

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

Mallory Strickland BS and Erica Stovsky MD

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**
 - 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**
 - Discontinue any non-essential drugs if drug-induced fever is suspected.
 - 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:

1. Dinarello CA, Porat R. Chapter 16. Fever and Hyperthermia. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012. Available at: <http://www.accessmedicine.com/content.aspx?aID=9095580>. Accessed March 22, 2012.
2. Zhukovsky DS. Fever and sweats in patient with advanced cancer. *Hematol Oncol Clin North Am*. 2002;16(3):579-88, viii. PMID: 12170569.
3. Zell JA, Chang JC. Neoplastic fever: a neglected paraneoplastic syndrome. *Support Care Cancer*. 2005;13(11):870-7. PMID: 15864658.
4. Oh DY, Kim JH, et al. Antibiotic use during the last days of life in cancer patients. *Eur J Cancer Care*. 2006; 15:74-79.
5. Vitetta L, Kenner D, Sali A. Bacterial infections in terminally ill hospice patients. *J Pain Symptom Manage*. 2000; 20:326-334.
6. Nakagawa S, Yoshie T, et al. Can anti-infective drugs improve the infection-related symptoms of patients with cancer during the terminal stages of their lives? *J Palliat Med*. 2010; 13:535-540.
7. Chen LK, Yu-Ching C, et al. Antibiotic prescription for fever episodes in hospice patients. *Supp Care Cancer*. 2002; 10: 538-541.
8. Acetaminophen (systemic). In: USP DI® Volume I: Drug Information for the Health Care Professional [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically.
9. Tabor PA. Drug-induced fever. *Drug Intell Clin Pharm*. 1986; 20:413-20.

Authors' Affiliation Drexel University College of Medicine, Philadelphia, PA (SM); University of Pittsburgh Medical Center, Pittsburgh, PA (ES).

Version History First electronically published in May 2012; re-copy-edited in November 2015 by Sean Marks MD

Fast Facts and Concepts are edited by Sean Marks MD (Medical College of Wisconsin) and associate editor Drew A Rosielle MD (University of Minnesota Medical School), with the generous support of a volunteer peer-review editorial board, and are made available online by the [Palliative Care Network of Wisconsin](#) (PCNOW); the authors of each individual *Fast Fact* are solely responsible for that *Fast Fact's* content. The full set of *Fast Facts* are available at [Palliative Care Network of Wisconsin](#) with contact information, and how to reference *Fast Facts*.

Copyright: All *Fast Facts and Concepts* are published under a Creative Commons Attribution-NonCommercial 4.0 International Copyright (<http://creativecommons.org/licenses/by-nc/4.0/>). *Fast Facts* can only be copied and distributed for non-commercial, educational purposes. If you adapt or distribute a *Fast Fact*, let us know!

Disclaimer: *Fast Facts and Concepts* provide educational information for health care professionals. This information is not medical advice. *Fast Facts* are not continually updated, and new safety information may emerge after a *Fast Fact* is published. Health care providers should always exercise their own independent clinical judgment and consult other relevant and up-to-date experts and resources. Some *Fast Facts* cite the use of a product in a dosage, for an indication, or in a manner other than that recommended in the product labeling. Accordingly, the official prescribing information should be consulted before any such product is used.