FAST FACTS AND CONCEPTS #256
FEVER NEAR THE END OF LIFE

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Introduction
Clinically significant fever is defined as an increase in body temperature (generally > 38.5°C) in conjunction with an elevation of the hypothalamic set point. Hyperthermia is an uncontrolled elevation in body temperature without a change in the thermoregulatory center. This Fast Fact reviews the key elements in assessment and treatment of fever in patients near the end-of-life.

Pathophysiology
Fever is mediated by exogenous pyrogens (microbes or their products) and pyrogenic cytokines (i.e. IL-1, IL-6, IFN α, TNF) which induce the synthesis of prostaglandin E2 (PGE2). Centrally, PGE2 increases production of cAMP, which raises the hypothalamic set point to febrile levels. Peripherally, this induces myalgias and arthralgias. Pyrogens/pyrogenic cytokines are produced by infection, inflammation, trauma/tissue necrosis, and tumors. Drugs can induce fever through various metabolic and immune responses as well as by mimicking endogenous pyrogens, inflicting direct tissue damage and interfering with heat loss. Common drugs in palliative care settings which cause fever include antibiotics, anti-psychotics (neuroleptic malignant syndrome) and opioid withdrawal. Fever associated with brain injuries is common, perhaps due to direct hypothalamic injury.

Assessment
The extent of evaluation will depend on the patient’s condition and overall goals of care. When indicated, a thorough history and physical exam is needed, looking for a) signs of infection, b) in cancer patients, evidence of disease progression, and c) a medication review. A typical infection laboratory and radiographic workup can be pursued if it will affect management. Common etiologies and clinical findings are reviewed below.

• Infection: look for a history of exposure (e.g. influenza), normal barrier violation (e.g. aspiration, skin ulcer), and neutropenia (for instance, if receiving chemotherapy). Associated signs/symptoms include elevated WBC, chills, spiking temperatures, and if severe, hypotension, tachycardia, mental status changes and neutropenia. Note: Newborns, the elderly, patients with chronic hepatic or renal failure, the immunocompromised, and those taking glucocorticoids can have serious infections without a fever.

• Neoplastic Fever: a diagnosis of exclusion. It is uncommon in solid tumors, more common in lymphomas. It is less likely to manifest as chills, hypotension, tachycardia, and mental status changes; however elevated ESR and CRP are common. It tends to be responsive to NSAIDs.

• Medication-Induced: there is no predictable time of onset from medication initiation to fever presentation. It resolves when suspected drug is stopped.

• DVT/PE: thought to cause fever through inflammation. Fever is inconsistently associated with DVT/PE in the literature, however these are common events in the end-of-life population.

Treatment
Benefits and burdens of all therapeutic options should be weighed in the context of the patient’s overall clinical picture, including whether a fever is actually distressing to a dying patient. When deciding if to treat the fever, ask patients who can communicate if the fever is uncomfortable, and whether or not breaking the fever is more uncomfortable than the fever itself. Although empiric, there is no compelling reason to think that treatment of fever actually reduces suffering for dying, unresponsive patients. Education and reassurance for family and other caregivers is most important in those situations.

• Non-pharmacological Interventions
  o Cooling blankets, ice packs, sponging, and fans. While these can bring down body temperature, they are noisy, labor-intensive, and distract family and other caregivers from more meaningful interactions at the death-bed.

• Pharmacologic Interventions
  o Discontinue any non-essential drugs if drug-induced fever is suspected.
  o Antipyretics work by inhibiting production of PGE2. Acetaminophen 650-1000mg* PO/PR/IV q4-6 hours PRN (maximum dose 4 g/day*) is considered first line given its low side effect profile. NSAIDs (oral, IV, rectal, subcutaneous) are also effective. Naproxen 250mg* q12hrs is particularly effective in neoplastic fever, and possibly diagnostic when infection is ruled out. The
order can state “PRN for symptomatic fever” to discourage focus on the temperature measurement alone.

- Antibiotic therapy has been shown to be inconsistently useful in alleviating fever symptoms in terminally ill patients. While evidence is unclear as to the utility of providing antibiotic therapy, discussions should address their use as a potential treatment that may or may not improve symptoms and prolong life/delay death; time-limited trials can be appropriate.

- Glucocorticoids (oral, IM, IV) are also purported to be effective, however most of the data supporting their use exist in the neurological and head injury literature.

*Discussed doses are for adults.

References:

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