

Pathophysiology and Management of Fever

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Fever is defined as the elevation of core body temperature above normal; in normal adults, the average oral temperature is 37°C (98.6°F). In oncology practice, a single temperature of more than 38.3°C (101°F) or three readings (at least 1 hour apart) of more than 38°C (100.4°F) are considered significant. Lower temperature elevations in the very young or old and in patients receiving steroids or other immunosuppressants are considered abnormal. Fever of an unknown origin (FUO) is defined as a febrile illness lasting more than 3 weeks, with temperatures exceeding 38.3°C on several occasions, and lacking a definitive diagnosis after 1 week of evaluation in the hospital.

Pathophysiology of Fever

The febrile response, of which fever is but one component, is a complex physiologic reaction to disease involving a cytokine-mediated rise in body temperature, generation of acute-phase reactants, and activation of numerous physiologic, endocrinologic, and immunologic systems.¹ The temperature of the body is dependent on maintaining a balance between the production and dissipation of heat. Under normal circumstances, heat is generated internally during metabolic processes or when external environmental temperatures exceed those of the body. Heat can also be produced by increased skeletal muscle activity, such as that which occurs with shivering. Heat loss occurs predominantly from the skin via evaporative losses and also, to some extent, via the lungs.

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Abstract The febrile response is a complex physiologic reaction to disease involving a cytokine-mediated rise in body temperature, generation of acute-phase reactants, and activation of numerous endocrinologic and immunologic systems. Understanding the basic mechanisms underlying this phenomenon helps to formulate rational approaches to treatment and interventions. In this article, the authors review the basic pathophysiology of fever, its contributing etiologies, and management approaches based on current evidence.

Much like other fundamental aspects of human biology, core body temperature is regulated closely by intricate control mechanisms, involving a complex interplay of autonomic, endocrine, and behavioral responses. The hypothalamus is central to this process, functioning as a thermostat, controlling thermoregulatory mechanisms that balance heat production with heat loss. Integral to the process are the heat-sensitive receptors located in the preoptic area of the anterior hypothalamus. These receptors, which are sensitive to elevations in blood temperature, increase signal output as the temperature rises above a fixed thermal setpoint (37.1°C average) and decrease output when the temperature drops below the setpoint. Similar receptors are in the skin, spinal cord, and abdomen, sending impulses to the hypothalamus via the spinal cord.

With core body temperature elevations, the sympathetic system is inhibited, leading to vasodilation of skin vessels and stimulation of the sweat glands to facilitate evaporative loss. This process prevails until the body temperature matches the thermal setpoint, when heat production matches heat loss. Similarly, when body temperature is below the thermal setpoint, a variety of responses are initiated to conserve and increase production of heat. They include activation of the sympathetic nervous system to induce vasoconstriction of skin blood vessels; inhibition of sweating; activation of the shivering center in the posterior hypothalamus, thereby increasing muscle heat production; and secretion of neurotransmitters,

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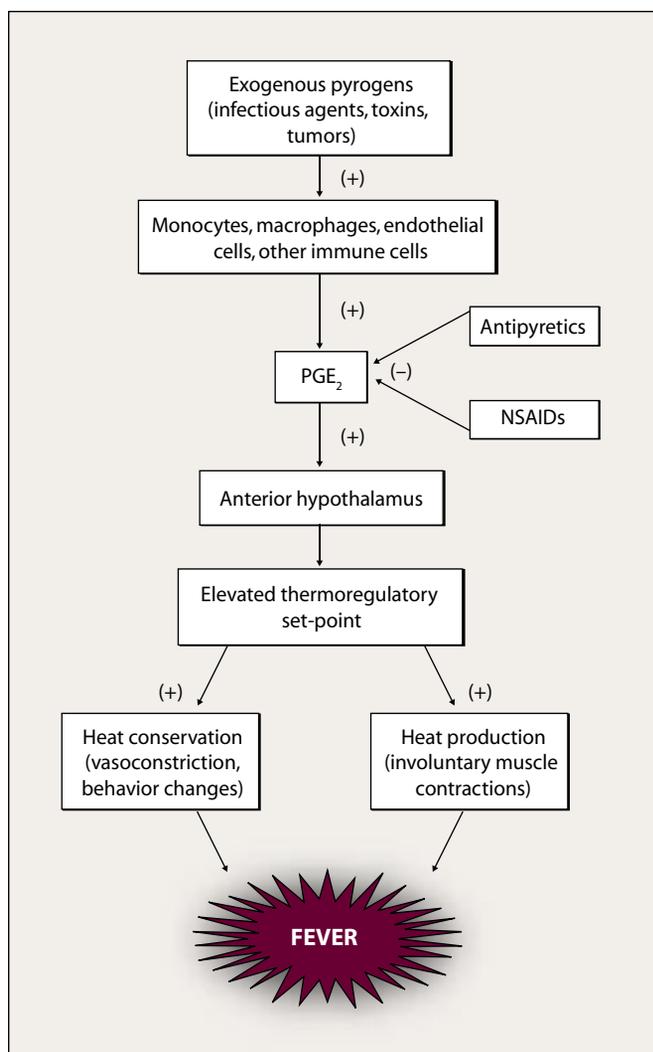


Figure 1 Pathophysiologic Mechanism of Fever

Abbreviations: NSAIDs = nonsteroidal anti-inflammatory drugs; PGE₂ = prostaglandin E₂

which increase cell metabolism and, consequently, heat production. The hypothalamus also affects behavioral influences in humans, with individuals changing clothes and/or seeking appropriate shelter to maintain body temperature. In vivo experiments with rabbits revealed that thermoregulation requires an intact sympathetic nervous system and can be modulated by various adrenoceptor antagonists.^{2,3}

THERMOREGULATORY SUBSTANCES

The stereotypic nature of the febrile response, regardless of the inciting event, has led to an improved understanding of the interactions between the immune and central nervous systems that cause fever. Fever is considered a hallmark of immune system activation, resulting in a regulated rise in body temperature. The regulation of this phenomenon is accomplished by the actions of two types of endogenous immunoregulatory proteins called cytokines, some functioning as pyrogens and others acting as antipyretics (Figure 1).

A number of exogenous substances can evoke fever in animal models. Lipopolysaccharide (LPS), a cell wall product derived from gram-negative bacteria, has been the most extensively studied exogenous pyrogen, although others such as superantigens, peptidoglycans, muramyl dipeptides (derived from gram-positive and gram negative bacteria), and viral products have also been investigated.

When injected systemically into experimental animals, exogenous pyrogens have been shown to induce the production of pro-inflammatory cytokines, such as interleukins 1 β (IL-1 β) and 6 (IL-6), interferon (INF)- α , and tumor necrosis factor (TNF), which enter the hypothalamic circulation and stimulate release of local prostaglandins, resetting the hypothalamic thermal setpoint. The action of these pyrogenic cytokines may be opposed by other cytokines, such as IL-10, and substances such as arginine vasopressin, melanocyte-stimulating hormone, and glucocorticoids, all of which have antipyretic properties, thus limiting the magnitude and duration of fever. TNF has been shown to have pyrogenic and antipyretic properties, depending upon the experimental conditions. Ultimately, it is the sum of the interactions of pyrogenic and antipyretic cytokines that is responsible for the height and duration of a febrile response.

Cytokines are thought to exert their effect on the brain via direct and indirect mechanisms.⁴ Peripherally produced cytokines reach the central nervous system (CNS) directly by crossing at leaky areas in the blood-brain barrier (BBB) via circumventricular vascular organs known as organum vasculosum laminae terminalis, which are networks of enlarged capillaries surrounding the hypothalamic regulatory centers.⁵ In disease states such as bacterial infections, the BBB can be compromised further, leading to an influx of cytokines from the periphery and accounting for several of the neurologic manifestations associated with sickness behavior, including fever.⁶ Cytokines are also produced locally within the CNS.⁷ This local production of cytokines in the CNS may account for the hyperpyrexia of CNS hemorrhage.

Evidence suggests that cytokines produced peripherally or centrally are involved directly in the complex autonomic febrile response.⁴⁻⁸ In the periphery, IL-1 and TNF induce an increased production of IL-6, the principal endogenous pyrogen.⁹ Among the cytokines measurable in plasma during LPS-induced fever, circulating levels of IL-6 have shown the best correlation with fever.¹⁰ Large amounts of IL-6 have been found to be present in all febrile diseases, and IL-6 induced by IL-1 or the combination of IL-1 plus TNF likely accounts for the clinical fever most often measured. Mice without the gene for IL-6 do not develop fever during bacterial infection,¹¹ whereas IL-10 knockout mice develop exacerbated fevers that correlate with enhanced plasma levels of IL-6.¹² Thus, endogenous IL-6 functions as a pyrogen, whereas IL-10 inhibits the production of IL-6, functioning as an endogenous antipyretic.

Although not fully understood, it is proposed that pro-inflammatory cytokines stimulate the central production of the inducible enzyme cyclooxygenase (COX) 2 and, subsequently,

the production of prostaglandins of the E series.¹³ These prostaglandins activate thermoregulatory neurons of the anterior hypothalamic area to elevate body temperature.¹⁴ Studies have shown that peripherally produced cytokines can also communicate with the brain indirectly in several ways, including the stimulation of terminal fibers of the autonomic nervous system.¹⁵ The vagal route is one of the best-known ways by which cytokines can influence the brain. Noradrenaline is the principal neurotransmitter, although several others, such as acetylcholine, endorphins, enkephalins, substance P, somatostatin, and vasoactive intestinal peptide, have also been implicated.¹⁶

Clinical Phases of Fever

Fever consists of three clinical phases: chill, fever, and flush. In the first phase, also known as the cold or chill phase, core temperature rises to reach the new thermal setpoint. Cutaneous vasoconstriction and increased muscle activity boost heat production, as manifested by chills and shivering. In the second, or fever, phase, a balance occurs between production and loss of heat at the elevated setpoint. The skin is warm, flushed, and dry. When the setpoint returns to normal, the body perceives itself to be too warm. Heat-dissipating mechanisms are then initiated, resulting in cutaneous vasodilation and diaphoresis, clinical manifestations of the third, or flush, phase.

Response to fever varies with age. Elderly patients are unable to regulate their body temperature to the same degree as young adults, making them susceptible to extremes of temperature.¹⁷ Clinical observations confirm that older patients with serious infections have a substantial prevalence (20% to 30%) of apyrexia and lower febrile responses than younger patients.¹⁸ Fever is often considered to be an important host-defense mechanism; thus, a lack of fever may contribute to lower resistance to infection, delayed recovery, and suboptimal outcome. Lower febrile responses to infection are associated with a higher mortality rate and poorer prognosis.¹⁹ In children between the ages of 6 months and 6 years, febrile convulsions may occur.

Etiologies of Fever in Cancer Patients

The major causes of fever in cancer patients include infection, tumor (paraneoplastic fever), allergic or hypersensitivity reaction to drugs, blood transfusions, graft-versus-host disease, and thrombosis.^{20,21} Other less common causes include malignant bowel syndrome, tumor embolization, CNS hemorrhage, and coexisting connective tissue disorders.

Evaluation of Fever

Nearly two thirds of cases of fever in patients with prolonged neutropenia may be attributed to infection,²² a major cause of morbidity in cancer patients. Fever in a cancer patient should be considered indicative of infection until proven otherwise, with appropriate assessment being instituted in a timely fashion. Febrile neutropenia (absolute neutrophil count < 500/ μ L) represents an absolute emergency.

Assessment of fever requires careful history taking, medication review, and a thorough physical examination of all major body systems. Individuals with suspected infection, especially those with neutropenic fever, should undergo meticulous evaluation of the skin and all body orifices, including the mouth, ears, nose, throat, urethra, vagina, rectum, venipuncture sites, biopsy sites, and skin folds (ie, breasts, axillae, abdomen, and groin). For patients with neutropenia, a specific site of infection is generally lacking.²³ In nearly two thirds of cases, the initial evaluation does not identify a focus of infection; this finding may relate in part to the high frequency of empiric treatment with broad-spectrum antibiotics, which may make it more difficult to determine the site of infection. Careful physical examination should be repeated at least daily in patients with neutropenia, even after the initiation of empiric antibiotics. Immunocompromised patients may be vulnerable to more than one infection, and different organisms may emerge during a single febrile episode.

PARANEOPLASTIC FEVER

Fever may be a common presentation with some malignancies, and their progression may parallel the occurrence of fever. Although Hodgkin's lymphoma has classically been associated with Pel-Ebstein fever (recurring periods of fever lasting for 3–10 days at a time), several other malignancies (acute leukemia, lymphoma, renal cell carcinoma, bone sarcoma, adrenal carcinoma, and pheochromocytoma) are also associated with paraneoplastic fever. Solid tumors of the breasts, lungs, and colon are less often associated with paraneoplastic fever. However, the presence of liver metastases from these tumors may result in fever. In addition, any solid tumor causing obstruction can result in fever.

Although the exact mechanism of tumor-associated fever is unclear, it is thought to involve inflammatory cytokines such as TNF- α , IL-1, and IL-6, which are produced either by host macrophages in response to the tumor or by the tumor itself.²⁴ These pyrogenic cytokines cause elevations in temperature by acting on the hypothalamic temperature setpoint.

TRANSFUSION-ASSOCIATED FEVER

Blood transfusions are extremely common in cancer patients and are frequently accompanied by febrile reactions, although the true incidence of fever has not been well established. In a retrospective study by Huh and Lichtiger,²⁵ the incidence of febrile reactions after transfusion of 100,000 U of packed red blood cells to more than 25,000 cancer patients over 4 years was found to be 0.3%, lower than that in other studies of patients without cancer. Of these patients, 51.3% had febrile nonhemolytic reactions, whereas 36.7% had allergic urticarial reactions. Only 17 hemolytic reactions were documented. This is comparable with findings from other studies in which the incidence has ranged from 0.2% to 0.7%.²⁶ The occurrence of fever is usually caused by the presence of antibodies to antigens on the donor's white blood cells, and its prevention by using leukodepleted blood components was demonstrated more than

two decades ago.^{27,28} Some studies have shown a correlation with storage time of platelets and the release of cytokines as another reason for the occurrence of febrile nonhemolytic reactions.^{29–31} The incidence of delayed hemolytic reactions in cancer patients is significantly lower than that reported for patients in non-oncologic hospital settings. This finding could result from the inability of cancer patients to produce alloantibodies against blood group antigens as frequently and efficiently as those with non-neoplastic conditions.

Infection may also be a source of fever in patients receiving blood transfusions.^{32–34} The prevalence of bacteria is estimated to be about 0.04%–2.0%, depending on the type of components, the number and age of the evaluated components, and the detection methodologies used.^{35–37}

DRUG-ASSOCIATED FEVER

Drug-associated fever is an ill-defined syndrome in which fever is the predominant manifestation of an adverse drug reaction. It is usually a diagnosis of exclusion, except when linked to use of certain drugs, such as biologic response modifiers, amphotericin B, and bleomycin, when the occurrence of fever is predictable. Other drugs commonly implicated as a cause of fever include antibiotics, cardiovascular agents, anticonvulsants, cytotoxics, and growth factors. In a review study by Mackowiak,³⁸ antimicrobials were found to be the most common offending agent in cancer patients, accounting for 31% of cases of drug-related fever.

In a retrospective chart review³⁹ of 50 patients who had received at least 100 mg of amphotericin B for at least 3 days, the incidence of fever was 34% and of chills was 56%, respectively, with rates of 2.6 and 3.5 mean episodes per patient per treatment course, respectively. Interferon therapy is associated with acute flu-like syndrome consisting of fever, chills, fatigue, myalgias, arthralgia, and headache, with some variation according to type of IFN, route of administration, schedule, dose, and age of patient.⁴⁰ The administration of growth factors is also associated with fever, being more common following granulocyte macrophage colony-stimulating factor administration than with granulocyte colony-stimulating factor administration. Bleomycin-associated fever occurs in 20%–50% of patients and is more common when administered intravenously. Fever is also associated with other cytotoxic agents such as cisplatin, streptozocin, 5-fluorouracil, and therapy with monoclonal antibodies.^{41–44}

General Interventions

GOALS OF CARE

The presence of fever is associated with potential metabolic consequences, including dehydration and increased oxygen consumption and metabolic rate,⁴⁵ which may be especially pronounced in debilitated cancer patients. If prolonged, fever may be associated with an increase in nutritional demands, which may be problematic if the patient already is compromised nutritionally. Prolonged fever may also lead to debilitat-

ing fatigue. Although fever may be beneficial for enhancing host defense,⁴⁶ other factors also deserve consideration, such as the patient's comfort and physiologic responses. Suppression of fever may help to alleviate uncomfortable, constitutional symptoms of fatigue, myalgias, diaphoresis, and chills. In addition to constitutional symptoms, focal findings related to the etiology of fever may contribute to the burden of symptoms. For example, the formation of an abscess is often associated with pain, whereas uncomfortable dyspnea and cough may be related to pneumonia.

The specific interventions used for fever management are determined by the underlying etiology together with patient-determined goals of care. Patients with advanced cancer may seek only nonspecific palliative measures and may opt not to treat the underlying etiology of fever. For instance, individuals seeking comfort-oriented care exclusively may decline parenteral antibiotic treatment of pneumonia to avoid hospitalization and remain at home. For others, treating the underlying etiology of fever with more aggressive interventions, such as surgical drainage of a painful abscess, will offer symptom palliation and potentially contribute to the prolongation of life.

NONSPECIFIC INTERVENTIONS

During febrile episodes, increasing fluid intake, removing excess clothing and linens, bathing or sponging with tepid water, and using antipyretics may offer relief. In the very sick, administration of fluids intravenously or subcutaneously may be warranted. Other comfort measures include applying a lubricant to dried lips and keeping mucous membranes moist with ice chips. Convective cooling via increasing air circulation using fans or an airflow blanket may be effective to reduce the temperature and improve patient comfort.⁴⁷ Additionally, clothes and bed linens should be dry and changed as needed.

Antipyretic agents, such as acetaminophen, aspirin, or nonsteroidal anti-inflammatory drugs (NSAIDs), act by lowering the elevated thermal setpoint by inhibiting COX. The synthesis of prostaglandin E₂ (PGE₂) depends upon the constitutively expressed enzyme COX. Inhibitors of COX, such as NSAIDs, are potent antipyretics and impair the ultimate transformation of arachidonic acid to prostaglandins. Acetaminophen, a weak COX inhibitor in peripheral tissue, is oxidized in the brain by the P-450 cytochrome and inhibits COX activity. There appears to be no role for PGE₂ in normal thermoregulation, based upon observations that chronic use of aspirin or NSAIDs does not reduce the normal core body temperature. Corticosteroids are also effective antipyretics; they reduce the synthesis of PGE₂ by inhibiting the activity of phospholipase A₂, which is needed to release arachidonic acid from the membrane. Corticosteroids also act by blocking the transcription of mRNA for pyrogenic cytokines.

Although antipyretics are commonly administered to enhance the comfort of hospitalized patients,⁴⁸ no studies have been performed on their use in the cancer population

Table 1**Empiric Antibiotic Regimens for Unexplained Neutropenic Fever in the Cancer Population**

REGIMEN	ROUTE	ANTIBIOTIC SELECTION	COMMENTS
1	Oral	Ciprofloxacin plus amoxicillin-clavulanate	For use in select adult patients: <ul style="list-style-type: none"> • in remission; • at low risk for serious life-threatening complications; • without comorbidities; or • on an outpatient basis if ready access to care, no signs of focal infection, and no signs of symptoms suggestive of systemic infection other than fever.
2	Intravenous	Monodrug regimen (without vancomycin): cefepime, ceftazidime, imipenem, or meropenem	Monodrug regimen as effective as multiple-drug combinations for uncomplicated neutropenic patients. Monitor closely for nonresponse, emergence of secondary infection, and drug resistance.
3	Intravenous	Aminoglycoside plus antipseudomonal penicillin or ceftazidime or carbapenem	Advantages include: <ul style="list-style-type: none"> • potential synergistic effects against some gram-negative bacilli. • minimal emergence of drug-resistant strains during treatment.
4	Intravenous	One or two drugs from regimen 2 or 3 with vancomycin	Restrict to: <ul style="list-style-type: none"> • institutions with a high prevalence of infections with penicillin-resistant or gram-positive bacteria; • suspected catheter-related cellulitis or bacteremia; • gram-positive bacteremia; or • evidence of septic shock.

Adapted from Nimmagadda et al²²

with fever, and carefully controlled efficacy studies have not quantified the degree to which antipyretic therapy enhances the comfort of febrile patients in other populations. In addition, the increase in core temperature during fever has not been found to induce thermal damage in patients.⁴⁹ Although patients with pulmonary and cardiovascular disorders may theoretically benefit from antipyretic therapy to minimize the impact of increased metabolic demands, determination of the risks versus benefits of this approach has not been made.

Similarly, antipyretic therapy has not been demonstrated to prevent febrile seizures in children.⁵⁰ Studies have confirmed that increasing the dose of acetaminophen from a moderate dosage (10 mg/kg every 4 hours, maximum 5 doses per day) to a relatively higher dosage (15–20 mg/kg every 4 hours, maximum 5 doses per day) in children failed to reduce the rate of recurrence of febrile seizures.⁵¹

Fever control may be enhanced by combining physical methods with antipyretics. A randomized, placebo-controlled trial of sponging with ice water, isopropyl alcohol, or tepid water (with or without acetaminophen) demonstrated that all combinations enhanced fever control in children, but comfort was greatest in those receiving placebo or sponging.⁵² Discomfort was found to be greatest when sponging with ice water or isopropyl alcohol, with or without concomitant administration of acetaminophen.

Like acetaminophen, aspirin may be effective in reducing fever but should be used with caution in patients with or at risk for thrombocytopenia due to its antiplatelet effect. In children, aspirin use is contraindicated due to the risk of Reye's syndrome with fever related to certain viral etiologies, including varicella and influenza.⁵³ Nonsteroidal anti-inflammatory

drugs should also be used cautiously in the cancer population, as they inhibit platelet function and may also cause gastrointestinal hemorrhage.

Primary Interventions

INFECTIONS

Patients should be instructed to seek medical help if a fever develops when the neutrophil count is low or declining. Before culture results are available, immediate initiation of broad-spectrum antibiotic treatment is imperative, as the mortality rate is 70% for patients not receiving antibiotics within 48 hours.⁵⁴ Since the cause of fever is not identifiable in up to 70% of patients,⁵⁵ initial antibiotic use is guided by knowledge of the treating institution's antimicrobial spectrum and antibiotic resistance pattern as well as the suspected cause. Although there is general consensus that empiric therapy is appropriate, there is no consensus as to which antibiotics or combinations of antibiotics should be used. The Infectious Diseases Society of America Fever and Neutropenia Guidelines Panel recommends empiric antibiotics based on the patient's clinical condition, the risk for complications, and the determination of the need for vancomycin in the initial regimen.⁵⁶ These four protocols are depicted in Table 1.

Treatment regimens may be further modified by the duration of fever and individual patient risk factors, such as the presence of central lines or other artificial devices and a history of steroid or injection drug use. After a specific pathogen is isolated, antibiotic therapy should then be changed to provide optimal therapeutic response.

The single most important determinant of successful discontinuation of antibiotics is the neutrophil count. If infec-

tion is not identified after 3 days of treatment, the neutrophil count is ≥ 500 cells/ μL for 2 consecutive days, and the patient is afebrile for ≥ 48 hours, antibiotic therapy may be discontinued. For neutropenic hosts with persistent or recurrent fever after 1 week of broad-spectrum antibiotic therapy, the addition of an antifungal agent is recommended, as continued granulocytopenia is usually associated with the development of nonbacterial opportunistic infections, particularly candidiasis and aspergillosis.

Acyclovir is the drug of choice in the treatment of herpes simplex or varicella zoster viral infection. Ganciclovir has activity against cytomegalovirus. Both agents can be used prophylactically in the management of patients at high risk for these infections. Foscarnet (Foscavir) is useful in the treatment of cytomegalovirus and acyclovir-resistant herpes simplex virus infections.

Various investigators have developed models predicting risk groups of febrile neutropenia, with implications for management strategies. Therapeutic options under evaluation include early hospital discharge, home intravenous antibiotic therapy, and oral antibiotic regimens. Due to rapid changes in the field, the reader is directed to specialized sources for specific management recommendations of febrile neutropenia.⁵⁷⁻⁵⁹

Several drugs, such as antipsychotics, may be associated with neuroleptic malignant syndrome causing hyperthermia and are discussed in pages to follow.

PARANEOPLASTIC FEVER

The best management for paraneoplastic fever remains the treatment of the underlying neoplasm with definitive antineoplastic therapy. If this approach is not possible, NSAIDs have been considered to be the mainstay of treatment, with naproxen being the most extensively studied. However, indomethacin and diclofenac have also been found to be effective.⁶⁰ Several studies suggesting that neoplastic fevers are more responsive to NSAIDs than are infectious fevers have led to advocacy of the “Naprosyn test” to differentiate between neoplastic and non-neoplastic fevers.⁶¹ However, this approach has not been validated.⁶²

Thalidomide (Thalomid), an immunomodulatory agent, has been shown to have modulatory and/or suppressive effects on several cytokines involved in paraneoplastic fever, such as TNF- α , IL-1, and IL-6,⁶³ and theoretically may play a role in the treatment of cancer patients with fever and sweats.⁶⁴ Despite reports of its antipyretic and antidiaphoretic activity,⁶⁵ thalidomide has not been formally tested in clinical studies with cancer patients for control of fever or sweats.

TRANSFUSION-ASSOCIATED FEVER

When clinically appropriate, transfusion-related febrile reactions can be minimized by use of leukocyte-depleted or irradiated blood products. Common clinical practice includes premedication with acetaminophen and diphenhydramine and use of steroids. The use of erythropoietin for cancer-related anemia may decrease the need for blood transfusions

and may be used for cancer-related anemia. Assessment of the risks versus benefits and cost of such prophylactic treatments to avoid or delay transfusion needs further investigation.

DRUG-ASSOCIATED FEVER

Drug-associated fever responds to the cessation of the offending agent, when possible. Fever and related symptoms caused by biologic response modifiers depend on the type, route, dose, and schedule used. These factors may sometimes be altered for fever control without sacrificing efficacy. Liposomal amphotericin B (AmBisome) is as effective as conventional amphotericin B for empiric antifungal therapy in patients with fever and neutropenia but is associated with decreased toxicity, including occurrence of fever and chills.⁶⁶ Fever may also be attenuated by the use of acetaminophen, NSAIDs, and steroid premedication; the same may be true for fever associated with some cytotoxic agents and antimicrobials (ie, amphotericin B). It is common clinical practice to administer meperidine to attenuate severe chills associated with a febrile reaction, although empiric data confirming its efficacy are not available.

Pathophysiology and Management of Hyperthermia

Although an elevated body temperature usually represents a fever in the vast majority of patients, there are a few instances in which an elevated temperature is secondary to hyperthermia: heat stroke syndromes, certain metabolic diseases (hyperthyroidism), and use of drugs that interfere with thermoregulation. Both conditions result in an elevation of body temperature, but they differ physiologically. With fever, thermoregulatory mechanisms remain intact, but the hypothalamic thermal setpoint is raised by exposure to endogenous pyrogens,⁶⁷ leading to behavioral and physiologic responses to elevate body temperature. In contrast to fever, during hyperthermia, the setting of the thermoregulatory center remains unchanged at normothermic levels, whereas body temperature increases in an uncontrolled fashion and overrides the ability to lose heat. Hyperthermia thus results from the peripheral heat-dissipating mechanisms being overwhelmed by disease, drugs, or excessive external or internal heat.⁶⁸

Exogenous heat exposure and endogenous heat production are mechanisms by which hyperthermia can result in dangerously high internal temperatures. Atropine may increase endogenous heat production by interfering with thermoregulation, in that it blocks sweating and vasodilation, thereby raising the core temperature.

Hyperthermia also occurs with neuroleptic malignant syndrome (NMS), an idiosyncratic reaction to dopamine receptor-blocking drugs such as antipsychotic agents, with haloperidol being the most common offender.⁶⁹ Atypical antipsychotic medications, including clozapine, risperidone (Risperdal), olanzapine (Zyprexa), and quetiapine (Seroquel), have also been associated with NMS.^{70,71} Cases of other medications causing NMS, including venlafaxine (Effexor), promethazine,

and metoclopramide, have been reported as well.^{72,73} Typically, NMS occurs within several days of the initiation of treatment, and dosages and serum concentration of these medications are usually within the therapeutic range. The probability of developing NMS is directly related to the antidopaminergic potency of the neuroleptic agent. In addition, specific polymorphisms of the dopamine D2 receptor may predispose some patients to NMS.⁷⁴

Malignant hyperthermia is a rare genetic disorder that manifests following treatment with anesthetic agents, most commonly succinylcholine and halothane.⁷⁵ Susceptible patients with autosomal-dominant disease have mutations in the gene for the skeletal muscle ryanodine receptor (RyR1), a homotetrameric calcium channel found in the sarcoplasmic reticulum of skeletal muscle.⁷⁶ In the presence of anesthetic agents, there is an uncontrolled efflux of calcium from the sarcoplasmic reticulum with subsequent tetany, increased skeletal muscle metabolism, and heat production.⁷⁷

MANAGEMENT OF HYPERTHERMIA

It is important to make the distinction between fever and hyperthermia because management approaches to these syndromes differ. A diagnosis of hyperthermia is often made because of a history of heat exposure or use of certain drugs that interfere with normal thermoregulation. There is no rapid way to differentiate elevated core temperature due to fever from hyperthermia. On physical examination, the skin is hot but dry in patients with heat stroke syndromes and in patients taking drugs that block sweating.

In patients diagnosed with hyperthermia, physical cooling should be started immediately with techniques such as removing bedclothes, sponging the patient with tepid water, and use of bed fans. More rapid reductions in body temperature can be achieved by sponging the patient with alcohol or by using hypothermic mattresses or ice packs. Immersion in ice water is the most effective means of physical cooling, but it should be reserved for true hyperthermic emergencies, such as heat stroke. In true emergencies, treatment may also include the in-

travenous or intraperitoneal administration of cool fluid, gastric lavage or enemas with ice water, and even extracorporeal circulation. No matter what technique is used, the body temperature must always be monitored closely to avoid hypothermia.

Antipyretic agents, such as acetaminophen and NSAIDs, act by lowering the elevated thermal setpoint; they are used in the treatment of fever but are ineffective for hyperthermia, where the thermal setpoint is normal. In hyperthermia, mechanisms for reducing body temperature are drugs that interfere with vasoconstriction, such as phenothiazines and agents that block muscle contractions or shivering. However, they are not true antipyretics, as they can reduce body temperature independently of hypothalamic control. These drugs are useful adjuncts in the management of hyperthermia. Shivering may be suppressed with intravenous benzodiazepines such as diazepam or lorazepam. Chlorpromazine (25–50 mg intravenously) may also be used for this purpose if NMS is not suspected.

Dantrolene, a nonspecific skeletal muscle relaxant also frequently considered in the management of malignant hyperthermia, acts by blocking the release of calcium from the sarcoplasmic reticulum.⁷⁸ This process, in turn, decreases the myoplasmic concentration of free calcium and diminishes the myocyte hypermetabolism that causes clinical symptoms. The drug is most effective when given early in the illness, before hyperthermia occurs, when maximal calcium can be retained within the sarcoplasmic reticulum.

Conclusion

Fever is commonly encountered in cancer patients and may be associated with considerable morbidity and mortality. Optimal management is contingent on meticulous patient assessment, with implementation of appropriate treatment interventions as befits patient-determined goals of care. Treatment options include nonspecific interventions as well as primary approaches targeted at contributing etiologies and pathophysiologic mechanisms. Alleviation of uncomfortable constitutional symptoms should be a priority.

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