuprofen 100 mg IV or 200 mg orally, achieving temperature control within 1 hour.[30] The use of cooling blankets has been associated with a 50 % reduction in vasopressor use, decreased 14-day mortality, and a higher rate of shock reversal.[31]

Of note, there are conditions in which temperature management has indeed been associated with reduced mortality and morbidity, especially in neurocritical patients and in those with malignant hyperthermia. Early recognition and management have an enormous impact on the patient.[32,33]

Conclusions

The febrile patient will continue to be a challenge, and the fundamental aspect is a structured evaluation from the standpoint of history and physical examination. Temperature management is not free of controversy, but at present there is no evidence pointing to greater harm and, on the contrary, it helps patient comfort.

Epilogue of case reports

The shift revealed the clinical diversity that may underlie a common symptom such as fever. The 85-year-old patient, after normalization of vital signs through the use of antipyretics and chest radiography warranted by his risk profile, was diagnosed with pneumonia without severity criteria and was able to be discharged with outpatient antibiotic management. In contrast, the young postpartum woman in septic shock required an immediate response with resuscitation and antibiotics before being transferred to the operating room for a uterine infectious focus. The young man with odynophagia, whose examination showed only pharyngeal congestion, returned home with clear instructions regarding alarm signs. All this reminds us that in the ED, fever may vary enormously in etiology and may be due to a wide range of diagnostic possibilities, from a trivial viral illness to an imminent life-threatening condition.

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