CHAPTER 105 — AN APPROACH TO THE FEBRILE ICU PATIENT

NEIL A. MUSHLIN • PAUL E. MARIK

Fever is a common problem in the intensive care unit (ICU), with approximately 70% of patients developing a fever at some point during their ICU stay. Infectious and noninfectious etiologies contribute almost equally to the causation of febrile episodes (1). The discovery of fever in an ICU patient has a significant impact on health care costs due to the blood cultures, radiologic imaging, and antibiotics that routinely follow. It is therefore important to have a good understanding of the mechanisms and etiology of fever in ICU patients, how and when to initiate a diagnostic workup, and when initiation of antibiotics is indicated.

The Society of Critical Care Medicine and the Infectious Disease Society of America consider a temperature of 38.3°C (101°F) in an ICU patient a fever that warrants further evaluation (2). This does not necessarily imply that a temperature below 38.3°C (101°F) does not require further investigation, as many variables determine a patient’s febrile response to an insult. In addition, it should be recognized that there is a daily fluctuation of temperature by 0.5°C to 1.0°C, with women having wider variations in temperature than men (3). Furthermore, with aging, the maximal febrile response decreases by about 0.15°C per decade (4).

Accurate and reproducible measurement of body temperature is important in detecting disease and in monitoring patients with an elevated temperature. A variety of methods are used to measure body temperature by combining different sites, instruments, and techniques. The mixed venous blood in the pulmonary artery is considered the optimal site for core temperature measurement. However, this method requires placement of a pulmonary artery catheter. Infrared ear thermometry has been demonstrated to provide values that are a few tenths of a degree below temperatures in the pulmonary artery and brain (5–9). Rectal temperatures obtained with a mercury thermometer or electronic probe are often a few tenths of a degree higher than core temperatures (10–12). However, patients perceive rectal temperatures as unpleasant and intrusive. Furthermore, access to the rectum may be limited by patient position, with an associated risk of rectal trauma. Oral measurements are influenced by events such as eating and drinking and the presence of respiratory devices delivering warmed gases (13). Many tachypneic patients are unable to keep their mouth closed to obtain an accurate oral temperature. Axillary measurements substantially underestimate core temperature and lack reproducibility. Body temperature is therefore most accurately measured with an intracavalricular thermistor; however, measurement by infrared ear thermometry or with an electronic probe in the rectum is an acceptable alternative (2).

PATHOGENESIS OF FEVER

Cytokines released by monocytic cells play a central role in the genesis of fever. The cytokines primarily involved in the development of fever include interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) (14–23). The interaction between these cytokines is complex, with each being able to up-regulate and down-regulate their own expression as well as that of the other cytokines. These cytokines bind to their own specific receptors located in close proximity to the preoptic region of the anterior hypothalamus (14,15). Here, the cytokine receptor interaction activates phospholipase A2, resulting in the liberation of plasma membrane arachidonic acid as substrate for the cyclo-oxygenase pathway. Some cytokines appear to increase cyclo-oxygenase expression directly, leading to the liberation of prostaglandin E2 (PGE2).

Fever appears to be a preserved evolutionary response within the animal kingdom (24,25). With few exceptions, reptiles, amphibians, fish, and several invertebrate species have been shown to manifest fever in response to challenge with microorganisms. Increased body temperature has been shown to enhance the resistance of animals to infection (24,25). Although fever has some harmful effects, it appears to be an adaptive response that has evolved to help rid the host of invading pathogens. Temperature elevation has been shown to enhance several parameters of immune function including antibody production, T-cell activation, production of cytokines, and enhanced neutrophil and macrophage function (26–29). Furthermore, some pathogens such as Strep-tococcus pneumoniae are inhibited by febrile temperatures (30).

Schulman et al. investigated whether it was beneficial to treat the fever of hospitalized patients admitted to a trauma ICU (31). Patients were randomized to an active treatment group, in which acetaminophen and cooling blankets were used to aggressively cool this subgroup, as compared to a permissive group, in which fever was only treated once it reached 40°C. In this study, there was a strong trend toward increased mortality in the active treatment group. It should, however, be noted that all the patients who died in the aggressive treatment group had an infectious etiology as the cause of the fever. Doran et al. demonstrated that children with varicella who were treated with acetaminophen had a more prolonged illness (32). Wein-stein et al. reported that patients with spontaneous bacterial peritonitis had improved survival if they had a temperature greater than 38°C (33). These data suggest that fever from an...
infectious cause should not be treated unless the patient has limited cardiopulmonary reserve.

In contrast to patients with infectious disorders, patients with cerebral ischemia or head trauma have worse outcomes with increased temperature. For these patients, the current recommendation is to maintain the patient’s temperature in the normothermic range (34). Antipyresis must always include an antipyretic agent, as external cooling alone increases heat generation and catecholamine production (35). Furthermore, acute hepatic metabolism may occur in ICU patients with reduced glutathione reserves (alcoholics, malnourished, etc.) who have received regular therapeutic doses of acetaminophen.

FEVER PATTERNS

Attempts to derive reliable and consistent clues from evaluation of a patient’s fever pattern are fraught with uncertainty and are not likely to be helpful diagnostically (14,36,37). Most patients have remittent or intermittent fever, which, when due to infection, usually follows a diurnal variation (36). Sustained fevers have been reported in patients with Gram-negative pneumonia or central nervous system (CNS) damage (36). The appearance of fever at different time points in the course of a patient’s illness may, however, provide some diagnostic clues. Fevers that arise more than 48 hours after the institution of mechanical ventilation may be secondary to a developing pneumonia. Fevers that arise 5 to 7 days postoperatively may be related to abscess formation (38). Fevers that arise 10 to 14 days after institution of antibiotics for intra-abdominal abscess may be due to fungal infections (39-41).

CAUSES OF FEVER IN THE INTENSIVE CARE UNIT

Any disease process that results in the release of the proinflammatory cytokines IL-1, IL-6, and TNF-α will result in the development of fever. While infections are common causes of fever in ICU patients, many noninfectious inflammatory conditions cause the release of the proinflammatory cytokines and induce a febrile response. Similarly, it is important to appreciate that not all patients with infections are febrile. Approximately 10% of septic patients are hypothermic and 35% normothermic at presentation. Septic patients who fail to develop a fever have a significantly higher mortality than febrile septic patients (42-44). The reason that patients with established infections fail to develop a febrile response is unclear; however, preliminary evidence suggests that this aberrant response is not due to diminished cytokine production (45).

The presence of fever in an ICU patient frequently triggers a battery of diagnostic tests that are costly, expose the patient to unnecessary risks, and often produce misleading or inconclusive results. It is therefore important that fever in ICU patients be evaluated in a systematic, prudent, clinically appropriate, and cost-effective manner.

Infectious Causes of Fever in the Intensive Care Unit

The prevalence of nosocomial infection in ICUs has been reported to vary from 3% to 31% (13, 46–49). In a point prevalence study conducted in 1992, the European Prevalence of Infection in Intensive Care (EPIC) study investigators reported on the prevalence of nosocomial infections in 10,038 patients hospitalized in 1,417 European ICUs (50). In this study, 20.6% of patients had an ICU-acquired infection, with pneumonia being most common (46.9%), followed by urinary tract infection (17.6%) and bloodstream infection (12%). The most common infectious causes of fever in ICU patients are listed in Table 105.1.

Catheter-related Blood Stream Infection

Intravascular catheters are a major source of infection in the ICU. According to the National Nosocomial Infections Surveillance (NNIS) system, the mean incidence of catheter-related bloodstream infection (CRBI) in the United States is 5.3 per 1,000 catheter-days. Coagulase-negative staphylococci account for up to 40% of cases (51). Other common causes of CRBI include enterococci, Staphylococcus aureus, Candida species, and aerobic Gram-negative bacilli. Methicillin-resistant S. aureus (MRSA) and vancomycin-resistant enterococci are now becoming important causes of CRBI. A number of different mechanisms likely lead to CRBI. Skin pathogens can infect the catheter exit site and then migrate down the tract along the external catheter surface. Pathogens can also contaminate the catheter hub, leading to intraluminal catheter colonization and infection. Hematogenous seeding of the external surface of the catheter may also occur (52). In addition, despite rigorous skin disinfection, viable microorganisms can be impacted during insertion of the distal tip of the catheter, causing infection (53). A number of factors have been identified as increasing the risk of CRBI, including the number of lumens in the central venous catheter, the number of stopcocks, transfusion of blood and blood products, parenteral nutrition, and an open infusion system (54-57). Catheter-related thrombosis is associated with an increased risk of catheter infection, while thrombocytopenia has been suggested to be protective against CRBI (55,58). The acquired immunodeficiency syndrome (AIDS) and hematologic malignancies have been found to be independent risk factors for CRBI (57).

The site of central venous catheter placement and the length of time it can be left indwelling has been a controversial topic for decades. Many studies have been published reporting conflicting data. Generally, however, subclavian catheters have been preferred...
been found to have a lower risk of infection than femoral catheters (59). It has also been suggested that placement of subcutaneous catheters may result in fewer catheter-related infections than internal jugular placement (60–62). However, a recent study found no difference in the risk of CRBI between subclavian, internal jugular, and femoral catheter placement (63). In this study, the vascular catheters were placed by experienced operators using strict aseptic techniques. While the risk of CRBI increases with the time the catheter remains in situ, changing catheters at regularly scheduled intervals has not been shown to reduce the risk of CRBI (64).

The diagnosis of CRBI can be challenging. Routine culture of blood withdrawn from the catheter is not recommended. However, the catheter exit site should be inspected daily for evidence of erythema or pus. The absence of local infection, unfortunately, does not exclude CRBI. In a patient with an indwelling central venous catheter who develops a fever, two sets of blood cultures should be drawn: one from the catheter and one from a peripheral source. If the patient has systemic signs of infection and no other identifiable source of infection, the catheter should be removed and empiric antibiotics commenced pending culture results. In patients with limited venous access, the central catheter may be replaced with a new catheter over a guidewire. However, both the catheter tip as well as the intratunnelous portion of the catheter should be sent for culture. If catheter culture returns positive (greater than 15 colony-forming units [CFU]), or the blood cultures are consistent with a CRBI, the catheter that was changed over a guidewire must be removed and replaced with a new catheter at a clean site (65,66). Follow-up blood cultures should be obtained in patients with CRBI. If blood cultures remain positive, a thorough investigation for septic thrombosis, infective endocarditis, and other metastatic infections should be pursued (67).

The usual approach to patients with suspected CRBI involves removal of the catheter. However, this subjects patients with negative cultures to the added risk of catheter placement. To avoid this problem, a number of methods have been investigated for the diagnosis of CRBI that do not require removal of the central venous catheter. Comparison of blood cultured from the central catheter with that from a peripheral venous site is currently the most useful technique. In patients with CRBI, quantitative culture counts are greater and time to positivity shorter with blood withdrawn from the catheter as opposed to the peripheral site (65). Acidine-orange leukocyte cytospin testing, available in some countries, is a rapid, inexpensive test that can also be used to prevent unnecessary removal of catheters (68–70). Endoluminal brushing, in which the central venous catheter is sampled within 3 to 5 cm of the catheter tip, has also been demonstrated to be useful in the diagnosis of CRBI (71,72). Experience with these alternative methods of diagnosing CRBI is, however, quite limited.

**Ventilator-associated Pneumonia**

Ventilator-associated pneumonia (VAP) is a common source of fever in the intubated patient. Intubation increases the risk of developing pneumonia from 6- to 21-fold (73). Between 10% and 25% of patients on mechanical ventilation will develop VAP during their ICU stay (74,75). VAP is associated with significant costs and has an attributable mortality of about 25% (76). The risk of acquiring VAP is highest in the first week, at 3% a day, thereafter decreasing to 2% a day in the second week, and down to 1% a day in the third and subsequent weeks (77). The risk of VAP is higher in trauma, burn, and neurosurgical units as compared to medical ICUs.

VAP is usually categorized as either early (occurring less than 48 hours after intubation) or late onset (occurring after 5 to 7 days of intubation) (78). The distinction between these two phases of VAP is vitally important, as they are associated with different pathogens. Early-onset VAP is associated with bacteria that are normally sensitive to antibiotics (methicillin-sensitive *S. aureus*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*). Late onset is typically associated with antibiotic-resistant bacteria (MRSA, *Pseudomonas aeruginosa*, *Acinetobacter* species, and *Enterobacter* species) (76,79,80).

The major risk factors for VAP include (74,81,82):

- Age over 60 years
- Male gender
- Chronic lung disease
- Acute respiratory distress syndrome
- Aspiration
- Sinusitis
- Nasogastric tube
- Transport in and out of the ICU
- Failure to elevate the head of the bed
- Endotracheal cuff pressures less than 20 cm of H₂O
- Increased severity of illness
- Delayed extubation
- Continuous sedation
- Cardiopulmonary resuscitation
- Medications including H₂ blockers and paralytic agents

The diagnosis of VAP is challenging. VAP should be suspected when a patient on mechanical ventilation develops a new infiltrate on a chest radiograph along with leukocytosis, fever, and purulent tracheobronchial secretions (83). The presence of a new infiltrate on chest radiograph, together with two of the above-cited clinical findings, has a sensitivity of 69% with a specificity of 75% for the diagnosis of VAP (84). The decision to treat a suspected VAP on clinical grounds alone will frequently overdiagnose the condition and lead to treatment that fails to cover the correct pathogen in patients with true VAP (85). Quantitative cultures of secretions obtained from the lower respiratory tract can facilitate making the diagnosis of VAP. The two most common techniques include protected specimen brush (PSB) sampling and bronchoalveolar lavage (BAL). These techniques can be performed bronchoscopically or blindly. Blind bronchial suctioning and mini-bronchoalveolar lavage are gaining popularity in intensive care units, and have been shown to be as effective as a protected specimen brush (86). These are generally safe, inexpensive tests that can be performed by respiratory therapists without a physician present. A threshold of 500 and 5,000 CFU/mL, respectively, as this increases the sensitivity of the tests (87). Microscopic examination of the BAL fluid has also been used to facilitate the diagnosis of VAP; if there is less than 50% neutrophils, pneumonia can be excluded (88). The role of quantitative culture of tracheal aspirates (as opposed to lower respiratory tract sampling) is unclear at this time. The effect of quantitative culture techniques on patient outcome is unclear; however, these techniques result in a significant reduction in the use of antibiotics (89–92).
strated that in hospitalized patients, bacteriuria with greater mortality (99). It is probable that most patients have “asymptomatic colonization of the urinary tract without bacterial invasion and an acute inflammatory response, while urinary tract infection implies an infection of the urinary tract (103). Criteria have not been developed for differentiating asymptomatic colonization of the urinary tract from symptomatic infection. Furthermore, the presence of white cells in the urine is not useful for differentiating colonization from infection, as most catheter-associated bacteriurias have accompanying pyuria (104). It is therefore unclear how many catheterized patients with greater than or equal to 10^5 CFU/mL actually have urinary tract infections.

While catheter-associated bacteriuria is common in ICU patients, data from the early 1990s indicate that less than 1% of catheter-associated bacteriuric patients will develop bacteremia caused by organisms in the urine (105). Therefore, the surveillance for, and treatment of, isolated bacteriuria in most ICU patients is currently not recommended (106). Bacteriuria should, however, be treated following urinary tract manipulation or surgery in patients with kidney stones, and in those with urinary tract obstruction. In a patient with systemic signs of infection together with bacteriuria and no other obvious source of infection, it would probably be prudent to treat this patient with a short course of antibiotics. Moreover, ultrasonography to exclude urinary tract obstruction and repeat urine culture is recommended. Treatment is clearly indicated in those patients with bacteriuria who develop bloodstream infection. Isolated Candida lower urinary tract infection is exceedingly uncommon; when this diagnosis is entertained, Candida infection of the kidney should be excluded.

**Sinusitis**

Sinusitis is an underappreciated cause of fever in the ICU and, as a result, the diagnosis is usually not considered or made until other, more common infectious causes of fever have been excluded. Sinusitis, if not diagnosed and treated in a timely fashion, can lead to nosocomial pneumonia and severe sepsis (107-109). Nasal colonization with enteric Gram-negative rods, nasonetic tubes, and a Glasgow Coma Scale score of less than 7 are all risk factors of acquiring nosocomial sinusitis. Patients who are orally intubated are less prone to develop sinusitis than those who are nasotracheally intubated (110). Indeed, up to 85% of nasally intubated patients will develop sinusitis within a week.

In patients with radiologic evidence of sinusitis, aspiration of the sinuses is required to confirm the diagnosis and to identify the causative pathogen (111). Several radiologic tests have been employed to identify this problem. While a computed tomography (CT) scan of the sinuses is considered the gold-standard study, if a patient is too ill to be transported out of the ICU, plain films of the sinuses may be obtained. In order to maximize the chances of making the diagnosis, multiple views of the sinuses are required (111). Bedside ultrasound has been gaining popularity in European countries over the last decade, and there are data to suggest that it is at least equivalent to CT scanning (108,112-114).

Once sinusitis is diagnosed, all nasal tubes should immediately be removed, with early sinus drainage (115). Broad-spectrum antibiotics should be commenced with coverage that includes Pseudomonas and MRSA. The antibiotics should then be de-escalated once culture data are available (116). Topical decongestants and vasoconstrictors, alone or combined with systemic decongestants and antihistamines, are also recommended (111).

**Clostridium difficile Colitis**

In patients who develop fever with concurrent diarrhea, *Clostridium difficile* must be considered. It is crucial to diagnose this disease early, as it can lead to severe sepsis, multiorgan system failure, and death. Patients with *C. difficile* often
present with a leukemoid reaction, with white blood cell counts that may reach greater than 35,000 cells/μL. A leukemoid reaction usually indicates leukemia, and this condition is associated with a worse prognosis and higher mortal-

ity rate (120).

Concurrent or prior antibiotic use is a strong risk factor for developing C. difficile colitis. Clindamycin, β-lactams (especially cephalosporins), and, more recently, quinolones have been the antibiotics most frequently associated with this form of colitis (121,122). Most patients in the ICU receive stress ulcer prophylaxis, with many receiving proton pump inhibitors (PPIs). PPIs have recently been associated with a higher risk of C. difficile infection (123–125); indeed, the number of cases of C. difficile colitis has doubled in university hospitals over the past 6 years (126). Recently, evidence of C. difficile infection have been reported in the United States and Canada (127–132); it is suggested that the increasing use of fluoroquinolones has played a role. This strain is associated with higher morbidity and mortality, as it produces significantly more toxins than do the other strains.

The diagnosis of C. difficile colitis is usually made by immunoassays of stool against both toxin A and toxin B. The presence of C. difficile antigen in the absence of the toxin sug-

gests colonization, rather than infection, with C. difficile. Due to the low sensitivity of the toxin assay, two stool specimens should be examined. The cytotoxic assay is more sensitive and specific than the immunoassay; however, this test is not readily available and takes longer to perform. In patients where the diagnosis is still in doubt, colonoscopy may be performed to look for pseudomembranes. CT scan may also be helpful, as 50% of patients will have changes that can be seen on imaging. Positive CT scans are associated with leukocytosis, abdominal pain, and diarrhea (133). If C. difficile colitis is suspected, emp-

tic treatment should be started until the diagnosis is excluded. It is important to note that alcohol-based hand hygiene, which has rapidly gained popularity in many hospitals, does not kill spore-forming organisms such as C. difficile and should not replace handwashing with soap when one is exposed to these patients.

Skin Infections

Skin infections, especially infected pressure ulcers, may be a source of infection in ICU patients. Several factors increase the risk of ICU patients developing pressure ulcers, including (134–136):

- Emergent admissions
- Severity of illness
- Extended ICU length of stay
- Malnutrition
- Age
- Diabetes
- Infusion of vasopressor agents
- Anemia
- Fecal incontinence

Protocols for the prevention of pressure ulcers should be routinely instituted in the ICU. In addition, physicians and nurses should routinely examine their patient’s skin, particularly high-pressure areas such as the sacrum and heels, to detect early signs of skin breakdown.

Chapter 105: An Approach to the Febrile ICU Patient

Other Infections

Nosocomial meningitis is exceedingly uncommon in hospital-
ized patients who have not undergone a neurosurgical proce-
dure (137,138). Lumbar puncture, therefore, does not need to be performed routinely in nonneurosurgical ICU patients who develop a fever, unless they have meningeal signs or contiguous infection (137,138). In patients who have undergone abdomi-
nal surgery and develop a fever, intra-abdominal infection must always be excluded, usually with an evaluation that includes CT scanning of the abdomen. Similarly, in patients who have undergone other operative procedures, wound infection must be excluded.

Noninfectious Causes of Fever in the Intensive Care Unit

A large number of noninfectious conditions result in tissue in-
jury with inflammation and a febrile reaction. Those nonin-
fec tors disorders that should be considered in ICU patients are listed in Table 105.2. For reasons that are not entirely clear, most noninfectious disorders usually do not lead to a fever in excess of 38.5°C (101°F); therefore, if the temperature increases above this threshold, the patient should be consid-
ered to have an infectious etiology as the cause of the fever (139). However, patients with drug fever may have a temper-
at ure greater than 102°F. Similarly, fever secondary to blood transfusion may exceed 102°F. In patients with a temperature above 40°C (104°F), neuroleptic malignant syndrome, malig-
nant hyperthermia, the “serotonin syndrome,” and subarach-

noid hemorrhage must always be considered. Most of those clinical conditions listed in Table 105.2 are clinically obvious and do not require additional diagnostic tests to confirm their presence. However, a few of these disorders require special con-
sideration.

Drug-induced Fever

Most ICU patients receive numerous medications, and all drugs have side effects, including fever. It is estimated that about 10% of inpatients develop drug fever during their hospital stay (140). Patients with human immunodeficiency virus (HIV) ap-
pear to be at a particularly high risk of developing a drug fever (141–143). The diagnosis of drug fever in ICU patients is chal-

lenging, as the onset of fever can occur immediately after ad-
m inistration of the drug or it can occur days, weeks, months, or even years after the patient has been on the offending med-
ication (140). Furthermore, once the implicared medication is discontinuated, the fever can take up to 3 to 4 days to resolve. Associated rashes and leukocytosis occur in less than 20% of cases (144). Pencillins, cephalosporins, anticonvulsants, hep-
arrin, and H2 blockers are commonly used medications in the ICU that are associated with drug fevers (145–148).

Five mechanisms have been described that give rise to drug fevers. First, and the most common mechanism, patients can have a hypersensitivity reaction to the drug. Second, medica-
tions can cause fever by disrupting the normal thermoregu-

latory mechanisms of the body. Third, drugs can cause fever directly related to administration of the drug (e.g., from con-
tamination of the solution with endotoxin or other exogenous pyrogens). The drug can also cause a chemical phlebitis or inflammation at the site of injection. The fourth mechanism
the muscle membrane causing an increase of calcium ions in
Malignant Hyperthermia. This is a rare genetic disorder of
syndrome, and glucose-6-phosphate dehydrogenase deficiency
neuroleptic malignant syndrome, serotonin syndrome typically have very high creatinine ki-
Syndrome, lysis, and the release of various pyrogenic substances. Their neuromuscular findings are
more consistent with hyperreactivity, and can include tremors, gastrointestinal dysfunction. Their neuromuscular findings are
more consistent with hyperreactivity, and can include tremors,
gastrointestinal bleeding. About 60% of patients develop clonus, ocular clonus, agitation or diaphoresis, tremor and hy-
Serotonin Toxicity Criteria are commonly used to evaluate the
likelihood that a patient has the serotonin syndrome. The cri-
teria include the following features in a patient recently ad-
imistered a serotoninergic agent: spontaneous clonus, inducible clonus, oclusus, agitation or diaphoresis, tremor and hy-
Serotonin Syndrome. Serotonin syndrome shares many of the clinical features found in neuroleptic malignant syndrome. Pats-
ents with serotonin syndrome typically have lower fevers than those with neuroleptic malignant syndrome, but have more
gastrointestinal dysfunction. Their neuromuscular findings are more consistent with hyperreactivity, and include tremors,
clonus, muscle spasm, and altered levels of consciousness (156,157); symptoms usually begin within days to weeks of starting the of-
fending drug. Patients typically have very high creatinine ki-
Serotonin syndrome has decreased from 80% in the 1960s to
less than 1% today (155). Neuroleptic Malignant Syndrome. This syndrome is character-
ized by high fevers, a change in mental status, muscle rigidity, extrapyramidal symptoms, autonomic nervous system distur-
bances, and altered levels of consciousness (156,157); symptoms usually begin within days to weeks of starting the of-
fending drug. Patients typically have very high creatinine ki-
Adrenal insufficiency
Agranulocytosis
Neutropenia
Endocrine
Hyperthyroidism
Hyperparathyroidism
Hypothyroidism
Diabetes mellitus
diameter may be beneficial (159,160).
Serotonin syndrome is due to the direct extension of the pharmacologic action of the
drug. This can be seen in chemotherapy with cell necro-
isis, lysis, and the release of various pyrogenic substances. This can also be seen with antimicrobial therapy with the release of bacterial products into the circulation, known as the Jarisch-Herxheimer reaction. Finally, patients can have id-
soyosomatic reactions, which include syndromes such as mali-
gnant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, and glucose-6-phosphate dehydrogenase deficiency (140,148-151).
Malignant Hyperthermia. This is a rare genetic disorder of the muscle membrane causing an increase of calcium ions in
the muscle cells. This can cause a variety of clinical problems, most commonly a dangerous hypermetabolic state after the use of agents such as succinylcholine and the potent inhaled anesthetic agents (152). This reaction typically occurs within 1 hour of anesthesia but can be delayed for up to 10 hours (153,154). Patients present with continually increasing fevers, muscle stiffness, and tachycardia. They can rapidly develop hemodynamic instability with progression to multiorgan fail-
ure. Since the introduction of dantrolene, the mortality of ma-
lignant hyperthermia has decreased from 80% in the 1960s to
less than 10% today (155).

Alcohol and Drug Withdrawal
Withdrawal from alcohol and medications is a common cause of noninfectious fever in hospitalized patients, and usually presents within the first few days of hospital admission. Drug withdrawal can present in a variety of ways including fever

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<th>TABLE 105.2</th>
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<tr>
<td>NONINFECTIOUS CAUSES OF FEVER IN THE INTENSIVE CARE UNIT</td>
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<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
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<tbody>
<tr>
<td>Drug-related</td>
<td>Drug fever, Neuroleptic malignant syndrome</td>
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<td>Malignant hyperthermia</td>
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<td>Serotonin syndrome</td>
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<td>Drug withdrawal (including alcohol and recreational drugs)</td>
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<td>IV contrast reaction</td>
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<td>Posttransfusion Fever</td>
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<tr>
<td>Neurologic</td>
<td>Intracranial hemorrhage, Cerebral infarction, Subarachnoid hemorrhage, Seizures</td>
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<td>Endocrine</td>
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<td>Hyperthyroid</td>
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<td>Paroxysmal seizures</td>
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<td>Rheumatologic</td>
<td>Crystal arthropathies, Vasculitis, Collagen vascular diseases</td>
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<td>Hematologic</td>
<td>Phlebitis, Hematoma</td>
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<td>Gastrointestinal/Hepatic</td>
<td>Acalculus cholecystitis, Ischemic bowel, Cirrhosis, Hepatitis, Gastrointestinal bleed, Pancreatitis</td>
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<tr>
<td>Pulmonary</td>
<td>Aspiration pneumonitis, Acute respiratory distress syndrome, Thromboembolic disease, Fat embolism syndrome</td>
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<tr>
<td>Cardiac</td>
<td>Myocardial infarction, Dresler syndrome, Pericarditis</td>
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<td>Oncologic</td>
<td>Neoplastic syndromes</td>
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Malignant Hyperthermia. This is a rare genetic disorder of the muscle membrane causing an increase of calcium ions in
alone, neuroleptic malignant-like syndromes, and fever with hemodynamic instability. Patients admitted to the ICU are often unable to provide histories and, thus, it is important to get an accurate list of their current medications at the time of admission. Drug withdrawal syndromes have been described with the use of baclofen, selective serotonin reuptake inhibitors (SSRI antidepressants), levodopa, narcotics, certain street drugs, and herbal remedies (169–173).

Crystal-associated Arthritis

Patients in the ICU are at increased risk of developing gout or pseudogout (174). A thorough physical exam focusing on the joints and an arthrocentesis to examine the synovial fluid are essential in making this diagnosis. Gout will typically present as a monoarthritis (174). Patients with increased body mass index, hypertension, alcohol consumption, and renal disease are at an increased risk for gout (175–179). Trauma, surgery, and severe infection are associated with an abrupt drop in uric acid level, which can trigger acute gout (180). Loop diuretics, iodinated contrast dye, and total parenteral nutrition may also precipitate gout (181,182). Calcium pyrophosphate dehydrate crystal deposition disease, also known as pseudogout, most commonly affects the knee. Pseudogout can be triggered by trauma, surgery, or severe medical illness (181–183). Electrolyte disorders such as hypermagnesemia and hypophosphatemia increase the risk for pseudogout. Pseudogout is also associated with endocrine and metabolic disorders such as hyperparathyroidism, hemochromatosis, Wilson disease, and hyperthyroidism (174,184–186).

Acalculous Cholecystitis

Acutely acalculous cholecystitis is a condition of inflammation of the gallbladder in the absence of calculi. It is a disease with significant morbidity and mortality, as it can lead to empyema, gallbladder gangrene, and gallbladder perforation. A high index of suspicion is required as this can be a difficult diagnosis to make, especially in the intubated and sedated patient. Initially patients present with very few symptoms. Clinical features include fever, leukocytosis, abnormal liver function tests, a palpable right upper quadrant mass, vague abdominal discomfort, and a palpable right upper quadrant mass, vague abdominal discomfort. Risk factors include fever, trauma, surgery, and severe medical illness. Notable risk factors for pseudogout include fever, trauma, surgery, and severe medical illness. It is crucial to differentiate these from other causes of infectious and noninfectious fever.

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Surgery alone can cause fever, which is self-limited. In the early postoperative period, a patient’s temperature may increase up to 1.4°C, with the peak occurring approximately 11 hours after surgery. Fifty percent of postoperative patients will develop a fever greater than or equal to 38°C, with 25% reaching 38.5°C or higher (200); the fever typically lasts for 2 to 3 days (200–202). Postoperative fever is believed to be caused by tissue injury and inflammation with associated cytokine release (203–205). The invasiveness of the procedure, as well as genetic factors, influences the degree of cytokine release and the febrile response (201,206,207). A good physical examination and history of the timing and sequence of events are crucial to help differentiate this from other causes of infectious and noninfectious fever. Reactions to medications, especially anesthesiology and blood products; and infections that might have existed prior to the surgery should be considered during a patient’s early postoperative course. Nosocomial and surgical site infections usually develop 3 to 5 days postoperatively.

Atelectasis

While atelectasis is commonly implicated as a cause of fever (38,208), even in standard ICU texts, they provide no primary reference source to support this assertion (38,208). Indeed, a major surgery text states that “…fever is almost always present (in patients with atelectasis)…” (38). During rounds, many medical students and house-staff have been taught that atelectasis is one of the “five” main causes of postoperative fever. However, there are very little data to support this widely held belief.

Engoren studied 100 postoperative cardiac surgery patients and was unable to demonstrate a relationship between atelectasis and fever (209). Furthermore, when atelectasis is induced in experimental animals by ligation of a mainstem bronchus, fever does not occur (210,211). However, Kisaal et al. demonstrated that IL-1 and TNF-α levels in macrophage cultures from atelectatic lungs were significantly increased compared with control lungs (212). While the role of atelectasis as a cause of fever is unclear, atelectasis probably does not cause fever in the absence of pulmonary infection.

Blood Transusions

A large number of patients in the ICU will receive transfusions of blood products. One study composed of 4,392 ICU patients demonstrated that 44% received a blood transfusion (213). In another study, 85% of patients in the ICU for longer than 1 week were reported to receive a blood transfusion (214). Febrile, nonhemolytic transfusion reactions are exceedingly common following transfusion of blood and blood products. This is likely mediated by the transfusion of cytokines such as IL-1, IL-6, IL-8, and TNF-α, which accumulate with increasing length of blood storage (215–218).

Febrile, nonhemolytic reactions normally manifest within the first 6 hours after transfusion, and are self-limiting. They can present with chills and rigors in addition to fever. It is crucial to differentiate these from febrile acute hemolytic transfusion reactions, which can be life threatening.
Leukoreduction has been shown to reduce the risk of febrile nonhemolytic transfusion reactions (219–221).

Thromboembolic Disease
Fever has been reported in 14% to 18% of patients with thromboembolic disease, and is generally an uncommon cause of fever in hospitalized patients (222–224). If present, the fever is typically low grade (37.5°C–38°C) (225).

AN APPROACH TO THE CRITICALLY ILL PATIENT WITH FEVER

From the foregoing information, the following approach is suggested in ICU patients who develop a fever (see Fig. 107.1). Due to the frequency and excess morbidity and mortality associated with bacteremia, blood cultures are recommended in all ICU patients who develop a fever. A comprehensive physical examination and review of the chest radiograph is essential. Noninfectious causes of fever should be excluded. In patients with an obvious focus of infection—purulent nasal discharge, abdominal tenderness, profuse green diarrhea—a focused diagnostic workup is required. If there is no clinically obvious source of infection, and unless the patient is clinically deteriorating—falling blood pressure, decreased urine output, increasing confusion, rising serum lactate concentration, falling platelet count, or worsening coagulopathy—or the temperature is in excess of 39°C (102°F), it may be prudent to perform blood cultures and then observe the patient before embarking on the further diagnostic tests and commencing empiric antibiotics. However, all neutropenic patients with fever, as well as patients with severe—as outlined above—or progressive signs of sepsis should be started on broad-spectrum antimicrobial therapy immediately after obtaining appropriate cultures.

In patients whose clinical picture is consistent with infection and in whom no clinically obvious source has been documented, removal of all central catheters that are more than 48 hours old—with semiquantitative or quantitative cultures performed on the intracutaneous segments—is recommended, as is stool culture for *Clostridium difficile* toxin in those patients with loose stools and CT scan of sinuses with removal of all nasal tubes. Urine culture is indicated only in patients with abnormalities of the renal system or following urinary tract manipulation. If the patient is at risk of abdominal sepsis or has any abdominal signs—tenderness, distention, inability to tolerate enteral feeds—a CT scan of the abdomen is indicated. Patients with right upper quadrant tenderness require an abdominal ultrasound or CT examination.

Reevaluation of the patients’ status after 48 hours, using all available results and the evolution of the patients’ clinical condition, is essential. If fever persists despite empiric antibiotics and no source of infection has been identified, empiric antifungal therapy may be indicated in patients with risk factors for
Candida infection. Additional diagnostic tests may be appro-
appropriate at this time, including venography, a differential blood
count for eosinophils to assist in the diagnosis of drug fever,
and abdominal imaging.

SUMMARY

Intensive care physicians are presented with patients who de-
velop a fever on a daily basis. The clinician should be aware of the
common infectious and noninfectious causes of fever in ICU
patients. A comprehensive history and physical examination as
well as a review of the patient's hospital course and medica-
tions are essential in formulating a diagnostic and therapeutic
care plan. Antibiotics are only recommended in patients with a
high likelihood of having an infectious cause of fever. The empiric
antibiotics should be based on the presumed site of infection
as well as the likely pathogens. De-escalation of the antibiotic
regimen is important once culture data are available. As a gen-
eral rule, patients with an infective cause of fever should not
be treated with antipyretic agents.

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Chapter 105: An Approach to the Febrile ICU Patient
CHAPTER 106  ■  SURGICAL INFECTIONS

PHILIP S. BARRE • FREDERIC M. PIERACCI • SOUMITRA R. EACHEMPATI

Infection is morbid and costly, but also preventable to some degree; therefore, it behooves every practitioner to do the utmost to prevent infection. An ensemble of prevention methods is recommended because no single method is universally effective. Infection control is paramount, but often underemphasized. Surgical incisions and traumatic wounds must be handled gently, inspected daily, and dressed if necessary using aseptic technique. Surgical incisions and traumatic wounds must be handled gently. Infection is morbid and costly, but also preventable to some degree.

Infection is morbid and costly, but also preventable to some degree. Surgical incisions and traumatic wounds must be handled gently, inspected daily, and dressed if necessary using aseptic technique. Surgical incisions and traumatic wounds must be handled gently. Infection is morbid and costly, but also preventable to some degree. Surgical incisions and traumatic wounds must be handled gently, inspected daily, and dressed if necessary using aseptic technique. Surgical incisions and traumatic wounds must be handled gently. Infection is morbid and costly, but also preventable to some degree.

Surgical patients are at particular risk of infection for many reasons. Surgery is inherently invasive, which creates portals (MDR) pathogens. Antibiotics should be used sparingly so as to minimize antibiotic resistance. Prophylactic and therapeutic techniques. Drains and catheters must be avoided if possible, and removal as soon as practicable. Prophylactic and therapeutic techniques. Drains and catheters must be avoided if possible, and removal as soon as practicable. Prophylactic and therapeutic techniques. Drains and catheters must be avoided if possible, and removal as soon as practicable. Prophylactic and therapeutic techniques. Drains and catheters must be avoided if possible, and removal as soon as practicable. Prophylactic and therapeutic techniques. Drains and catheters must be avoided if possible, and removal as soon as practicable. Prophylactic and therapeutic techniques. Drains and catheters must be avoided if possible, and removal as soon as practicable.