Fever in the critically ill medical patient

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Fever, commonly defined by a temperature of ≥38.3°C (101°F), occurs in approximately one half of patients admitted to intensive care units. Fever may be attributed to both infectious and noninfectious causes, and its development in critically ill adult medical patients is associated with an increased risk for death. Although it is widespread and clinically accepted practice to therapeutically lower temperature in patients with hyperthermic syndromes, patients with marked hyperpyrexia, and selected populations such as those with neurologic impairment, it is controversial whether most medical patients with moderate degrees of fever should be treated with antipyretic or direct cooling therapies. Although treatment of fever may improve patient comfort and reduce metabolic demand, fever is a normal adaptive response to infection and its suppression is potentially harmful. Clinical trials specifically comparing fever management strategies in neurologically intact critically ill medical patients are needed. (Crit Care Med 2009; 37[Suppl.]:S273–S278)

KEY WORDS: fever; temperature control; hyperpyrexia; hyperthermic syndromes; neurologic injury

Fever is among the most frequently detected abnormal signs observed in patients admitted to intensive care units (ICUs). It may arise attributable to either infectious or noninfectious causes, and its presence frequently prompts changes in patient management (1–4). The acquisition of fever in the ICU is associated with an increased risk for adverse outcomes in medical ICU patients (5). Although a wealth of epidemiologic and experimental data are available on many subpopulations of critically ill patients, especially those with neurologic impairment, much less is known about the occurrence and impact of fever in adult medical ICU populations.

The purpose of this article is to review the contemporary literature investigating the occurrence, determinants, and management of fever in the critically ill adult medical patient. Because immune-compromised patients represent a special niche that merits separate consideration, and because trauma, neurologically impaired, and liver failure patients are reviewed in detail elsewhere within this supplement of *Critical Care Medicine*, these patient populations are not specifically addressed in this review.

Search Strategy

A semistructured literature review was conducted. Published articles focusing on fever and ICU were initially searched using PubMed from 1966 to September 5, 2008, using the search terms *fever*, or *hyperthermia* and *intensive care unit*. Abstracts were screened for relevance, and relevant full-length articles were retrieved for appraisal. The author's personal files and bibliographies of selected papers were also screened for other articles of relevance.

Definitions

Normal body temperature is approximately 37.0°C (98.6°F), although it varies among different non–acutely ill individuals. In addition, a normal variability of 0.5°C (0.9°F) occurs within individuals based on time of day, with a low in the early morning and a peak in late afternoon and early evening (6). Because of this variability and given that the magnitude and significance of an elevated temperature will depend on the specific patient population, a wide range of definitions for fever have been reported in the literature. A core body temperature ≥38.3°C (101°F) may be generally accepted to represent fever in patients admitted to ICUs (4).

Although most abnormal temperature elevations are fever, abnormally elevated body temperatures that occur in association with a normal or an elevated hypothalamic set point are defined as hyperthermia or fever, respectively. Fever and hyperthermia are often difficult to differentiate at the bedside. In this review, for simplicity, patients with abnormally elevated temperatures are collectively referred to as having fever unless specifically indicated otherwise.

In the medical ICU, temperature can be measured using a number of different techniques including thermistors on pulmonary artery or bladder catheters, esophageal or rectal probes, and infrared tympanic membrane and temporal artery thermometers. Oral thermometers are rarely practical in the critically ill patient, and axillary temperature measurement is not routinely recommended (4). Although the pulmonary artery catheter is considered the "gold standard" measurement technique, in most situations relatively small differences exist among the other commonly used measurement techniques (4, 7). In any case where an exact temperature measurement is critical to patient management or when a measure does not appear clinically reasonable, confirmation with another device is prudent.

Cause of Pyrexia in the Medical ICU

The major causes of abnormally elevated temperatures in the critically ill can be broadly classified as the hyperthermia syndromes and infectious and noninfectious fevers (Table 1). The hyperthermia syndromes include environmental hyper-

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Table 1. Potential causes of abnormally elevated body temperature in the medical intensive care unit patient

Category	Examples
Hyperthermia syndromes	Environmental (heatstroke) Drug-induced (neuroleptic malignant syndrome, malignant hyperthermia, serotonin syndrome) Endocrine (thyrotoxicosis, pheochromocytoma, adrenal crisis)
Infectious fever	Community- and hospital-acquired infections: bacterial, fungal, viral, and protozoa
Noninfectious fever	Drug hypersensitivity Hematologic (transfusion reactions, hematomas at deep body sites, deep vein thrombosis, pulmonary embolus/infarct, acute hemorrhage) Intra-abdominal (acalculous cholecystitis, pancreatitis, organ transplant rejection) Pulmonary (fibroproliferative phase of acute respiratory distress syndrome, aspiration pneumonitis) Collagen vascular (systemic lupus erythematosus, adult Still's disease, and others) Neoplastic (Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, multiple myeloma, sarcoma, and tumors of the liver, brain, kidney, colon, gallbladder and pancreas) Vascular (stroke, myocardial infarction)

thermia (heatstroke); drug-induced hyperthermia, including neuroleptic malignant syndrome, malignant hyperthermia, and serotonin syndrome; and endocrine causes including thyrotoxicosis, pheochromocytoma, and adrenal crisis (8–10). Although the focus in this review is on fever, the hyperthermia syndromes represent an important group of conditions that need to be differentiated from fever in the critically ill medical patient. A brief description of the hyperthermia syndromes is presented.

Heatstroke can be defined clinically as a core temperature >40°C associated with central nervous system impairment and multisystem tissue injury (9, 11). Classic heat stroke results from a high external temperature that overwhelms the individual's thermoregulatory capacity to dissipate it. This form typically occurs among elderly, chronically ill, and debilitated individuals during heat waves (9, 11). On the other hand, exertional heat stroke arises from excessive heat production such that thermal homeostasis cannot be achieved. It typically occurs in young, otherwise healthy individuals undergoing strenuous physical activity. Complications of heat stroke include kidney and liver failure, disseminated intravascular coagulation, rhabdomyolysis, and severe metabolic derangements not limited to hypoglycemia, lactic acidosis, and hyperkalemia (12). Malignant hyperthermia is a syndrome characterized by rapid onset of muscle rigidity, hyperthermia, and acidosis that is usually triggered by inhalational anesthetics and depolarizing paralytic agents (8). Neuroleptic malignant syndrome is characterized by insidious onset of hyperthermia, muscle rigidity, and mental status changes that occur most commonly because of administration of neuroleptic agents. Serotonin syndrome presents with hyperthermia and other signs of autonomic instability and with cognitive and neuromuscular changes primarily in patients who are taking selective serotonin reuptake inhibitors (10).

A vast list of bacterial, viral, fungal, and protozoal infections can cause fever in the ICU. Common sites of infection in otherwise immunocompetent medical ICU patients include the lower respiratory tract, urinary tract, bloodstream, sinus, skin/soft tissue, and intra-abdominal/gastrointestinal tract (13–18). The species, focus, and antimicrobial resistance profile of infections will depend at least in part on underlying health status, treatments rendered, and presumed location of acquisition (13). Malacarne et al (19) recently reported on the occurrence of infection among nearly 10,000 patients (approximately half of them medical patients) admitted to 71 ICUs in Italy and found that 12% of all admissions had community-acquired infections and 19% had nosocomial infections, of which 11% were ICU acquired.

Bacteria are common agents of both community-acquired and nosocomial infections and usually have an identifiable clinical focus or are culture positive. Although in endemic areas dimorphic fungi can be important causes of community-acquired infection, fungal infections tend to be acquired in the hospital setting. Invasive yeast infections may be occult to clinical focus and have negative blood cultures in approximately one third of cases. Patients who are colonized and who have prolonged admission, underlying medical comorbid illnesses, and invasive catheters and who are recipients of parenteral nutrition, hemodialysis, immunosuppressive therapy, and broad-spectrum antibacterials are at increased risk (20, 21). Mold infections tend to present subacutely, and chronic obstructive lung disease and corticosteroid therapy are risk factors (22, 23). Viral illnesses (i.e., influenza, parainfluenza, rhinovirus, adenovirus, respiratory syncytial virus, coronaviruses, human metapneumovirus, West Nile virus, varicella zoster) usually present as community-acquired infections (24). However, there has been increasing recognition of the role of reactivation of latent herpes viruses, most notably herpes simplex virus and cytomegalovirus, as causes of febrile infections with onset after admission to ICU (24, 25). Fever is a common complication of human immunodeficiency virus infection, and this diagnostic possibility should not be overlooked. Protozoal diseases such as malaria and babesiosis are usually considerations only in the appropriate exposure context.

Noninfectious causes of fever are common in the medical ICU (4, 14, 26). Transfusion reactions and drug hypersensitivity, in particular to antimicrobial agents, are frequent causes of noninfectious fever. Hematomas at deep body sites as well as deep vein thrombosis, pulmonary embolus/infarct, myocardial infarction, and acute hemorrhage all can cause fever. Intra-abdominal sources include acalculous cholecystitis, pancreatitis, and organ transplant rejection. Although lung atelectasis *per se* is controversial as a cause of noninfectious fever, it is accepted that the fibroproliferative phase of acute respiratory distress syndrome and aspiration pneumonitis are established. Systemic lupus erythematosus, adult Still's disease, and other collagen vascular/rheumatic diseases are relatively uncommon but also potential causes of fever, as is occult malignancy, most notably Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, multiple myeloma, sarcoma, and tumors of the liver, brain, kidney, colon, gallbladder, and pancreas (27).

Epidemiology

There is only a small body of literature investigating the epidemiology of fever in adult medical ICU populations (5, 28, 29). Circiumaru et al (28) reported a study of 100 consecutive admissions among 93 patients to a general medical-surgical ICU in London. Each patient was assessed by a single investigator with daily follow-up. They found that 70% of admissions were associated with at least one fever (≥ 38.4°C). Fever was attributed to infectious causes in 37 (53%) cases, of which 15 were lower respiratory tract infections, nine were blood infections, and five were of abdominal source. The principal cause of noninfectious fever was attributed to postoperative fever. Prolonged fever (>5 days) occurred in 16 patients, of whom infection was identified in all cases (three patients also had noninfective processes occurring concomitantly). Overall, patients who had fever did not suffer a statistically significant higher mortality than those without (26 of 70 [37%] vs. eight of 30 [27%], $p = 0.38$), but those with prolonged fever were more likely to die (63% [ten of 16] vs. 30% [16 of 54], $p < 0.0001$). Although this study involved careful and detailed clinical observation of patients, it was limited by its small size and conduct in a single ICU. In addition, the majority of the patients were surgical, with only 18 listed as having primarily medical admission diagnoses. Thus, the specific features and outcome related to medical patients could not be discerned from the report.

Peres Bota et al (29) reported fever (≥38.3°C) in 139 (28%) of 493 patients admitted to a large medical-surgical ICU in Brussels, Belgium. The cause of fever was deemed to be infection in 76 patients (55%), postoperative in 27 (19%), cerebral hemorrhage in 20 (14%), trauma in five (4%), adult respiratory distress syndrome in three (4%), pancreatitis in three (4%), gastrointestinal bleeding in three (4%), and myocardial infarction in two (1%). Compared with normothermic patients, patients with fever were more likely to have a medical compared with surgical diagnosis and have longer durations of mechanical ventilation and ICU length of stay. Patients with fever had a significantly higher mortality rate of 35% compared with 10% for normothermic patients. Although it was calculable that 88 of 274 (32%) patients in the study were medical ICU patients with fever, the clinical features and outcomes specific to the medical patients could not be determined from the published report (29).

We recently reported a large, retrospective cohort study evaluating the epidemiology of fever ≥38.3°C and high fever ≥39.5°C among all adults (n = 20,466) admitted to ICUs in Calgary, Canada, during 2000–2006 (5). The cumulative frequency (incidence density per 100 ICU days) of fever was 44% (24.3), and this was 43% (21.8) in medical, 36% (17.5) in cardiac surgical, 65% (38.2) in trauma/neurologic, and 45% (22.8) in other surgical patients. Male gender, Acute Physiology and Chronic Health Evaluation II score <25, and younger age were associated with a higher frequency of fever. Prolonged fever and high fever lasting for ≥5 days in the ICU occurred in 18% and 11% of febrile patients, respectively. After we controlled for Acute Physiology and Chronic Health Evaluation II score, Therapeutic Intervention Scoring System score, gender, age, and the presence of shock at admission to the ICU in a logistic regression model, the influence of fever on ICU mortality varied significantly according to its timing of onset, degree, and main admission category. Specifically in the medical patients, compared with those who did not have any documented fever during admission, those who were either afebrile or 38.3°C–39.4°C at admission and subsequently developed a fever to ≥39.5°C were at adjusted odds ratios (95% confidence intervals) of 1.29 (0.85–1.96) and 1.91 (1.36–2.70) for death, respectively.

Rationale For and Against Treatment of Fever in the Medical ICU

Although there is a relative lack of evidence-based data, it is widely accepted that treatment to lower temperature is indicated for patients who have hyperthermia syndromes (30). Principles of therapy include discontinuation of offending drugs, initiation of direct cooling, and administration of antidotes and specific therapies as appropriate. Specific therapies include intravenous dantrolene for patients with malignant hyperthermia and possibly heatstroke (8), potentially dantrolene and/or bromocriptine for neuroleptic malignant syndrome (31), and cyproheptadine for serotonin syndrome (10). Thyrotoxic crisis is usually treated with propylthiouracil or methimazole, glucocorticoids, and β-blockers; pheochromocytoma with α-blockade using phenoxybenzamine; and adrenal crisis with corticosteroids. Given that hyperthermia syndromes are not associated with an elevated hypothalamic set point, antipyretic agents are not usually effective, may be harmful, and are not routinely recommended.

Unlike with hyperthermia syndromes, where measures to lower temperature are a key aspect of treatment, several arguments exist for and against the treatment of fever in neurologically intact, critically ill adult medical patients. At very high levels of elevated temperature, such as >40°C–41°C, increasing concerns exist for risk of brain damage and the initiation or worsening of multisystem failure (32). It is widely viewed that lowering temperature from extreme levels is indicated. However, at lesser degrees of fever, such as <40°C–41°C, there are a number of theoretical arguments and experimental data both in favor of and against the treatment of fever to normal or even subnormal levels.

Proponents of treating fevers in neurologically intact, critically ill medical patients argue for improved patient and caregiver comfort and reduction of metabolic demand and cardiovascular stress. Although no clinical trials have assessed the subjective effects of antipyretic therapy in critically ill medical patients, anecdotal experiences and studies in non-ICU populations have supported improved patient symptoms with antipyretic therapy (33, 34). Manthous et al (35) studied 12 ventilated patients and found that as temperature was reduced from 39.4°C ± 0.8°C to 37.0°C ± 0.5°C, oxygen consumption decreased from 359 ± 65 mL/min to 295 ± 57 mL/min ($p < 0.01$). Thus, in the setting of severe or refractory shock, treatment of fever results in an improved supply-demand balance that may reduce tissue hypoxic injury. It is also widely recognized that the presence of fever frequently prompts clinicians to perform diagnostic testing and administer antimicrobial therapies (3, 4). Although empirical study evidence is lacking, it may be argued that treatment of fever can reduce excessive investigation, antibiotherapy, and cost of care. Lowering temperature may also have benefits in acute respiratory distress syndrome (or adult respiratory distress syndrome) and myocardial infarction, which frequently complicate patients' clinical courses in the medical ICU (36–38).

Fever is an innate adaptive response to infection, and several lines of evidence

argue against routine treatment of fever in the critically ill medical patient. High temperatures inhibit growth of microorganisms, may reduce the expression of virulence factors, increase susceptibility to antimicrobials, and enhance host immune responses (1, 39–41). It is well established in observational studies that naturally hypothermic septic patients are at higher risk for death than those who have fever (29, 42, 43). Although methods of treatment of fever include direct cooling with fans and sponges, ice packs, cool fluids, and devices, more frequently antipyretic medications such as acetylsalicylic acid, nonsteroidal anti-inflammatory agents, and acetaminophen are used (44). These agents run a not-insignificant risk for bleeding, hepatic and renal toxicity and may contribute to hypotension (45, 46). Use of active cooling methods may also cause increases in metabolic rate and cause discomfort in nonsedated patients (47). Although fever-suppression therapy may reduce excessive investigation and treatment in patients with noninfectious benign causes of fever, it may also delay the early diagnosis and empirical therapy of serious infections for which delays in treatment may be detrimental (48). Studies have demonstrated inconsistent effects with fever reduction on the outcome of experiment animal models of sepsis (41, 49, 50).

Clinical Evidence Evaluating Treatment of Fever in the Medical ICU Patient

Few randomized clinical trials have compared strategies of fever control in critically ill patients, and none have specifically assessed neurologically intact medical ICU patients (51–53). Until studies are completed in medical ICU patients, potential effects of treatment must be inferred from other patient populations.

Bernard et al (51) reported on a randomized, double-blind, placebo-controlled trial comparing 10 mg/kg intravenous ibuprofen every 6 hrs for eight doses in 455 patients with fever (≥38.3°C or hypothermia <35.5°C) and sepsis and at least one organ failure. Infection sources included lung in 47% of patients, peritoneum in 15%, urinary tract in 10%, and other or unknown in 27%. Significant decreases in temperature, heart rate, oxygen consumption, and lactic acidosis were observed in the ibuprofen group compared with placebo. Ibuprofen therapy did not affect the frequency or duration of shock or adult respiratory distress syndrome and did not significantly alter the mortality rate (95% confidence interval) of 37% (31–44%) for ibuprofen vs. 40% (34–46%) for placebo. However, although ibuprofen is an antipyretic agent, this study was not specifically designed to assess effects of fever control per se. Significant and differential co-intervention with acetaminophen occurred with approximately one third of patients in both groups receiving this agent at enrollment. Importantly, this rate decreased to 22% in ibuprofen-treated patients and increased to 44% within 24 hrs of enrollment in the placebo-treated patients. If treatment of fever truly does improve outcome, then in this study the differential co-intervention with acetaminophen in the placebo group would be expected to cause a bias toward a null finding.

Schulman et al (52) conducted an open, randomized, prospective clinical trial comparing an aggressive fever treatment strategy (650 mg acetaminophen every 6 hrs for fever >38.5°C and a cooling blanket added if >39.5°C) with a permissive strategy (treatment reserved for fever >40°C only) in patients admitted ≥3 days to a trauma surgery ICU. The primary end point was development of culture-proven infection. Patients with acute brain injury, malignant hyperthermia, heat stroke, neuroleptic malignant syndrome, hepatic cirrhosis, acute hepatic failure, or a history of stroke, seizure, or previous traumatic brain injury were excluded. The aggressive treatment group had a higher rate of infections compared with the permissive treatment group (131% vs. 85%) and a higher rate of antibiotic use (77% vs. 71% of days on therapy). No significant differences between the total number of cultures sent per patient or length of ventilation or ICU stay were observed. The study had to be prematurely stopped because of safety concerns after interim analysis revealed an excess mortality rate of seven of 44 (16%) in the aggressive group compared with one of 38 (3%) in the permissive group ($p = 0.06$). Although this study represents a major contribution to the surgical critical care literature, its results may not be generalizable to a medical ICU population.

Gozzoli et al (53) conducted a randomized trial comparing external cooling with no treatment in 38 surgical ICU patients with fever ≥38.5°C and systemic inflammatory response syndrome. Patients with neurotrauma or severe hypoxemia were excluded. External cooling was achieved using cooling blankets, ice packs, or cloths; was stopped when the patient's temperature was 37.5°C; and was restarted if the temperature increased to ≥38.5°C. The primary outcome measure was defervescence at 24 hrs after intervention, and secondary outcomes included patient discomfort as determined by visual analog scale. Among the 18 externally cooled patients and the 20 control patients, temperature and discomfort decreased similarly in both groups after 24 hrs. No significant differences in recurrence of fever, frequency of infection, antibiotic therapy, intensive care unit and hospital length of stay, or mortality rate were observed. Although this study demonstrated that in the surgical population external cooling did not significantly influence either the duration of fever or patient discomfort, the investigation was underpowered to assess major outcomes such as mortality. Like with the study by Schulman et al (52), it is not known whether the results reported by Gozzoli and colleagues (53) can be generalized to critically ill medical patients.

Summary and Conclusion

Although fever is common in critically ill patients and prompts clinical attention and changes in management, it is surprising how little is known about its epidemiology and effect on outcome in adult medical ICU patients. Although fever development has been documented as a marker for adverse outcome, it is not known whether active treatment with antipyretic therapy and/or physical cooling methods affects the outcome of neurologically intact, critically ill medical ICU patients. Clinical trials in critically ill surgical patients have demonstrated null or potentially harmful effects of treatment of moderate degrees of fever. However, these results are questionably generalized to medical patients because the effect of fever on outcome may be different among populations of medical and surgical ICU patients. No clinical trial has specifically evaluated fever management strategies in critically ill adult medical patients. Given the frequency of febrile episodes and the numerous potential risks and benefits of fever treatment, randomized clinical trials of fever management in neurologi-

cally intact medical ICU patients are needed.

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