Thirty percent of medical patients will become febrile during their hospitalization, while up to 90% of critically ill patients with severe sepsis will experience fever during their stay in the intensive care unit (ICU).\(^1\) This febrile response is a complex physiologic reaction to disease (inflammation and/or infection), which involves a cytokine-mediated rise in core body temperature, generation of acute phase reactants, and activation of numerous physiologic, endocrinologic and immunologic systems presenting from the other side beneficial and deleterious effects because of the increase of several parameters of immune function (cytokine production, T-cell activation, neutrophil, and macrophage function).\(^2\)

Critically ill patients commonly present a newly elevated temperature at a certain time of their hospitalization, triggering a set of many diagnostic and laboratory tests. In these cases, a prudent and cost-effective manner of assessment is necessary, otherwise treatment is time-consuming, with elevated costs, and a disruptive result to the patient (eg, unneeded radiation, transport outside the controlled environment of the ICU, blood loss) and the caregiver staff are noted.\(^3\) Fever in critically ill patients may be of infectious, noninfectious, or mixed origin and the confirmation of the source is often difficult, which leads to a diagnostic dilemma (ie, a difficult decision: “to treat or not to treat”) and a variability of treating response from the medical and nursing staff institutionally.

In febrile, critically ill patients, traditionally a pharmacologic and/or mechanical antipyretic therapy is administered before the confirmation of the cause, indicating with this approach: (a) the misconceptions about the detrimental effects of fever especially
in the children (eg, seizures, brain damage); and (b) the response on the part of the physicians to the psychological pressure, especially from the family. \(3,4\) This medical practice, despite the evidence that fever in the majority of the cases is a beneficial response to the disease, leads to an increased medical cost (eg, use of antipyretic drugs, icepacks, cooling blankets) and occasionally in organ dysfunction development (eg, volume-depleted patients, individuals with renal diseases). \(4,5\)

According to the American College of Critical Care Medicine of the Society of Critical Care Medicine and the Infectious Diseases Society of America, the goal for the treatment of a new temperature elevation in a previously afebrile, critically ill patient in whom the source of the fever is not obvious merits a detailed evaluation of the patient’s medical history and a careful physical examination before the order of any laboratory or imaging procedure or before the administration of any drug; the goal is to promote the rational consumption of different resources and the efficient evaluation of the new event. \(3\)

**DEFINITION, PHYSIOLOGY AND PATHOGENESIS OF THE FEVER**

The mean body temperature in healthy individuals is 36.8°C (98.2 °F) with a range of 35.6°C (96 °F) to 38.0°C (100.8 °F) and a slight diurnal/circadian variation of between 0.5 and 1.0°C and during the heavy exercise a rise by 2° to 3°C is observed. \(6\) The presence of fever is defined when a core temperature >38.0°C (100.4 °F) is measured or when two consecutive measurements reveal elevations of temperature >38.3°C (101.0 °F). In neutropenic patients, a single measurement of oral temperature of > 38.3°C (101.0 °F) in the absence of an obvious environmental cause or an elevation of >38.0°C (100.4 °F) for a time period of more than 1 hour establishes the diagnosis of fever. \(7\) The body temperature is measured and monitored using a variety of methods and techniques (especially in ICU patients) at different body sites (Table 1).

After the action of exogenous stimuli (eg, infections, inflammatory or autoimmune diseases, vascular occlusive diseases, drugs), a release of large proteins (15,000–30,000 daltons) called “endogenous pyrogens” (interleukin-1 [IL-1], tumor necrosis factor [TNF]), IL-6, and interferons by monocyctic cells is observed binding to specific receptors that are located in the preoptic region of the anterior hypothalamus. \(8\) At this

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Measurement of fever using different techniques at different body sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Method</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>Mixed venous blood</td>
</tr>
<tr>
<td>Infrared ear</td>
<td>Thermometer</td>
</tr>
<tr>
<td>Rectal temperature</td>
<td>Mercury thermometer or electrical probe</td>
</tr>
<tr>
<td>Oral measurement</td>
<td>Thermometer</td>
</tr>
<tr>
<td>Axillary measurement</td>
<td>Thermometer</td>
</tr>
</tbody>
</table>
site, a blood-brain barrier acts as a valve permitting the entrance of a limited quantity of those proteins into the brain. After the entrance, these pyrogens come into contact with neurons with the aid of small neuronal cells with fenestrated capillaries called “circumventricular organs” and a direct response of the neurons within the organum vasculosum of the lamina terminalis or of astrocytes or microglia to cytokines is noted, resulting in arachidonic acid metabolites production (prostaglandin E2 and thromboxane A2) and an up-regulation of the thermostatic set point. The brain responds by sending signals able to activate effector mechanisms (through the spinal/supraspinal motor system or throughout the sympathetic nervous system), which in their turn generate heat, reduce heat loss, and increase core body temperature to match the up-regulation of the thermostatic set point. The activation of arachidonic acid metabolites act as substrate for the cyclo-oxygenase-2 (COX-2) pathway, which in turn leads to further elevation of prostaglandins levels, a decreased rate of firing of sensitive neurons, and an increased heat production. The role of COX-2 is important for the development of fever although its activity is inhibited by selective inhibitors, including nonsteroidal anti-inflammatory drugs (NSAIDS) and acetaminophen.

Fever is characterized by beneficial and deleterious effects and by cardiovascular and metabolic demands (Fig. 1). The beneficial effects have been shown: (a) in mammalian models where the increased body temperature was associated to an enhanced resistance to infection; and (b) in clinical trials in adults where a positive correlation was recorded between maximum temperature on the bacteremia day and survival or between a temperature of >38°C and survival in spontaneous bacterial infection.

Fig. 1. Responses of different organs to fever.
peritonitis. The deleterious effects of fever affect mainly: (a) patients with cardiorespiratory diseases because fever is poorly tolerated because of the increased cardiac output, the increased oxygen consumption, the elevated carbon dioxide production, and the increased energy expenditure; and (b) the neurosurgical patients who have head injuries and cerebrovascular accidents because moderate elevations of brain temperature exacerbate the injuries. Upon the appearance of fever, elevated oxygen consumption (for each °C increase in body temperature a 13% increase in oxygen consumption is noted), increased heart rate, elevated cardiac output, and increased serum catecholamine production are noted, aiming to ameliorate oxygen delivery to meet tissue demands. According to the phase of fever, the patient manifests different signs and symptoms. During the initiation phase, chills in response to the elevation in temperature set point, increased insulation, decreased skin surface exposure, and shivering are associated with increased metabolic rate; during the plateau phase, the body temperature equilibrates the new thermostatic set point in the brain; and, during defervescence of the fever, effector mechanisms are activated, such as sweating, and the patient exhibits behaviors such as removing blankets with the aim to lose heat.

CAUSES, DIAGNOSTIC APPROACH AND TREATMENT OF FEVER IN THE ICU

Generally, critically ill patients frequently show single spikes of elevated temperatures that return to normal without treatment. These events are considered without clinical significance and related to different interventions, enodtracheal suctioning, urinary catheter placement, and transfusion of blood products. The fever that is related to an invasive procedure or manipulation of an indwelling device with or without transient bacteremia frequently resolves spontaneously, while fever caused by underlying chronic diseases, current medical illness or its complications, or reactions following drug therapy may be persistent.

Noninfectious Causes of Fever in the ICU

Half of fever episodes in the ICU are of noninfectious origin, without the temperature usually exceeding 38.3°C, and additional necessary diagnostic procedures (Table 2). The medical history, including recent interventions along with the physical examination, aids the clinician in narrowing down the differential diagnosis. However, the type of ICU population (eg, medical, surgical, trauma, neurosurgery and burn patients), the specific type of patients (eg, immunocompromized, elderly), the history of recent epidemics and the local epidemiology must be taken into account.

In cardiac care units (CCUs), the main causes of noninfectious fever include: myocardial infraction, Dressler’s syndrome with pericarditis, thromboemolism, thrombolytic therapy with hemorrhagic complications and antiarrythmic medication (eg, procainamide, quinidine), and deep venous thrombosis without necessarily routine venography performance.

In neurosurgical ICU, patients’ posterior fossa syndrome is a common cause of noninfectious origin of fever that mimics meningitis with stiff neck, low level of glucose/increased level of protein, and predominance of polymorphonuclear leukocytes in cerebrospinal fluid (CSF) as result of blood insertion in CSF. The differential diagnosis from bacterial meningitis is based on the negative cultures and the gradual lessening of meningeal symptoms as the number of red blood cells decreases in the CSF with time. Other causes are: central fever caused by intracranial lesion or trauma affecting the brain or hypothalamus that is resistant to antipyretics, exceeds 39°C (106°F), and is characterized by absence of perspiration; the use of
anticonvulsive medications; and deep venous thrombosis, including fat embolism in trauma patients. In the acute phase after head injury, the appearance of pyrexia is extremely frequent and deleterious for cerebral perfusion (CCP) and intracranial pressure (ICP); while lack of treatment by antipyretics has been correlated with a longer ICU stay.²¹

Acalculus cholecystitis, frequently unrecognized, is the result of gallbladder ischemia and bile stasis with an estimated incidence of 1.5%, especially in septic patients or in patients recovering from abdominal sepsis, because of the nonspecific clinical signs and laboratory workup (pain in the right upper quadrant, nausea,}

<table>
<thead>
<tr>
<th>System</th>
<th>Infectious Causes</th>
<th>Noninfectious Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Meningitis, encephalitis</td>
<td>Posterior fossa syndrome, central fever, seizures, cerebral infraction, hemorrhage,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cerebrovascular accident</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Central line, infected pacemaker, endocarditis, sterna osteomyelitis, viral pericarditis</td>
<td>Myocardial infarction, myocardial/perivalvular abscess, balloon pump syndrome, postpericardectomy syndrome</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>VAP, mediastinitis, tracheobronchitis, empyema</td>
<td>Pulmonary emboli, ARDS, atelectasis (without pneumonia), BOOP, bronchogenic carcinoma without postobstructive pneumonia, systemic lupus erythemaous pneumonitis</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Intra-abdominal abscess, cholangitis, cholecystitis, viral hepatitis, peritonitis, diarrhea (&lt;i&gt;Clostridium difficile&lt;/i&gt;)</td>
<td>Pancreatitis, acalculus cholecystitis, ischemia of the bowel, bleeding, cirrhosis, ischemic colitis, irritable bowel syndrome</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>Catheter-associated bacteremia, urosepsis, pyelonephritis, cystitis</td>
<td>Underestimates core temperature, lacks reproducibility</td>
</tr>
<tr>
<td>Skin/soft tissue</td>
<td>Decubitus ulcers, cellulitis, wound infection</td>
<td>—</td>
</tr>
<tr>
<td>Bone/joint</td>
<td>Chronic osteomyelitis, septic arthritis</td>
<td>Acute gout</td>
</tr>
<tr>
<td>Other</td>
<td>Transient bacteremia, sinusitis</td>
<td>Adrenal insufficiency, phlebitis/thrombophlebitis, neoplastic fever, alcohol/drug withdrawal, delirium tremens, drug fever, fat emboli, deep venous thrombosis, postoperative fever (48 h), fever after transfusion.</td>
</tr>
</tbody>
</table>
vomiting, fever). The radiologic investigation using ultrasound (wall thickness >3 mm, intramural lucencies, gallbladder distension, pericholecystic fluid and intramural sludge) and CT scanning (high sensitivity and specificity) are helpful, while hepatobiliary scintigraphy is characterized by a high false-positive rate (>50%). Frequently, the diagnosis is delayed and the disease progresses to ischemia, gangrene and perforation, indicating in this manner that the necessary high index of suspicion from physicians’ part, while the treatment choice is the percutaneous cholecystectomy.

Fever caused by drug hypersensitivity or drug-related fever or “drug fever” is characterized by unknown incidence (3%–7% of febrile episodes are attributed to drug reactions, but many cases remain undiagnosed), a temperature ranged from 38.8°C(102 °F) to 40°C(104 °F), difficult diagnosis (usually established by exclusion because of the non-specific signs and laboratory tests), shaking chills and spiking temperatures. A concomitant maculopapular rash makes the diagnosis simple but accompanies the fever in only 5%–10% of cases, while rarely an increased WBC count with a left shift, a moderate elevation of serum transaminases, peripheral eosinophilia, and a markedly elevated erythrocyte sedimentation rate (>100 mm/h) are recorded. The signs that are associated with drug-fever are a lack of appropriate pulse rate response and a relative bradycardia in the absence of intrinsic conduction defects or beta-blockade. Any drug can cause fever due to hypersensitivity producing fever alone, with local inflammation at the site of administration (phlebitis, sterile abscess, soft tissue reaction) or because of the delivery systems (diluent intravenous fluid, intravascular delivery devices). The high-risk agents for drug-fever are all antibiotics (especially β-lactams), anti-epileptic drugs (especially phenytoin), antiarrhythmics (mainly quinidine and procainamide), antihypertensives (a-methyldopa), diuretics, anti-seizures drugs, and stool softeners. Antibiotics with lower risk for drug-fever development are: clindamycin, vancomycin, chloramphenicol, aztreonam, doxycycline, erythromycin, imipemem, quinolones, and aminoglycosides. The time between initiating a drug and fever appearance is estimated to be 21 days (median 8 days) while the fever resolves usually within 72 hours after removing the offending drug. When a rash is present it persists for days or weeks. The usual scenario of drug-fever in the ICU includes a patient in whom an already diagnosed infection is resolving and after an initial defervescence in temperature a recurrence of fever is noticed. In this patient, the antibiotics should be discontinued if the infection has been resolved or has not been detected another infectious site. If the patient is stable, but the infection has not been resolved, then the presumed offending agent should be removed and a modification to antibiotics, without potential sensitizing, according to the spectrum of pathogens should be performed.

Postoperative fever is common within the first 72 hours after surgery, usually caused by the release of endogenous pyrogens into the bloodstream. However, this type of fever warrants a careful evaluation to rule out infection, which is increasingly likely with time (after a patient is >96 hours febrile), while specific predisposing factors (type and site of surgery) and underlying comorbidities must be taken into account (pneumonia is common in upper abdominal surgery or thoracic surgery, wound infections in upper abdominal surgery, urinary infections in lower abdominal surgery). In these patients, during the first 72 hours and if fever is the only indication, a chest radiograph or urine cultures are not mandatory, while surgical wounds should be examined daily for infection and a high level of suspicion should be maintained for obstructive vascular events (pulmonary embolism, deep venous thrombosis, superficial thrombophlebitis).

Malignant hyperthermia (MH) and malignant neuroleptic syndrome (MNS) should be kept in mind in critically ill patients when fever is especially high. MH is more common
in the operating room than in the ICU and occurs after general anesthesia with depolarizing agents including mutation in the calcium channel of sarcoplasmic reticulum. MH can be caused by succinylcholine and inhaled anesthetics administration (especially halothane). MNS is a consequence of blockade of dopamine receptors from antipsychotic agents (phenothiazines, thioxanthenes, butyrophenones). Both, MH and MNS inhibit hypothalamic heat-conserving mechanisms generating high fever, muscular rigidity, and increased creatinine phosphokinase concentrations. The main difference among those two clinical entities is the initial muscle contraction (central in MNS) while frequently serotonin syndrome (excessive stimulation of the 5-HTIA-receptor by various psychiatric disorders), which may be exacerbated by the concomitant use of linezolid, is confused with MNS. The treatment of MH and MNS include the removal of the offending drug and the administration of dantrolene or dopamine agonists (bromocryptine) to prevent tissue damage.

Other noninfectious causes of fever in critically ill patients are heatstroke (in patients under psychotropic medication or anticholinergic drugs needing discontinuation of the offending agent and external cooling of the body), withdrawal of certain drugs often with associated tachycardia, diaphoresis, and hyperreflexia (eg, alcohol, opiates, barbiturates, benzodiazepines), atelectasis or acute respiratory distress syndrome (ARDS) without pneumonia as a result of inflammatory process and blood transfusion (especially platelets), which is associated to an incidence of 0.5% and appears 30 min to 2 hours after the transfusion is begun and last 2–24 hours preceded by chills.

Infectious Causes of Fever in the ICU

The ICU-acquired infections show a prevalence of between 10% (NNIS) and 20.6% (EPIC study) with ventilator-associated pneumonia (VAP) being the most common, followed by sinusitis, bloodstream and catheter-related infections, nosocomial diarrhea, and wound infections.

Infections of the respiratory system

VAP occurs in 25% of mechanically-ventilated patients presenting with leukocytosis, purulent tracheal secretions, and new or worsening infiltrates on the chest roentgenogram, while in immunocompromised patients, especially in solid organ transplant patients, VAP could be developed without the presence the above clinical manifestations. The differential diagnosis includes ARDS, left ventricular failure (LVF), and tracheobronchitis because of the same pattern of the appeared pulmonary infiltrates. ARDS is characterized by the low lung volumes in chest radiographs and LVF from the immediate and permanent improvement of pulmonary infiltrates after the administration of aggressive, mainly diuretic, therapy. The initial evaluation includes: (a) a chest imaging study with chest radiograph and CT scan; (b) cultures of secretions obtained from lower respiratory tract before antibiotics administration (expectorated sputum, tracheal secretions, Bronchoalveolar Lavage [BAL] obtained by fiberoptic bronchoscopy); and (c) in case of pleural effusion, stain culture and cytology of the pleural fluid. Although the quantitative cultures have not been standardized sufficiently, they provide useful information, while blood cultures and other blood tests (PCR, CMV antigen, galactomannan and beta-D-glucan) could add in the diagnostic procedure.

Catheter-related infections

Bloodstream infections originate mainly from gastrointestinal and genitourinary tracts in the absence of an IV-line or catheters, while catheter related are the infections caused by a pathogen that has colonized a vascular device. The majority of ICU patients have
at least one central venous catheter (CVC), while most of them have some type of tunneled, cuffed CVCs, or subcutaneous central venous port. Catheter-related infections show an incidence of 10 infections/1,000 catheter days, while the relative risk for their appearance depends on the length of time with the catheter in situ, the number of ports, the number of manipulations, the type of the device, the patient population, and the techniques used in insertion. The diagnosis is based on clinical signs including: the difficulty of drawing or infusing through the catheter, the presence of inflammation at the insertion site, and the recovery of microorganisms in multiple blood cultures. For the evaluation of those signs, two peripheral blood cultures or one drawn percutaneously and one drawn through the catheter should be obtained, while blood cultures drawn through intravascular devices provide excellent sensitivity. Different methods have been proposed aiming to reduce catheters’ colonization, including topical administration of antibiotics and antimicrobial solutions, subcutaneous tunneling of catheters, and silver-impregnated subcutaneous cuffs. The gold standard for the diagnosis and treatment is the removal and culture of the catheter with semiquantitative or quantitative catheter tip methods.

**Sinusitis**

Sinusitis has an incidence of 5% of all nosocomial infections in the ICU affecting mainly trauma or neurosurgical patients, characterized by fever and leukocytosis, while purulent nasal discharge is often lacking (ie, it is present in only 25% of proved cases). The predisposing factors for sinusitis development include: nasotracheal or nasogastric tube placement, nasal packing, facial fractures, and steroid administration, while the diagnosis is made by plain radiographs, CT scan or magnetic resonance imaging of the sinus. Nasal endoscopy, in conjunction with plain radiography, increases the accuracy of diagnosis, depending on the skill of the practitioner.

**Nosocomial diarrhea**

Critically ill patients frequently manifest diarrhea (ie, defined as more than two stools per day that conform to the container in which they are placed), which is caused by enteral feeding or by infectious causes. The commonest cause of febrile diarrhea in critically ill patients is *Clostridium difficile* (10%–25% of all cases of antibiotic-associated diarrhea), which “…..should be suspected in any patient with fever or leukocytosis and diarrhea who received an antibacterial agent or chemotherapy within 60 days before the onset of diarrhea.” Nosocomial diarrhea caused by *C difficile* can be caused by any antibacterial agent, but the main causes are clindamycin, cephalosporins, and fluoroquinolones. The gold standard for the diagnosis is the tissue culture assay, which presents, however, a 24–48 hour delay in results and high cost, while an enzyme immunoassay test (EIA) for toxin A and B is commercially available, easy to perform, and able to provide results within minutes to hours. In case of severe illness and negative rapid tests for *C difficile*, flexible sigmoidoscopy procedure remains a secure option for the diagnosis, while in HIV patients or patients exposed in different epidemiologic conditions, stool cultures for other pathogens is indicated.

**Intra-abdominal and surgical site infections**

Intra-abdominal infections could be the main cause of ICU admission or a secondary cause after abdominal surgery (abscess formation, biliary sepsis). The diagnosis is facilitated by CT scan of the abdomen, ultrasound, and nuclear medicine techniques (gallium-67, indium-111 white blood cell scintigraphy). CT scan and ultrasound are used for the detection of focal findings (CT scan is used mainly for mid-lower abdomen/peritoneal cavity, while ultrasound for infections in the pelvis and right upper quadrant abdomen). Surgical site infections include mainly: the contamination of the
surgical incision depending on the medical comorbidities of the patient; the duration of the operation; and whether antimicrobial prophylaxis was administered before incision.26

**Fungal infections**

Fungi (mainly *Candida* species) are a main cause of infections; development in critically ill patients is: associated with specific risk factors; characterized by difficult diagnosis because of the lack of a diagnostic tool able to discriminate colonization from infection; and showing an epidemiologic shift toward non-*albicans* species.53–57 The definite diagnosis is made by the identification of the fungi from histologic or, sterile specimen obtained.

**Other infections**

**Urinary tract infections** In critically ill patients, urinary tract infections (UTIs) (mainly catheter-associated bacteriuria or candiduria) usually reflect colonization, are rarely symptomatic, and are not considered as a significant cause of morbidity or attributable mortality, while the traditional clinical signs and symptoms are rarely reported by the patient.58,59

**Cytomegalovirus antigenemia, central nervous system infections** During recent years, cytomegalovirus (CMV) antigenemia has been proposed as a cause of unexplained prolonged fever in severely ill, immunocompetent patients in the ICU, but the significance of CMV detection is unknown; however, patients with detectable CMV tend to have a higher morbidity and mortality compared with patients in whom the virus remains undetectable.60 In neurocritical patients, fever occurs in 25% of the cases, but almost half of these fevers are of noninfectious origin. In these patients, the suspicion of infection development must be of high index because of the inherent limitations of the neurologic examination, the low yield of lumbar puncture in nonimmunocompromized patients, and the contraindications for lumbar puncture performance, which frequently are met in critically ill patients.61,62 The diagnosis for a critically ill patient with a new episode of fever is made usually by imaging study (CT scan of the brain), culture of cerebrospinal fluid, and removal and culture of the placed catheter or other intracranial device.63

**APPROACHING THE FEBRILE CRITICALLY ILL PATIENT AND TREATMENT OF THE FEVER**

The initial approach to the febrile patient includes: (a) the overview of the medical record; (b) the physical examination; and (c) the evaluation of characteristics of the fever (magnitude, duration, relationship to patient’s pulse rate, and temporal relationship to diagnostic and therapeutic interventions). In all febrile patients before the initiation of any treatment, at least two blood cultures by separate needles from different sites as well as other appropriate cultures must be obtained (Fig. 2). The clinician always has to consider that chills and fever appear 1–2 hours after the presence of microorganisms in the blood (initiating event), which explains the commonly observed negative blood cultures at the time of the temperature spike.64

In the case of unexplained or unknown origin fever that is associated to unexplained leukocytosis, anion gap acidosis, hypotension or persistent tachycardia and tachypnea, the initial evaluation should be focused on ruling out septic syndrome development originated by urinary tract infection, VAP/nosocomial pneumonia, phlebitis, wound infections, or bacteremia.2,23 In patients who have progressive signs of severe sepsis and in all neutropenic patients with fever, broad-spectrum antimicrobial therapy should be started immediately after cultures have been obtained, while all
the central lines placed for > 48 hours and the nasal tubes should be removed and cultured using semiquantitative or quantitative cultures; however, in the case of diarrhea, stool cultures for WBC count and toxin against *C. difficile* should be performed.\(^2,23\) In patients who have abdominal sepsis or signs of abdominal infection, including tenderness and distension, CT scan of the abdomen is indicated. If the fever persists 48–96 hours after antibiotic treatment and without the cause or the source of the infection being identified, the patient must be reevaluated for risk factors associated with fungal infections (initiation of empiric antifungal treatment is indicated), while additional diagnostic tests, including venography, complete blood count (CBC) for eosinophils (drug fever), and abdominal imaging are indicated.\(^2,23\)

During recent years, several biomarkers have been proposed as adjunctive markers for the evaluation of fever, aiming to discriminate true infection from noninfection or other inflammatory diseases. These biomarkers include: serum procalcitonin assays with variable cut-off points, endotoxin detection systems, trigering receptor expressed on myeloids cells-1 (TREM-1), C-reactive protein, tumor necrosis factor-\(\alpha\) and Interleukin-6.\(^65-68\) From all the above biomarkers, serum procalcitonin assay is approved for the early detection of bacterial infection/sepsis during the first day of ICU admission, while the rest of them have not yet been validated.\(^69\)

The methods used for the suppression of the fever in the ICU include the administration of antipyretic agents (acetaminophen, cyclooxygenase 2 and nonsteroidal agents, metamizol and propacetamol) and external cooling techniques performance.\(^70,71\) Antipyretic agents are agents able to block or reverse the cytokine-mediated rise in core temperature caused by fever without affecting body temperature and must be distinguished from hypothermic agents that are able to lower core temperature even in the absence of fever.\(^72\) The external cooling methods include the placement of hypothermia blankets, which, however, are characterized by certain side effects including the large temperature fluctuations, the development of rebound hyperthermia, the appearance of hypermetabolism, and increased oxygen consumption, leading to elevated levels of epinephrine and norepinephrine.\(^73\)
REFERENCES

40. McConell SA, Gubbins PO, Anaissie EJ. Are antimicrobial-impregnated catheters effective? Replace the water and grab your washcloth, because we have a baby to wash. Clin Infect Dis 2004;39(12):1829–33.


