Fever in the ICU*

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Fever is a common problem in ICU patients. The presence of fever frequently results in the performance of diagnostic tests and procedures that significantly increase medical costs and expose the patient to unnecessary invasive diagnostic procedures and the inappropriate use of antibiotics. ICU patients frequently have multiple infectious and noninfectious causes of fever, necessitating a systematic and comprehensive diagnostic approach. Pneumonia, sinusitis, and bloodstream infection are the most common infectious causes of fever. The urinary tract is unimportant in most ICU patients as a primary source of infection. Fever is a basic evolutionary response to infection, is an important host defense mechanism and, in the majority of patients, does not require treatment in itself. This article reviews the common infectious and noninfectious causes of fever in ICU patients and outlines a rational approach to the management of this problem.

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Key words: cytokines; fever; ICU; sinusitis; urinary tract infection; ventilator-associated pneumonia

Abbreviations: CDC = Centers for Disease Control and Prevention; CFU = colony-forming units; ELISA = enzyme-linked immunosorbent assay; IL = interleukin; TNF = tumor necrosis factor; UTI = urinary tract infection; VAP = ventilator-associated pneumonia

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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 (IL) 1, IL-6, and tumor necrosis factor (TNF)-α.2–13 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.2,3 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 liberation of prostaglandin E2. This small lipid mediator diffuses across the blood brain barrier, where it acts to decrease the rate of firing of preoptic warm-sensitive neurons, leading to activation of responses designed to decrease heat loss and increase heat production.2,14 In a small proportion of hospitalized patients, hyperthermia may result from increased sympathetic activity with increased heat production.

Significance of Fever

Fever appears to be a preserved evolutionary response within the animal kingdom.15–20 With few exceptions, reptiles, amphibians, and fish, as well as several invertebrate species, have been shown to manifest fever in response to challenge with microorganism.15–19 Increased body temperature has been
shown to enhance the resistance of animals to infection.\textsuperscript{21,22} Although fever has some harmful effects, fever 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.\textsuperscript{23–26} Furthermore, some pathogens such as *Streptococcus pneumoniae* are inhibited by febrile temperatures.\textsuperscript{27}

It has long been known that increasing body temperature is associated with improved outcome from infectious diseases. The preantibiotic era provides abundant, although uncontrolled data, on the deliberate use of elevated body temperature to treat infections. The beneficial effects of hot baths and malarial fevers in syphilis were noted as early as the 15th century.\textsuperscript{28} In mammalian models, increasing body temperature results in enhanced resistance to infection.\textsuperscript{28–32} In a retrospective analysis of 218 patients with Gram-negative bacteremia, Bryant and colleagues\textsuperscript{33} reported a positive correlation between maximum temperature on the day of bacteremia and survival. Similarly, Weinstein and colleagues\textsuperscript{34} reported that a temperature > 38°C increased survival in patients with spontaneous bacterial peritonitis. Dorn and colleagues\textsuperscript{35} reported that children with chickenpox who were treated with acetaminophen had a longer time to crusting of lesions than when treated with placebo.

An elevated body temperature may, however, also be associated with a number of deleterious effects, most notably an increase in cardiac output, oxygen consumption, carbon dioxide production, and energy expenditure.\textsuperscript{36} Oxygen consumption increases by approximately 10% per degree Celsius.\textsuperscript{36} These changes may be poorly tolerated in patients with limited cardiorespiratory reserve. In patients who have suffered a cerebrovascular accident or traumatic head injury, moderate elevations of brain temperature may markedly worsen the resulting injury.\textsuperscript{37} Maternal fever has been suggested to be a cause of fetal malformations or spontaneous abortions.\textsuperscript{38,39} However, this association has not been rigorously tested.

**Definitions and Measurement of Fever**

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, 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.\textsuperscript{40–42} 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.\textsuperscript{43–46} Rectal temperatures obtained with a mercury thermometer or electronic probe are often a few tenths of a degree higher than core temperature.\textsuperscript{47–49} Rectal temperatures are perceived by patients 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.\textsuperscript{43} Axillary measurements substantially underestimate core temperature and lack reproducibility.\textsuperscript{33} Body temperature is therefore most accurately measured by an intravascular thermistor, but measurement by infrared ear thermometry or with an electronic probe in the rectum is an acceptable alternative.\textsuperscript{47} Normal body temperature is generally considered to be 37.0°C (98.6°F) with a circadian variation of between 0.5 to 1.0°C.\textsuperscript{2,14} The definition of fever is arbitrary and depends on the purpose for which it is defined. The Society of Critical Care Medicine practice parameters define fever in the ICU as a temperature > 38.3°C (≥ 101°F).\textsuperscript{47} Unless the patient has other features of an infectious process, only a temperature > 38.3°C (≥ 101°F) warrants further investigation.

**Fever Patterns**

Attempts to derive reliable and consistent clues from evaluation of a patient’s fever pattern is fraught with uncertainty and not likely to be helpful diagnostically.\textsuperscript{2,14,48} Most patients have remittent or intermittent fever that, when due to infection, usually follow a diurnal variation.\textsuperscript{48} Sustained fevers have been reported in patients with Gram-negative pneumonia or CNS damage.\textsuperscript{48} 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 > 48 h after institution of mechanical ventilation may be secondary to a developing pneumonia.\textsuperscript{49,50} Fevers that arise 5 to 7 days postoperatively may be related to abscess formation.\textsuperscript{51} Fevers that arise 10 to 14 days postinstitution antibiotics for intra-abdominal abscess may be due to fungal infections.\textsuperscript{52–54}

**Causes of Fever in the ICU**

As outlined above, 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 the commonest cause of fever in ICU patients, many noninfectious inflammatory conditions cause the release of the proinflammatory cytokines with a febrile response.\(^{55-61}\) Similarly, it is important to appreciate that not all patients with infections are febrile. Approximately 10% of septic patients are hypothermic and 35% are normothermic at presentation. Septic patients who fail to develop a temperature have a significantly higher mortality than febrile septic patients.\(^{62-64}\) 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.\(^{65}\)

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 patient be evaluated in a systematic, prudent, clinically appropriate, and cost-effective manner.

**Noninfectious Causes of Fever in the ICU**

A large number of noninfectious disorders result in tissue injury with inflammation and a febrile reaction. Those noninfectious disorders that should be considered in ICU patients are listed in Table 1.\(^{1,55,66-68}\) For reasons that are not entirely clear, most noninfectious disorders usually do not lead to a fever > 38.9°C (102°F); therefore, if the temperature increases above this threshold, the patient should be considered to have an infectious etiology as the cause of the fever.\(^{67}\) However, patients with drug fever may have a temperature > 102°F.\(^{69-71}\) Similarly, fever secondary to blood transfusion may be > 102°F.\(^{72,73}\)

Most of those clinical conditions listed in Table 1 are clinically obvious and do not require additional diagnostic tests to confirm their presence. However, a few of these disorders require special consideration. Although drug-induced fever is commonly cited as a cause of fever,\(^{74}\) < 300 cases of this condition have been reported in the literature.\(^{70}\) Furthermore, only a single case of drug fever has been reported in an ICU patient population.\(^{1}\) However, on the basis of the number of medications administered to patients in the ICU, one would expect drug fever to be a relatively common event. Although the true incidence of this disorder is unknown, drug fever should be considered in patients with an otherwise unexplained fever, particularly if they are receiving β-lactam antibiotics, procainamide, or diphenylhydantoin.\(^{70}\) Drug fever is usually characterized by high spiking temperatures and shaking chills.\(^{70}\) It may be associated with leukocytosis and eosinophilia. Relative bradycardia, although commonly cited, is uncommon.\(^{67,70,74}\)

Atelectasis is commonly implicated as a cause of fever. Standard ICU texts list atelectasis as a cause of fever, although they provide no primary source.\(^{51,75}\) Indeed a major surgery text states that “fever is almost always present [in patients with atelectasis].”\(^{71}\) However, Engeron\(^{76}\) studied 100 postoperative cardiac surgery patients and was unable to demonstrate a relationship between atelectasis and fever. Furthermore, when atelectasis is induced in experimental animals by ligation of a mainstem bronchus, fever does not occur.\(^{77,78}\) However, Kisala and coworkers\(^{79}\) demonstrated that IL-1 and TNF-α levels of macrophage cultures from atelectatic lungs were significantly increased compared with the control lungs. The role of atelectasis as a cause of fever is unclear; however, atelectasis probably does not cause fever in the absence of pulmonary infection.

Fever reactions complicate about 0.5% of blood transfusions, but may be more common following platelet transfusion.\(^{72,80,81}\) Antibodies against membrane antigens of transfused leukocytes and/or platelets are responsible for most febrile reactions to cellular blood components.\(^{72}\) Febrile reactions usually begin within 30 min to 2 h after a blood-product transfusion is begun. The fever generally lasts be-

| Table 1—Noninfectious Causes of Fever in the ICU |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Noninfectious Causes |
| Alcohol/drug withdrawal |
| Postoperative fever (48 h postoperative) |
| Posttransfusion fever |
| Drug fever |
| Cerebral infarction/hemorrhage |
| Adrenal insufficiency |
| Myocardial infarction |
| Pancreatitis |
| Acute ulcer of cholecystitis |
| Ischemic bowel |
| Aspiration pneumonitis |
| ARDS (both acute and late fibroproliferative phase) |
| Subarachnoid hemorrhage |
| Fat emboli |
| Transplant rejection |
| Deep venous thrombosis |
| Pulmonary emboli |
| Gout/pseudogout |
| Hematoma |
| Cirrhosis (without primary peritonitis) |
| GI bleed |
| Phlebitis/thrombophlebitis |
| Adrenal insufficiency |
| IV contrast reaction |
| Neoplastic fevers |
| Decubitus ulcers |
between 2 h and 24 h and may be preceded by chills. An acute leucocytosis lasting up to 12 h commonly occurs following a blood transfusion.

Patients with the ARDS may progress to a "chronic" stage characterized by pulmonary fibroprolifera
tion and fevers. Meduri and coworkers have demonstrated that fever and leukocytosis may result from the inflammatory-fibrotic process present in the airspace of patients with late ARDS in the absence of pulmonary infection. Corticosteroids appear to be associated with an improvement in lung injury and reduced mortality. Some authors recommend an open lung biopsy prior to commencing corticosteroid therapy, in order to obtain histologic evidence of the fibroproliferative phase of ARDS and to exclude infection.

Acalculous cholecystis occurs in approximately 1.5% of critically ill patients. While relatively uncommon, acalculous cholecystitis is an important "noninfectious" cause of fever in critically ill patients, as it is frequently unrecognized and therefore potentially life threatening. The pathophysiology of acalculous cholecystitis is related to the complex interplay of a number of pathogenetic mechanisms, including gallbladder ischemia, bile stasis with inpis
ation in the absence of stimuli for emptying of the gallbladder, positive-end expiratory pressure, and parenteral nutrition. Bacterial invasion of the gallbladder appears to be a secondary phenomenon.

The diagnosis of acalculous cholecystitis is often exceedingly difficult and requires a high index of suspicion. Pain in the right upper quadrant is the finding that most often leads the clinician to the correct diagnosis, but it may frequently be absent. Nausea, vomiting, and fever are other associated clinical features. The clinical findings and laboratory workup in patients with acalculous cholecystitis are, however, often nonspecific. The most difficult patients are those recovering from abdominal sepsis who deteriorate again, misleadingly suggesting a flare-up of the original infection. Rapid diagnosis is essential because ischemia may progress rapidly to gangrene and perforation, with attendant increase in the already high morbidity and mortality. The diagnosis should therefore be considered in every critically ill patient who has clinical findings of sepsis with no obvious source.

Radiologic investigations are required for a presumptive diagnosis of acalculous cholecystitis. Ultrasound is the most common radiologic investigation used in the diagnosis of acalculous cholecystitis; features include increased wall thickness, intramural luccencies, gallbladder distension, pericholecystic fluid, and intramural sludge. Wall thickness ≥ 3 mm is reported to be the most important diagnostic feature on ultrasound examination, with a specificity of 90% and a sensitivity of 100%. In ICU patients, hepatobiliary scintigraphy has a high false-positive rate (> 50%), limiting the value of this test. However, a normal scan virtually excluded acalculous cholecystitis. CT scanning has been reported to have a high sensitivity and specificity; however, no prospective studies have been performed comparing ultrasonography with CT scanning in the diagnosis of acalculous cholecystitis.

The management of acalculous cholecystitis is somewhat controversial. However, with the development of more advanced radiologic imaging techniques, percutaneous cholecystostomy may be the procedure of choice. It has been reported to have a high sensitivity and specificity; however, no prospective studies have been performed comparing ultrasonography with CT scanning in the diagnosis of acalculous cholecystitis.

While fever may occur in patients with deep venous thrombosis, in patients suspected of deep venous thrombosis, the predictive value of fever is poor. Furthermore, in critically ill ICU patients, fever without other features of ileofemoral thrombosis is uncommon and does not warrant routine venography as part of the initial diagnostic workup of pyrexia in ICU patients.

**Infectious Causes of Fever**

The prevalence of nosocomial infection in ICUs has been reported to vary from 3 to 31%. Data from the National Nosocomial Infection Surveillance system database from 1986 to 1990 documented nosocomial infection in 10% of the 164,034 patients, with a strong correlation between ICU length of stay and the development of infection. In a point prevalence study conducted in 1992, The EPIC Study Investigators reported on the prevalence of nosocomial infections in 10,038 patients hospitalized in 1,417 European ICUs. In this study, 20.6% of patients had an ICU-acquired infection, with pneumonia being the most common (46.9%), followed by urinary tract infection (17.6%) and blood stream infection (12%). This data must, however, be interpreted with some caution. The presence and type of infection in these studies was documented according to the "standard definitions" of the Centers for Disease Control and Prevention (CDC). The definitions of nosocomial infection published by the...
CDC may, however, not be applicable to ICU patients. For example, according to the most recent definitions published in 1988, the presence of rales and purulent sputum or the presence of new chest radiographic findings and change in sputum character were used to diagnose pneumonia. In patients receiving mechanical ventilation, less than a third of patients with these features would be considered to have pneumonia using invasive diagnostic methods. Similarly, fever and a urine culture of $ \geq 10^5$ colony-forming units (CFU)/mL was considered diagnostic of urinary tract infection. As is discussed below, the presence of these two finding in catheterized critically ill ICU patients does not represent infection of the urinary tract.

The most common infections reported in ICU patients are pneumonia, followed by sinusitis, bloodstream infection, and catheter-related infection. Table 2 lists the most important sites of infection in ICU patients. As is discussed below, urinary tract infection is probably unimportant in most ICU patients.

### Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) occurs in approximately 25% of patients undergoing mechanical ventilation. The impact of VAP on patient outcome has been much debated, however, Fagon and colleagues reported an attributable mortality of 27%. The optimal management of patients with suspected VAP requires confirmation of the diagnosis and identification of the responsible pathogen(s) in order to provide appropriate antimicrobial therapy. The diagnosis of VAP remains one of the most difficult clinical dilemmas in critically ill patients receiving mechanical ventilation. Clinical criteria alone have been shown to be unreliable in the diagnosis of this condition. A number of invasive and minimally invasive techniques have been reported to aid in the diagnosis of VAP. The number of methods currently available attest to the fact that no single method is ideal.

### Table 2—Common Infectious Causes of Fever in the ICU

<table>
<thead>
<tr>
<th>Infectious Causes</th>
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<tbody>
<tr>
<td>VAP</td>
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<tr>
<td>Sinusitis</td>
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<tr>
<td>Catheter-related sepsis</td>
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<tr>
<td>Primary Gram-negative septicemia</td>
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<tr>
<td><em>C. difficile</em> diarrhea</td>
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<tr>
<td>Abdominal sepsis</td>
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<td>Complicated wound infections</td>
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The optimal technique(s) for diagnosis of VAP remains unclear as a uniformly agreed on “gold standard,” for the diagnosis is lacking. The impact that diagnostic tests for VAP have on patient outcome is controversial. Using a decision analysis method, Sterling and coauthors demonstrated that invasive or semi-invasive microbiological diagnostic techniques improved the outcome of patients with suspected VAP. However, Luna and colleagues and Rello and coworkers have demonstrated that the most important factor affecting outcome in patients with VAP is the early initiation of appropriate antibiotic therapy. In the study by Luna et al., the mortality of patients who were changed from inadequate antibiotic therapy to appropriate therapy based on the results of the BAL was comparable to the mortality of those patients who continued to receive inadequate therapy. Kollef and Ward, using noninvasive mini-BAL to diagnose VAP, confirmed these findings. It should however be noted that patients who have clinical features of VAP and in whom VAP is “excluded” based on quantitative culture of lower respiratory tract secretions and in whom antibiotics are stopped have a significantly lower mortality than those patients who are culture positive. Invasive or noninvasive sampling of lower respiratory tract sections with quantitative culture therefore allows for the safe discontinuation of antibiotics in the “culture negative” patients. Furthermore, as the initial empiric antibiotic regimen must be broad and cover both Gram-positive and negative organisms, these techniques allow for narrowing of the spectrum once a pathogen has been isolated in those patients with confirmed pneumonia. This approach to suspected VAP will result in significant cost savings and reduce the selection of resistant organisms.

### Sinusitis

Because paranasal sinusitis is usually clinically silent in intubated patients, it is not widely appreciated that nosocomial sinusitis is an important source of infection and fever in critically ill patients. Furthermore, many ear, nose, and throat surgeons are of the belief that paranasal sinusitis in intubated patients receiving mechanical ventilation does not cause fever or systemic signs of infection. Nosocomial sinusitis is particularly common following nasal intubation, with an incidence of up to 85% after a week of intubation. The incidence of nosocomial sinusitis appears to be lower in patients in whom both the endotracheal and gastric tubes are placed orally. The diagnosis of sinusitis requires a CT scan and cannot be accurately assessed.
Catheter-Associated Sepsis

Catheter-associated sepsis is defined as blood stream infection due to an organism that has colonized a vascular catheter. Approximately 5% of patients with indwelling vascular catheters (uncoated) will develop blood stream infection (∼10 infections/1,000 catheter days). The incidence of catheter-associated sepsis increases with the length of time the catheter is in situ, the number of ports, and increases with the number of manipulations. Approximately 25% of central venous catheters become colonized (> 15 CFU), and approximately 20 to 30% of colonized catheters will result in catheter sepsis.

Staphylococcus aureus and coagulase-negative staphylococci are the most common infecting (and colonizing) organisms, followed by enterococci, Gram-negative bacteria, and Candida species.

A number of methods of reducing catheter colonization and blood stream infection have been studied, including topical antibiotics, antimicrobial flush solutions, subcutaneous tunneling of catheters, and silver-impregnated subcutaneous cuffs. These studies have generally shown poor or inconsistent results. It has been suggested that antimicrobial bonding of central venous catheters may be the most effective method of reducing the rate of catheter colonization and catheter-related sepsis.

Several types of antiseptic or antimicrobial coatings have been developed, including catheters coated with chlorhexidine gluconate and silver sulfadiazine, as well as with minocycline and rifampin. While a number of studies have demonstrated the incidence of catheter-related sepsis to be lower with chlorhexidine/sulfadiazine-coated catheters, not all studies have duplicated these findings. Furthermore, Darouiche and colleagues have demonstrated that central venous catheters impregnated with minocycline and rifampin are associated with a significantly lower rate of catheter colonization and bloodstream infection than catheters coated with chlorhexidine and silver sulfadiazine.

Central venous catheterization via the femoral and internal jugular veins are reported to have a similar infection rates, which are higher than that for catheters inserted via the subclavian approach. Replacement of a colonized catheter over a guidewire is associated with rapid recolonization of the replacement catheter. If catheter sepsis is suspected, the catheter should be changed to a new site, with culture (quantitative or semiquantitative) of the catheter tip. In patients with limited venous access or in patients in whom catheter sepsis is less likely, the catheter can be changed over a guidewire; however, withdrawal blood cultures and culture of the catheter tip should be performed and the catheter removed if the cultures are positive.

Urinary Tract Infection

Urinary tract infections (UTIs) have been reported to be common in ICU patients, where they are reported to account for between 25 to 50% of all infections. However, it is likely that most of these patients had “asymptomatic bacteriuria” rather than true infections of the urinary tract. The use of antibiotics in patients with asymptomatic bacteriuria is based on a single study performed in the early 1980s that may not be applicable today. Platt and colleagues demonstrated that in hospitalized patients bacteriuria with ≥ 10^5 CFUs of bacteria per milliliter of urine during bladder catheterization was associated with a 2.8-fold increase in mortality. Based on this study, thousands of ICU patients with urinary tract colonization have been treated with antibiotics.

Most ICU patients require an indwelling urinary...
Catheter for monitoring fluid balance and renal function. The patients’ colonic flora rapidly colonizes the urinary tract in these patients. Stark and Maki have demonstrated that in catheterized patients, bacteria in the urinary system rapidly proliferate to exceed 10^5 CFU/mL over a short period of time. Bacteriuria, defined as a quantitative culture of ≥ 10^5 CFU/mL, has been reported in up to 30% of catheterized hospitalized patients. The terms “bacteriuria” and “UTI” are generally although incorrectly used as synonyms. Indeed, most studies in ICU patients have used bacteriuria to diagnose a UTI. Bacteriuria implies colonization of the urinary tract without bacterial invasion and an acute inflammatory response. UTI implies an infection of the urinary tract. 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. It is therefore unclear how many catheterized patients with > 10^5 CFU/mL actually have UTI.

While catheter-associated bacteruria is common in ICU patients, data for the early 1980s indicates that < 3% of catheter-associated bacteriuric patients will develop bacteremia caused by organisms in the urine. Therefore, the surveillance for and treatment of isolated bacteriuria in most ICU patients is currently not recommended. Bacteriuria should, however, be treated following urinary tract manipulation or surgery, in patients with kidney stones, and in patients with urinary tract obstruction.

**Clostridia difficile Colitis**

*C difficile*, the agent that causes pseudomembranous colitis and antibiotic-associated diarrhea, has become a common nosocomial pathogen. Approximately 20% of all hospitalized patients become “infected” with *C difficile*, of whom only about a third develop diarrhea. The majority of hospital inpatients infected with *C difficile* are asymptomatic. *C difficile* infection commonly presents with mild to moderate diarrhea, sometimes accompanied by lower abdominal cramping. Symptoms usually begin during or shortly after antibiotic therapy but are occasionally delayed for several weeks. Severe colitis without pseudomembrane formation may occur with profuse, debilitating diarrhea, abdominal pain, and distension. Common systemic manifestations include fever, nausea, anorexia, and malaise. A neutrophilia and increased numbers of fecal leukocytes are common. Pseudomembranous colitis is the most dramatic manifestation of *C difficile* infection; these patients have marked abdominal and systemic signs and symptoms and may develop a fulminant and life-threatening colitis.

Stool assay for toxins A or B are the main clinical tests used to diagnose *C difficile* infection. The “gold standard” test is the tissue culture cytotoxicity assay. This test has a high sensitivity (94 to 100%) and specificity (99%). The major disadvantages of this test are its high expense and the time needed to complete the assay (2 to 3 days). For these reasons, this test is no longer routinely performed. Toxin enzyme-linked immunosorbent assay (ELISA) tests are less sensitive (70 to 90%) than the cytotoxicity test, but demonstrate excellent specificity (99%) and can be rapidly processed, and have largely replaced the cytotoxicity assay. It is suggested that two stool specimens be examined for leukocytes and toxin ELISA test. Should the ELISA be negative and a high index of suspicion for *C difficile* exist, the following are recommended: (1) sigmoidoscopy, and/or (2) cytotoxicity assay, and/or (3) CT scan of abdomen looking for thickened colonic wall.

**Candida Infections**

Candida species are important opportunistic pathogens in the ICU. The CDC National Nosocomial Infection Study reported that 7% of all nosocomial infections were due to candidal species. In the EPIC study, 17% of nosocomial ICU infections were due to fungi. Candida infections should be considered in febrile ICU patients who have been in the ICU for > 10 days and have received multiple courses of antibiotics. Candida species are particularly important pathogens in patients with ongoing peritonitis. It is important to realize that Candida species are constituents of the normal flora in about 30% of all healthy people. Antibiotic therapy increases the incidence of colonization by up to 70%. It is probable that most ICU patients become colonized with Candida species soon after admission. Not all patients colonized with Candida will become infected with Candida. Nonneutropenic patients with isolation of Candida species from pulmonary samples (tracheal aspirates, bronchoscopy or blind sampling methods), even in high concentrations, are unlikely to have invasive candidiasis. Indication for initiation of antifungal therapy in these patients should be based on histologic evidence or identification from sterile specimens. Similarly, isolation of Candida species from the urine in ICU patients with indwelling catheters usually represents colonization rather than infection. Although candiduria may be
observed in up to 80% of patients with systemic candidiasis, candidemia from a urinary tract source is extremely rare.54

**OTHER INFECTIONS**

Nosocomial meningitis is exceedingly uncommon in hospitalized patients who have not undergone a neurosurgical procedure.196,197 Lumbar puncture, therefore, need not be performed routinely in ICU patients (nonneurosurgical) who develop a fever unless they have meningeal signs or contiguous infection.196,197 In patients who have undergone abdominal surgery and develop a fever, intra-abdominal infection must always be excluded. CT scanning of the abdomen is indicated in these patients. Similarly, in patients who have undergone other operative procedures, wound infection must be excluded.

**DIAGNOSTIC EVALUATION**

It is important that blood cultures as well as other appropriate cultures be performed before the initiation of antibiotic therapy. The impact of antibiotic therapy on culture positivity is illustrated in patients with suspected VAP, where a number of studies have demonstrated that both prior and current antibiotic therapy reduces the predictive accuracy of invasive diagnostic testing.198,199

**BLOOD CULTURES**

Bacteremia and candidemia have been documented in up to 10% of ICU patients and are an important cause of morbidity and mortality in the ICU.200–203 Blood cultures are therefore indicated in all febrile patients. Surveillance blood cultures, however, are expensive and add very little to the management of patients in the ICU.204 Bennett and Beeson205 reported that the presence of microorganisms in the blood is the initiating event leading to fever and chills 1 to 2 h later, and that blood cultures are frequently negative at the time of the temperature spike. Thus blood cultures are ideally drawn prior to the onset of a temperature spike. In reality, this is not possible; therefore, spreading out the collection of blood cultures increases the likelihood of blood collection during bacteremia. It is therefore recommended that at least two and no more than three sets of blood cultures should be obtained by separate needle sticks from different venipuncture sites.206 Colonization of the lumen of central venous catheters occurs within a short period of time after placement. Therefore, blood cultures should not be obtained through intravascular catheters unless the catheter has been recently placed.207

The volume of blood drawn in adult patients is the single most important factor governing the sensitivity of blood cultures.180,206,208,209 Therefore, it is recommended that a minimum of 10 mL and preferably 20 mL of blood be removed per draw divided among the minimum number of blood culture containers as recommended by the manufacturer.150,206,209,209 Resin-containing medium offers little clinical benefit to the majority of ICU patients.210 Once bloodstream infection is identified, repeated or follow-up cultures are not necessary in most cases. Subsequent blood cultures may be justified in patients who deteriorate clinically or those who fail to improve despite therapy. However in some cases bacteremia may be prolonged, necessitating further blood cultures during treatment (eg, staphylococcal bacteremia).

**SCINTIGRAPHY, CT SCANNING, AND ULTRASOUND EXAMINATIONS**

Scintigraphic scanning techniques have a low sensitivity and specificity in ICU patients and are therefore not recommended.1,211,212 The advantages of CT scanning and/or ultrasound over scintigraphy is that the results of the test can be obtained immediately with superior anatomic resolution, which can be used to guide drainage procedures.

**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 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 infections (eg, 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 BP, decreased urine output, increasing confusion, rising serum lactate concentration, falling platelet count, or worsening coagulopathy), or the temperature is > 39°C (102°F), it may be prudent to perform blood cultures and then observe the patient before embarking on further diagnostic tests and commencing empiric
antibiotics. However, all neutropenic patients with fever and 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 lines > 48 h old (with semiquantitative or quantitative culture) is recommended as well as stool for WBC count and C difficile toxin in those patients with loose stools, and CT scan of the 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, distension, unable to tolerate enteral feeds) CT scan of abdomen is indicated. Patients with right upper quadrant tenderness require an abdominal ultrasound.

Reevaluation of the patient’s status after 48 h 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 if the patient has risk factors for candidal infection. Additional diagnostic tests may be appropriate at this time, including venography, a differential blood count for eosinophils (diagnosis of drug fever), and abdominal imaging.

TREATMENT OF FEVER IN THE ICU

Almost all febrile ICU patients are treated with acetaminophen and external cooling methods to render the patients “afebrile.” However, fever is a basic evolutionary response to infection and may be an important host defense mechanism. The preponderance of evidence suggests that temperature in the range of the usual fever renders host defenses more active and many pathogens more susceptible to these defenses. Therefore, it seems illogical to treat fever per se. In addition, temperature is an important physical sign, allowing the physician to monitor the response to treatment. Furthermore, acute hepatitis may occur in ICU patients with reduced glutathione reserves (alcoholics, malnourished, etc.) who have received regular therapeutic doses of acetaminophen. Based on this data, it is recommended that febrile episodes not be routinely treated with antipyretic therapy; an evaluation of the relative benefits and risks of antipyretic treatment should be evaluated in each individual case. Fever should, however, be treated in patients with acute brain insults, patients with limited cardiorespiratory reserve (ie, ischemic heart disease), and in patients in whom the temperature increases above 40°C (104°F).2,14,37,213–217

Hypothermia blankets are frequently used in ICU patients with febrile episodes.218 However, studies have demonstrated that hypothermia blankets are no more effective in cooling patients than are antipyretic agents.218 Furthermore, the use of hypothermia blankets is associated with large temperature fluctuations and rebound hyperthermia.218 In addition, there is a fundamental illogic to the use of external application of cold to lower temperature in a patient with true fever. Because of the altered hypothalamic set point, the patient is already responding as if to a cold environment. External cooling may result in augmented hypermetabolism and a persistent fever. Indeed, Lenhardt and colleagues219 demonstrated that active external cooling in volunteers with induced fever increased oxygen consumption by 35 to 40% and was associated with a significant increase in epinephrine and norepinephrine levels.

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