Fever: Fact and Fiction

James E. Barone, MD, FACS, FCCM

Abstract: The significance and management of fever in surgical patients involves several misconceptions that have been perpetuated over the years. This review addresses nine such misconceptions and using evidence from the literature, attempts to clarify such diverse issues as the concept of normal body temperature, the investigation and rationale for the treatment of postoperative fever, the beneficial effects of fever and the potential adverse effects of suppressing fever.

Although much is known about fever, many misconceptions persist. The purpose of this review is to attempt to clarify some of these. The pathogenesis of fever and the differences between fever and hyperthermia will not be discussed as those topics are better left to the basic scientists. Temperatures are described in Celsius, with Fahrenheit conversions in parentheses.

Misconception 1: Normal Body Temperature Is Fairly Constant and Is Usually 37°C (98.6°F)

As part of a study of a vaccine against Shigella, Mackowiak et al. studied 148 healthy individuals who had several oral temperatures recorded for more than 2 1/2 days. The mean normal temperature was 36.8°C (98.2°F), with a median of 36.8°C (98.2°F) and a mode of 36.7°C (98.0°F). Normal temperatures ranged from 35.6°F (96.0°F) to 38.2°C (100.8°F). The authors concluded that 37.7°C (99.9°F) should be regarded as an upper limit of normal. A literature review from Scandinavia looked at the question: what is normal body temperature in adults? The authors systematically reviewed all studies on the subject from 1935 to 1999. There were 20 studies that the authors considered worthy of inclusion. They concluded that the range of normal oral temperature was 35.6°C (96.1°F) to 38.2°C (100.8°F) and that women had slightly higher normal body temperatures than men.

Roberts et al.1 reported the presence of fever in 40% of 270 patients who had undergone elective abdominal surgery. When fever was defined as a temperature ≥37.7°C (99.9°F), chest X-ray film evidence of atelectasis was found in 57% of the febrile patients. If fever was considered as a temperature of ≥38.0°C (100.4°F), only 47% of patients had atelectasis. A study of 100 postoperative cardiac surgery patients who had daily chest X-ray by Engoren4 showed that the incidence of atelectasis increased as the incidence of fever decreased with each successive postoperative day. Atelectasis was associated with neither fever nor severity of fever. In fact, the higher the fever, the less likely were the patients to have atelectasis. As stated below, many of the early postoperative fevers are more likely to be due to the inflammatory response to the trauma of surgery rather than atelectasis.

Misconception 2: The Most Common Cause of Fever in the First Few Postoperative Days Is Atelectasis

A study of 271 postoperative thoracic, vascular, and abdominal surgery patients from Johns Hopkins University showed that >50% had a maximum core temperature of ≥38°C (100.4°F) and half of those patients had a maximum core temperature of ≥38.5°C (101.3°F). The authors concluded that there is an elevated thermostatic set point in postoperative patients that is associated with an inflammatory response, not an infection. This was supported by data from a subset of 34 patients. Those with fevers of ≥38.5°C (101.3°F) had levels of interleukin-6 that were statistically significantly higher than those without fevers <38.5°C (101.3°F). Another group6 found that of 211 patients who had undergone cardiac surgery, there was no difference in the rate of infection of any type in 115 (55%) patients with fever compared with those without fever. Vermeulen et al. analyzed 284 general surgery patients, who had 2,282 temperatures taken. Fever ≥38°C (100.4°F) was noted in 61 patients, and infection was found in 7 (11.5%). Infection was diagnosed in 12 of 223 patients (5.4%) without fever (p = 0.162). As a predictor of infection, a temperature of ≥38°C (100.4°F) had a sensitivity of 37%, a specificity of 80%, a likelihood ratio of a positive test of 1.8, and a likelihood ratio of a negative test of 0.8%. The positive predictive value of each individual temperature was only 8%. In addition, 6 of 8 patients with severe infections had temperatures <38°C (100.4°F). Another study8 was comprised of 871 general surgery patients, of whom, 113 patients (13%) had 132
There were 55 wound infections, 44 urinary tract infections, 27 respiratory infections, and 6 assorted other infections. There were 81 unexplained fevers, and 72% of those patients were febrile within the first 2 postoperative days. The authors concluded that fevers occurring within the first 2 days are often not associated with infection.

Freischlag and Busuttil looked at 464 postoperative patients. Fever was found in 71 (15%). Only 19 of 71 (27%) had an infection—6 urinary tract infections, 5 wound infections, 2 pneumonia, and 6 other types of infections. The authors observed that 14 of the 19 infections were discovered by history and physical examination. Laboratory and radiologic studies were remarkably poor at discriminating infections (Table 1). Similar findings were noted in a study of 676 postoperative gynecology patients. Of the 194 (29%) who had fever, laboratory and radiologic workup had a low yield (Table 1). They found that infection was associated with surgery for malignancy, bowel resection, number of afebrile days, a relatively higher fever, and moderately increased leukocytosis.

The authors concluded that blood cultures were being drawn too often and were very expensive for the low yield. They found that a positive blood culture was more likely after the first 3 postoperative days and that neither white blood cell count nor magnitude of fever was useful in predicting a positive blood culture. Remarkably similar findings were noted by Darby et al. who looked at the records of 206 patients who had at least one set of blood cultures obtained while in a surgical ICU. Of 1,106 cultures drawn, 83 (7.5%) were positive, with contaminants found in 39 or 3.5% of the total. Despite the low yield, current guidelines for the evaluation of new fever in critically ill patients call for the obtaining of blood cultures when a noninfectious cause for the fever cannot be found.

**Misconception 4: Fever Should Be Treated Because Fever Makes Patients Uncomfortable**

Lenhardt et al. induced fever in healthy volunteers by injecting interleukin-2 and randomized the subjects into three groups, control (no treatment), forced air cooling at 15°C (59°F), or forced air warming adjusted to comfort by the subject. They found that the subjects were most uncomfortable when being cooled and most comfortable when they could adjust the temperature with forced air warming. Oxygen consumption and plasma catecholamine levels were statistically significantly higher when the subjects were being actively cooled.

**Misconception 5: Fever Should Be Treated Empirically With Antibiotics**

Infection caused by *Clostridium difficile* is becoming more virulent and is reaching the status of an epidemic. Despite the risks of *C. difficile* colitis, emergence of resistant organisms, and drug fever, antibiotics are often administered empirically when patients develop fever. This practice was questioned as long ago as 1990 by DiNubile, an infectious disease specialist. He recommended treating febrile patients with antibiotics only when they were profoundly neutropenic, asplenic, hemodynamically unstable without an obvious noninfectious cause, or if they had a clinically significant established bacterial infection. These sentiments were recently echoed by Rizoli and Marshall in a review of the diagnosis and treatment of sepsis. They recommended that febrile patients without an obvious source should have invasive lines changed and antibiotics should be stopped.

<table>
<thead>
<tr>
<th>TABLE 1. Results of Diagnostic Workups for Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive Test</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>WBC</td>
</tr>
<tr>
<td>Urinalysis</td>
</tr>
<tr>
<td>Urine culture</td>
</tr>
<tr>
<td>Sputum culture</td>
</tr>
<tr>
<td>Blood culture</td>
</tr>
<tr>
<td>Chest X-ray studies</td>
</tr>
</tbody>
</table>

Values in parentheses denote %, numerator a positive test, and denominator number of patients tested.
* Fever ≥38.5°C (103.3°F).
† Fever ≥38°C (100.4°F).
‡ Fever defined as two temperatures ≥38° (100.4°) or one temperature ≥38.6°C (101.5°F).

WBC, white blood cell count.
Misconception 6: Patients Who Have Fever Within 24 Hours of Anticipated Discharge Should Be Kept in the Hospital

This long-held belief has not been studied extensively. A recent article looked at 300 consecutive patients with a hospital length of stay of ≥5 days discharged from surgical services. Fever was defined as a temperature of ≥37.8°C (100°F). Follow-up was available for 86.7% of the patients. Fever within 24 hours of discharge occurred in 45 patients (15.0%). The mean temperature was 38°C (100.5°F), with a range of 37.8°C (100°F) to 39.9°C (102.1°F). Of the 45 patients with fever, 7 (15.6%) were readmitted compared with 31 readmissions (12.2%) in the 25 nonfebrile patients. The difference in the rate of readmission was not statistically significant. The conclusion was that the presence or absence of fever within 24 hours of patient discharge had no impact on the rate of readmission within 30 days.

Misconception 7: Fever Is a Bad Thing and Suppressing Fever Will Eliminate Its Bad Effects

Many studies of the effects of fever on the progression of illness have been performed on animals. Bernheim and Kluger studied iguanas (normal body temperature 38°C [100.4°F]) because a cold-blooded animal will seek the temperature that is optimal for survival. When iguanas injected with live bacteria were placed in chambers of varying temperature, the rate of survival of the animals depended on the temperature in each chamber, with the animals in the higher temperature chambers surviving at greater rates. When iguanas were injected with dead bacteria and placed in a chamber with areas of different ambient temperature, they moved to the area that was 42°C (107.6°F). A recent study of surgical patients with bacteremia showed that among 823 episodes of bloodstream infections, 148 (18%) resulted in death. A higher temperature in the first 24 hours was associated with a statistically significantly higher rate of survival.

Misconception 8: Reducing Core Temperature in Febrile Patients Has No Ill Effects

Physical methods of antipyresis such as immersion in water, ice packs, evaporation, and cooling blankets have been used in hospitals for years. Adverse effects of these practices include cutaneous vasoconstriction, shivering, increased oxygen consumption, and increased levels of catecholamines. Gozzoli et al. performed a randomized clinical trial of 38 surgical intensive care patients, 18 of whom had their fevers treated with external cooling, whereas 20 were observed. They found that aggressive cooling had no effect on outcomes such as ICU or hospital length of stay or mortality rates. Administration of antipyretic drugs has also been a common response to fever in hospitalized patients. A study of antipyretic use in infected lizards demonstrated that all the animals whose fever response was blocked died, and their deaths were caused by the inability to elevate their temperatures, not by a toxic effect of the antipyretic. Aspirin, acetaminophen, and ibuprofen given to volunteer subjects infected with rhinovirus led to a longer duration of viral shedding and more turbinate edema. In another experiment, antipyretics given to patients with influenza resulted in them being symptomatic for an average of 3.5 days longer than those not treated with pharmacologic fever suppression. Nonsteroidal anti-inflammatory drugs also have potential side effects. For example, they have been associated with acute renal failure, membranous nephritis and nephrotic syndrome, and adverse gastrointestinal events.

As was demonstrated in a study by Su et al., treating fever may in fact be harmful. These authors induced sepsis in sheep and randomly cooled some of them using external cooling and acetaminophen. They found that sheep allowed to have high fever (>39°C or 102.2°F) had statistically significantly higher PaO₂/FIO₂, lower lactate levels, and improved survival compared with those sheep with mild fever, normothermia, and hypothermia. Schulman et al. performed a randomized prospective study of the effect of treating fever with acetaminophen on outcomes of critically ill patients with trauma. Fever was defined as a temperature ≥38.5°C (101.3°F). The study was stopped after the enrollment of 82 patients because the mortality rate in the treatment group was 7 of 44 versus 1 of 38 in those not treated with acetaminophen (p = 0.06).

Misconception 9: Fever in Critically Ill Patients Must Be Treated

Fever is common in critically ill patients. Circumaru et al. studied 100 consecutive admissions to the ICU. Fever was noted in 70% of the patients. Half of the febrile patients did not have an infection, with more than half of those without infection having only early postoperative fever. In a population-based study from Canada, 44% of patients admitted to ICUs of all types developed at least one episode of fever. Moderate fever was defined as a temperature of ≥38.3°C (101.0°F) to 39.4°C (102.9°F), and high fever was defined as a temperature of ≥39.5°C (103.1°F). Moderate fever had no impact on the mortality rate. High fever was associated with an increased risk of death. Of note is the fact that critically ill trauma and neurologic patients had a decreased risk of death if they had a fever at any time during their intensive care stay.

Noninfectious causes of fever in critically ill patients include alcohol/drug withdrawal, posttransfusion, drug, cerebroinfarction/hemorrhage, adrenal insufficiency, myocardial infarction, pancreatitis, acalculous cholecystitis, ischemic bowel, aspiration pneumonia, acute respiratory distress syndrome, subarachnoid hemorrhage, fat emboli, transplant rejection, deep venous thrombosis, pulmonary emboli, gout/pseudogout, hematoma, cirrhosis (without primary peritonitis), gastrointestinal bleed, intracranial bleed, phlebitis/thrombophlebitis, stroke, intravenous contrast reaction, neoplasia, pericardial injury syndrome, and decubitus ulcers.

Note that the above may not apply to patients with neurologic diseases or trauma. There is evidence in such patients that elevated body temperature is associated with longer ICU and hospital lengths of stay and higher mortality rates. However, this association has not been proven to be a cause of worse outcomes. In a recent review article, Axelrod and Diringer advocate the aggressive treatment of...
noninfectious fever in critically ill neurologic patients while acknowledging the fact that there is no evidence that treating fever in such patients is efficacious.

In summary, there is marked variation in the “normal” body temperature. Fever is not bad. The most common cause of fever in the first few postoperative days is not atelectasis but rather a normal inflammatory response to the trauma of surgery. Fever is neither a good predictor of infection nor should it automatically trigger a workup. Fever should not be treated with antibiotics. Patients who have fever within 24 hours of anticipated discharge should not be necessarily kept in the hospital. Suppressing fever is unnecessary and possibly harmful in most patients.

REFERENCES


