

## Evaluation of Nosocomial Fever

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Fever is defined as a body temperature, which exceeds that found in the 99<sup>th</sup> percentile of healthy individuals: 37.2 degrees Centigrade or 98.9° Fahrenheit at 6a.m. and 37.7° C (99.9° F) at 4 p.m. Fever typically represents an increase of at least 1° to 2°C from baseline.<sup>1</sup> Inflammatory cells may be stimulated by microorganisms, antibody complexes or tissue trauma to release "endogenous" pyrogenic cytokines which act on the hypothalamic thermoregulatory center altering the set point upward and causing pyrexia. Hyperthermia is distinguished by an increase in body temperature occurring when heat production overcomes heat loss in the setting of a normal thermoregulatory set point. Hyperpyrexia denotes temperatures over 41.5°C (106°F) and most commonly occurs following intracranial hemorrhages.

Hospitalized patients are at especially high risk for developing fever-causing illnesses and hyperthermia given the potential exposure to various infectious pathogens, invasive procedures, catheter/tubing devices, medications and blood products. While nosocomial sources of fever are common, the opportunity to diagnose pyrexia due to coexisting diseases such as neoplasms, vasculitides or granulomatous disorders should not be missed. Few studies address etiologies, risks and outcomes of nosocomial fever in all populations. However, Arbo et al.<sup>2</sup> published a case controlled study which concluded that bacterial etiologies were prevalent and diabetes was an independent predictor of bacteria-related fever. Patients with fever had more preceding invasive procedures than controls and had longer hospital stays, although 30-day mortality and readmission rates were the same.

The evaluation of the hospitalized adult who develops fever requires careful attention to three objectives that will guide the differential diagnosis and recommendations for treatment. These include establishing the host's immunocompetency, assessing risks for infection or hyperthermia specifically related to inpatient procedures or treatment, and finally pursuing coexisting disease. Occasionally, all three areas may factor into the differential diagnosis. For example, a febrile HIV patient with non-Hodgkin's lymphoma and a peripheral IV may have an opportunistic infection, neoplastic fever or septic thrombophlebitis.

Immunocompromise and immunosuppression represent excessive risk for infectious causes of fever in the hospital. Many hematologic neoplasms as well as some solid neoplasms and their cytotoxic

therapies produce host defense defects such as neutropenia and impaired cell-mediated or humoral immunity. Donowitz<sup>3</sup> adequately reviewed the epidemiology of fever in immunocompromised patients and the approach to evaluation and treatment. Identifying the host defense defect related to the specific underlying disease or chemotherapy is critical to predicting the infectious agent responsible. Neutropenia due to acute nonlymphocytic leukemia for example, confers host susceptibility to gram-negative infections, especially those caused by Enterobacteriaceae and *Pseudomonas aeruginosa*, which are frequent colonizers in inpatients. Solid organ or bone marrow transplant recipients and patients with connective tissue disorders requiring chronic immunosuppressive therapy, diabetics, asplenic and geriatric patients likewise suffer varying deficiencies in humoral and cell-mediated host defense. Certainly despite age, the critically and/or chronically ill, malnourished and alcoholic patients should be addressed similarly.

Febrile inpatients with advanced absolute CD4 cell depression related to HIV disease are at risk for the myriad of opportunistic infections and neoplasms seen in the outpatient setting and should be approached with similar suspicion.<sup>4</sup> Atypical presentations of *M. tuberculosis* infections however may occur at any stage of HIV disease.

Many modalities of inpatient care whether surgical, medical or procedural impart significant risk for fever or hyperthermia and awareness of these risks is essential for the consultant. Any breach of skin or other mucosal barrier, especially with indwelling devices, represents a risk of focal if not disseminated infection due to locally colonizing pathogens. Central and peripheral IV catheters, bladder catheters, endotracheal and nasogastric tubing among numerous other indwelling devices and procedures exemplify common sources of infection. Specifically, septic phlebitis or cellulitis at an IV or central line site, pyuria plus positive urine cultures representing a catheter-related urinary tract infection and sinusitis following prolonged nasotracheal or nasogastric intubation are common examples.

Surgical patients commonly develop fever postoperatively, yet studies reveal infection is seldom the cause within the first 48 hours.<sup>5</sup> Subsequently, wound infection, urinary tract infection and pneumonia lead the list of potential fever sources however deep venous thrombosis, pulmonary emboli, myocardial infarction and medications are less common but important

considerations. Overall, acute postoperative fever by itself is an unreliable indicator of infection until later in the hospital course and suspicion should be based on additional clinical findings.

Drug fever (without cutaneous manifestations) occurs in about 10% of inpatients and commonly results in unnecessary diagnostic studies and prolonged hospital stays.<sup>6</sup> Five mechanisms account for fever following drug administration. Drugs may cause:

- 1) hyperthermia by increasing metabolism (L-thyroxin, epinephrine, cocaine) or by impairing heat dissipation and sweating (anticholinergics),
- 2) thermoregulatory alterations due to pyrogenic properties of the drug (amphotericin B, bleomycin, vaccines contaminated with endotoxin) or administration phlebitis (potassium, cephalothin),
- 3) release of pyrogens following antimicrobial treatment (Jarish-Herxheimer reaction) or cytotoxic treatment of malignant cells containing pyrogens,
- 4) idiosyncratic reactions such as malignant hyperthermia (inhaled anesthetics), neuroleptic malignant syndrome due to dopaminergic receptor blockade (haloperidol, thiothixene and phenothiazines) and G-6PD – related hemolysis and endogenous pyrogen release (sulfonamides, antimalarials, nitrofurantoin, quinidine and others) and most commonly,
- 5) immune-mediated hypersensitivity reaction, which may trigger pyrogen release (beta-lactams, sulfonamides, procainamide, many others). Generalized pruritic rash, relative bradycardia or eosinophilia help support a diagnosis of drug fever but their absence does not lessen the likelihood.

Finally, while ruling out nosocomial sources, coexisting febrile diseases<sup>7</sup> not necessarily related to hospitalization must be considered. Historical clues suggesting outpatient-derived infections may come from social habits or exposures, prior antimicrobial exposure, travel history, ethnic background (familial Mediterranean fever), trauma, and tick exposures to name a few. Neoplastic fever may develop when malignant cells release pyrogens or when infection and/or inflammation are associated. Lymphomas, acute and chronic myelogenous leukemias and renal cell carcinoma for example, produce such pyrogens. Chronic granulomatous diseases such as tuberculosis, sarcoidosis or Crohn's disease and the collagen

vascular/hypersensitivity diseases may also present with fever. Factitious fever may be intentional as in Munchausen's syndrome or unintentional due to poor thermometry technique and further underscores the importance of confirming fever and correlating clinical findings prior to an aggressive workup and treatment.

Proceeding toward differential diagnoses and treatment recommendations for inpatients with fever begins with reviewing the admission history for outpatient risks of disease and assessing the inpatient history for immunocompromise or interventional risks. The physical exam should focus first on assessing hemodynamic stability and level of consciousness since sepsis would require immediate empiric antimicrobial therapy and intensive care management. Next, a thorough skin exam focusing on IV sites, wounds, pressure points, distal extremities and, in neutropenic patients, the peri-rectal area for signs of inflammation, cellulitis, rashes or embolic stigmata of endocarditis. Finally, a complete organ system exam is necessary with attention to identified risks (e.g. ruling out sinusitis in the nasally intubated patient or opportunistic pneumonia in the dyspneic HIV patient).

Judicious use of lab and diagnostic imaging should be driven by narrowed clinical suspicion. Initially, a complete blood count with manual differential, electrolytes, urinalysis and 2 sets of blood cultures will help exclude white cell abnormalities, hemolysis, anion gap acidosis, pyuria and bacteremia. Culturing and replacing central lines, chest or sinus X-rays, sputum evaluation and CSF examination exemplify second tier assessments when risk factors, history or physical exam produce concern. Further testing for coexisting diseases like vasculitis or neoplasm similarly should be pursued when exam or historical findings are suggestive. Future practical diagnostic tools may include tests to identify pyrogens associated with infectious versus noninfectious causes and specific antigen PCR testing to identify causative microorganisms rapidly.

Empiric broad spectrum, antipseudomonal antimicrobials are recommended for the unstable and immunocompromised inpatient along with coverage for locally prevalent or resistant organisms such as methicillin-resistant *Staphylococcus aureus* if necessary. Stable immunocompetent patients without an identifiable source of fever may be observed or covered empirically pending blood culture results however blind treatment without evidence of bacteremia often hinders future attempts at diagnosis.

Not uncommonly, the source of fever is undetermined despite a thorough diagnostic evaluation. Fever of unknown origin (FUO) may be categorized into nosocomial, neutropenic, HIV-associated and classic forms depending on particular exposures and immunocompetence.<sup>7</sup> As a result of improved diagnostic technology and organism drug resistance, the epidemiology and eventual diagnoses of FUO is changing.

In conclusion, nosocomial fever is common with an extensive list of possible causes for the inpatient. Methodically assessing risks for immunocompromise or immunosuppression, interventional sources, and coexisting disease will direct clinical suspicion and thus testing and treatment recommendations.

### **References**

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