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Review

Evaluation of fever in the emergency department☆,☆☆

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ABSTRACT

Background: Fever is one of the most common complaints in the emergency department (ED) and is more complex than generally appreciated. The broad differential diagnosis of fever includes numerous infectious and non-infectious etiologies. An essential skill in emergency medicine is recognizing the pitfalls in fever evaluation.
Objective of review: This review provides an overview of the complaint of fever in the ED to assist the emergency physician with a structured approach to evaluation.
Discussion: Fever can be due to infectious or non-infectious etiology and results from the body's natural response to a pyrogen. Adjunctive testing including C-reactive protein, erythrocyte sedimentation rate, and procalcitonin has been evaluated in the literature, but these tests do not have the needed sensitivity and specificity to definitively rule in a bacterial cause of fever. Blood cultures should be obtained in septic shock or if the results will change clinical management. Fever may not be always present in true infection, especially in elderly and immunocompromised patients. Oral temperatures suffer from poor sensitivity to diagnose fever, and core temperatures should be utilized if concern for fever is present. Consideration of non-infectious causes of elevated temperature is needed based on the clinical situation.
Conclusion: Any fever evaluation must rigorously maintain a broad differential to avoid pitfalls that can have patient care consequences. Fever is complex and due to a variety of etiologies. An understanding of the pathophysiology, causes, and assessment is important for emergency physicians.

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1. Introduction

Fever is one of the most common patient complaints in the Emergency Department (ED), accounting for approximately 15% of visits in the elderly and 5% in adults [1]. While many fevers represent an infectious source of pathology, other sources of fever include pulmonary embolism, intracranial hemorrhage, medication, or malignancy (see Table 1). There are numerous potential pitfalls both in failing to consider non-infectious etiologies of fever but also in the infectious evaluation of fever. This review focuses on infectious sources of fever, the pitfalls in testing, situations when fever may not be present yet the patient does indeed have infectious pathology, and finally some considerations involving non-infectious causes of fever.

2. Discussion

2.1. Fever pathophysiology

Fever, also known as pyrexia, results from an increase in the body's temperature set point. The hypothalamus controls body temperature by balancing inputs from the peripheral nerves that utilize warm/cold receptors in the skin, while also analyzing the temperature of blood in the surrounding area [3,4]. Fever is typically caused by a pyrogen, a chemical substance that provokes fever. One such example is an exogenous pyrogen, such as those seen in gram-positive bacteria (*Staphylococcus aureus* enterotoxins) and the superantigens associated with *Group A streptococcus* and *Group B streptococcus* microbial infections [1,3]. Many bacteria and fungi trigger the production and release of cytokines, small proteins that trigger the inflammatory cascade. These cytokines lead to prostaglandin-2 release in peripheral tissues, raising the hypothalamic temperature set point through cAMP release [1,3]. This process also occurs in malignancy, autoimmune diseases, and other

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disease states that cause inflammation. Central nervous system cytokines are responsible for the hyperpyrexia seen in neurologic trauma and infection [1,3]. A 2015 randomized controlled study from the *New England Journal of Medicine* evaluated treatment of fever with acetaminophen in the intensive care unit, finding fewer ICU-free days in those given acetaminophen versus placebo [5]. However, the study failed to show a mortality benefit in treating fever at 28 days or 90 days [5].

2.2. Infectious vs. non-infectious

When evaluating a febrile patient in the ED, a key clinical question is whether infection is likely enough to warrant antimicrobial administration. A detailed history and physical examination, the past medical history, current medications (e.g. chemotherapy, glucocorticoids), and recent use of antibiotics help shape the pre-test probability of infection. However, it is common to utilize laboratory testing and radiographic imaging to further evaluate the source of fever. Basic testing in the ED often involves a complete blood count (CBC), urinalysis (UA), and Chest X-ray (CXR). The emergency physician (EP) may deem it appropriate to send urine culture, blood cultures, and add viral antigen testing in selected cases. Blood cultures may not be necessary in cases of urinary tract infection (UTI) or pneumonia in patients being discharged; however, they would be useful in cases of severe sepsis or septic shock to further tailor antibiotic therapy. Adjunctive serologic testing such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and procalcitonin may be utilized to further refine the clinical suspicion of infectious pathology [6,7].

Table 1
Differential diagnosis of fever in the emergency department [1,2].

Infectious causes of fever	Non-infectious causes of fever
Bacterial infections	Malignancy (e.g. leukemia, lymphoma, pheochromocytoma)
– UTI	Autoimmune (e.g. rheumatoid arthritis, systemic lupus erythematosus)
– Tubo-ovarian abscess	Drug reaction
– Prostatitis	– Allergic reaction
– Meningitis	– Metabolic consequences of drug
– Cavernous sinus thrombosis	– Ingestion (anticholinergic, sympathomimetic)
– Brain abscess	Seizure
– Cholangitis	Environmental fever
– Appendicitis	– High external temperatures (e.g. heat stroke)
– Cholecystitis	– Excess exercise
– Diverticulitis	Hyperthyroid
– Cellulitis	– Thyroid storm
– Necrotizing fasciitis	Neurologic
– Osteomyelitis	– Intracranial/subarachnoid hemorrhage
– Pneumonia	Embolic vs. Thrombosis vs. Infarction
– Retropharyngeal abscess	– Myocardial infarction
– Otitis media	– Renal infarct
– Sinusitis	– Pulmonary embolus
– Endocarditis	Blood transfusion reaction
– Pericarditis	Factious fever
– Myocarditis	– Munchausen's vs. Munchausen's by proxy
Viral infections	Neuroleptic malignant syndrome
– Pharyngitis	Malignant hyperthermia
– Gastroenteritis	Serotonin syndrome
– Aseptic meningitis	
– HIV	
– Influenza	
Parasitic infections	
– Malaria	
– Toxoplasmosis	
– Giardiasis	
Arthropod infections	
– Lyme	
– Rocky Mountain Spotted fever	
– Babesiosis	
Fungal infections	
– Candidiasis	
– Blastomycosis	
– Histoplasmosis	

C-reactive protein is an acute phase reactant that rises in response to inflammatory stimuli. Serum CRP levels surge within 4–6 h after stimulation, double every 8 h, and peak after 35–60 h [8,9]. In patients who present with fever onset >12 h, serum CRP is elevated significantly in those with bacterial infections [10]. The initial form of CRP testing was qualitative and positive in almost all disease states. Since then, a specific monoclonal antibody and immunological methods of measurement are available, making the current CRP test more valuable in clinical practice. In a review published by Povoa in 2002, a CRP value between 50 and 79 mg/l had sensitivity for sepsis between 72 and 98% and specificity between 66 and 75% [7].

Unfortunately, C-reactive protein is non-specific and has been found to be elevated in numerous other conditions such as malignancy, obstructive sleep apnea, and chronic vascular disease [11-13]. It is used most frequently to provide adjunctive information in the search for more unusual sources of infection, such as osteomyelitis. It should not be used as a stand-alone test to confirm or exclude infection as the cause of fever.

Much like CRP, erythrocyte sedimentation rate (ESR) is occasionally utilized in the ED often as an adjunctive piece of information. However, it suffers from a lack of specificity especially in the older population with numerous comorbid conditions [14]. It should not be relied upon alone to exclude or confirm an infectious source of fever.

Procalcitonin (PCT) is a 116-amino acid peptide that rises in response to infectious etiologies. It is much more likely to be elevated in bacterial, as opposed to viral infections [15,16]. Serum procalcitonin levels increase significantly in severe systemic infections [15]. The use of PCT in the clinical setting to diagnose and treat acute respiratory infections has been shown to decrease overall antibiotic consumption, however there is no mortality benefit from the use of PCT [17]. Currently its use is not prevalent in the ED, and it has not been validated in the ED to support decisions regarding antibiotic use in patients with severe sepsis or septic shock. Much like CRP and ESR, it is an adjunctive piece of information EPs may use to help shape their pre-test probability of infection.

2.3. Blood cultures in fever

The potential utility and indication for blood cultures in the febrile patient is a frequent concern in the ED. Blood cultures are generally not recommended in patients who will be discharged, have uncomplicated infectious disease presentations, or in situations where the results of the cultures will not change management [18]. However, in patients with severe sepsis or septic shock, it is incumbent upon EPs to try and obtain blood cultures prior to initiation of antibiotics [18]. Patients who are immunocompromised (e.g. diabetes, cirrhosis) have a higher likelihood of bacteremia with infectious pathology and may warrant blood cultures even if they are stable and will be admitted to a non-ICU setting [18]. Additionally, it is important to be aware of situations where blood cultures may be needed to detect clinically important infectious diseases such as occult bacteremia due to *S. aureus*, as this often leads to worse clinical outcomes and cannot be diagnosed without blood cultures [19]. Blood cultures should also be obtained in cases of septic shock [18,20]. In cases of unclear benefit, it is reasonable to discuss with the admitting provider whether blood cultures are warranted. Such situations could include hemodynamically stable (i.e. will not require ICU level of care) patients being admitted for community-acquired pneumonia or cellulitis [20]. This course of action promotes antimicrobial stewardship, as there is a risk of false positive blood

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