Kentucky Antimicrobial Stewardship Innovation Consortium

Educational Pearl

Non-Infectious Causes of Fever

Fever is an elevation in body temperature beyond the normal range. Fever, like leukocytosis, can be a clinical sign of infection and is a common cause for initiating or broadening antibiotic regimens. Is this appropriate? Are temperature readings uniform? How does fever relate, or not relate, to infection?

Is there a consensus definition of fever?

Normal body temperature is variable. Rectal temperatures are higher on average when compared to oral, tympanic, and axillary temperatures. Additionally, patients ≥ 60 years old have lower average body temperatures than younger patients.[1] As a result, no consensus definition for fever exists, but temperature ≥ 38.0 °C (100.4 °F) or ≥ 38.3 °C (101 °F) have been used.[2]

What causes fever?

Fever is the result of exogenous pyrogens (e.g., bacterial and endotoxins, medications) and endogenous pyrogens (e.g., prostaglandins, interleukin-1) increasing the hypothalamus' temperature set point.[3] As numerous exogenous pyrogens exist, multiple etiologies can induce fever. Read on for specific examples.

Table 1: Etiologies of Fever[2,4,5]

Etiology	Comments
Infectious diseases	Bacterial, viral, fungal, and parasitic infections
Medication-induced	Drug fever (antimicrobials, anticonvulsants, antineoplastics, immunosuppressants), withdrawal (alcohol, opioids), neuroleptic malignant syndrome, serotonin syndrome, malignant hyperthermia (anesthesia meds), Jarisch-Herxheimer reaction
Neoplastic	Leukemias, lymphomas, tumor lysis syndrome
Cardiovascular	Acute myocardial infarction, pulmonary embolism, venous thrombosis, Dressler syndrome
Neurologic	Stroke, status epilepticus, intracranial hemorrhage
Respiratory	Pneumonitis (with or without infection), atelectasis, acute respiratory distress syndrome
Intra-abdominal	Pancreatitis, acalculous cholecystitis
Other	Transplant rejection, immune reconstitution syndrome, blood product transfusion, gout

Should antibiotics be started or broadened in patients with fever?

A comprehensive workup should be conducted when evaluating the source of a fever. Associated signs and symptoms, relevant past medical history, imaging, and microbiology can be utilized to help diagnosis the etiology of fever. The 2023 guidelines for assessing new fever in the ICU recommend utilizing tailored diagnostics for individual patients with new fever. Empiric antibiotics targeted at the suspected source of infection should be initiated in febrile patients who are hemodynamically unstable or have symptoms of infection.[2] If the diagnostic workup remains negative, de-escalation or watching off antibiotics should be considered. Conversely, a lack of fever despite signs and symptoms of infection should prompt empiric antibiotics especially in critically ill patients.[6,7]

Key Takeaway: While fever is considered a hallmark sign of infection, many non-infectious causes exist. If non-infectious causes of fever are suspected, monitoring off antibiotics is warranted in hemodynamically stable patients.

References:

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