

# Approach to the Febrile Patient in the Intensive Care Unit

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## 1.1 Introduction

Fever occurs in approximately one-third of all medical patients during their hospital stay and in more than 90 % of critically ill patients with severe sepsis [1]. According to the Society of Critical Care Medicine (SCCM) and the Infectious Diseases Society of America (IDSA), a temperature above 38.3°C (101°F) should be considered as fever necessitating a clinical assessment. The mean body temperature in healthy individuals is 36.8°C (98.2°F), with a range of 35.6°C (96°F) to 38.2°C (100.8°F) and a slight diurnal/circadian variation of between 0.5 and 1.0°C [2, 3]. Patients with elevated temperature in the ICU are in a closed monitoring system undergoing accurate and reproducible measurements using a variety of methods (instruments and techniques) at different body sites (Table 1.1) [4].

The febrile response (fever is one of the components) is a complex physiological reaction to disease involving a cytokine-mediated rise in core body temperature, generation of acute-phase reactants and activation of numerous physiological, endocrinologic and immunologic systems. Fever, with its beneficial and deleterious effects, occurs as a response to infection, increasing several parameters of immune function (cytokine production, T-cell activation, neutrophil and macrophage function).

However, the management of the critically ill febrile patient can be characterized as a diagnostic dilemma (*infectious or non-infectious cause*) and a response from the physician and staff (*to treat or not to treat*) which varies institutionally. Frequently in the same ICU fevers of mixed causes are seen on evaluation of the patient, and before the cause of fever is confirmed pharmacologic and/or mechanical antipyretic therapy is administered. This traditional point of view shows the misconceptions about the detrimental effects of fever (seizures, brain damage, etc.) and the response from the physician to psychosocial pressure, which however leads to increased medical costs (use of paracetamol, icepacks, cooling blankets) and organ dysfunction (in volume depleted patients or in those with renal and kidney diseases) despite the evidence that fever is a beneficial response to infection [5, 6].

## 1.2 Physiology and Pathogenesis of Fever

After the action of exogenous stimuli (endotoxin, viruses, etc.), different endogenous pyrogens [interleukin (IL)-1, tumor necrosis factor (TNF), IL-6 and interferons] released by monocytic cells bind to specific receptors located to the preoptic region of the anterior hypothalamus [7]. The subsequent manifestation of fe-

**Table 1.1.** Measurement of fever

Site	Method	Comment
Pulmonary artery	Mixed venous blood	Pulmonary artery catheter
Infrared ear	Thermometer	Values a few tenths below values in the pulmonary artery catheter and brain
Rectal temperature	Mercury thermometer or electronic probe	A few tenths higher than core temperature
Oral measurement	Thermometer	Unpleasant and intrusive for patients Influenced by warmed gases delivered by respiratory devices, by eating and drinking
Axillary measurement	Thermometer	Underestimates core temperature, lacks reproducibility

ver appears to be an upregulation of the thermostatic set point for body temperature in this preoptic area. The brain is protected from large proteins, such as pyrogens (15,000–30,000 daltons), entering in a sufficient quantity by a blood-brain barrier recognizing them at certain sites known as circumventricular organs, which represent small neuronal cell groups with fenestrated capillaries allowing neurons to come into contact with different circulating substances directly from the bloodstream. This leakage allows the central nervous system to sense the presence of endogenous pyrogens, which lead to the production of fever from the organum vasculosum of the lamina terminalis (direct response of the neurons within the organum vasculosum to cytokines or response of astrocytes or microglia to cytokines by producing prostaglandins) [8]. The interaction of the cytokine receptors leads to phospholipase A<sub>2</sub> production, arachidonic acid liberation as substrate for the cyclo-oxygenase-2 (COX-2) pathway and elevation of prostaglandin E<sub>2</sub> levels, decreasing the rate of firing of sensitive neurons and leading to decreased heat loss and increased heat production [9, 10]. The role of COX-2 is important because these components induce fever development while its activity is inhibited by selective inhibitors including NSAIDs (non-steroidal anti-inflammatory drugs) and acetaminophen [11].

The febrile response is characterized by endocrine/metabolic, autonomic and behavioral components (Fig. 1.1) [8]. A slight elevation of body temperature improves the efficiency of macrophages in killing invading bacteria, impairs the replication of many microorganisms, minimizes the availability of glucose (substrate for bacterial growth), reduces the demands of muscles for energy expenditure, produces acute-phase reactants which bind divalent cations necessary for the

proliferation of microorganisms and increases cortisol and corticotropin secretion, aiding the organism to cope with the stress. The beneficial effects of fever have been shown (a) in mammalian models where the increased body temperature led to enhanced resistance to infection and (b) in clinical trials in adults with a positive correlation between maximum temperature on the bacteremia day and survival or between a temperature >38°C and survival in spontaneous bacterial peritonitis [12, 13]. The deleterious effects of fever affect mainly patients with cardiorespiratory symptoms (poorly tolerated due to the increased cardiac output, elevated oxygen consumption, increased carbon dioxide production and elevated energy expenditure) and neurosurgical patients with head injuries or cerebrovascular accidents (moderate elevations of brain temperature exacerbate the resulting injury) [14, 15].

### 1.3 Causes of Fever in the ICU

Fever in the ICU arises from non-infectious and infectious causes. The non-infectious causes (Table 1.2) account for half of fevers in the ICU not usually exceeding 38.3°C (101°F) [16]. These diseases are often obvious without additional diagnostic procedures being necessary. The medical history (recent medical interventions, transfusions, recent antibiotics, other medications) along with the physical examination aids the clinician in narrowing down the differential diagnosis.

In Cardiac Care Units the non-infectious causes of fever [which rarely exceeds 38.3°C (101°F)] include myocardial infarction, Dressler’s syndrome with pericarditis, thromboembolism (complications >10% of

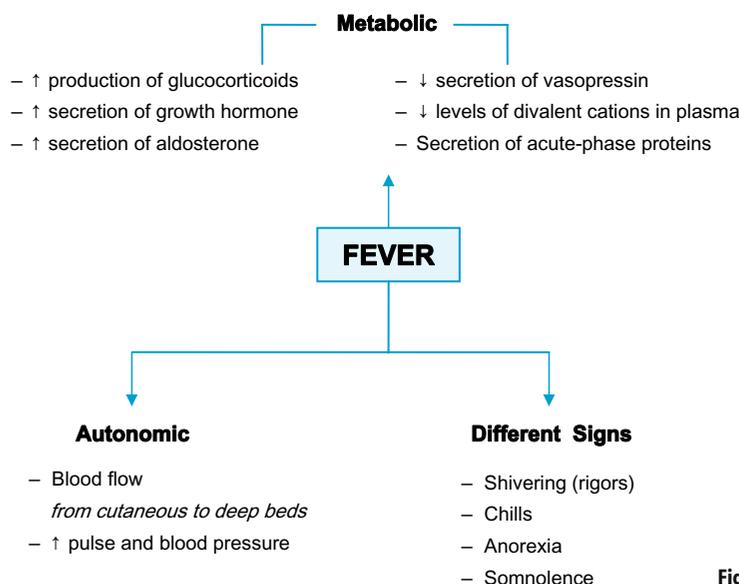


Fig. 1.1. Fever and responses from different organs

**Table 1.2.** Causes of fever in the ICU

System	Infectious causes	Non-infectious causes
CNS	Meningitis, encephalitis	Posterior fossa syndrome, central fever, seizures, cerebral infarction, hemorrhage, cerebrovascular accident
Cardiovascular	Central line, infected pacemaker, endocarditis sternal osteomyelitis, viral pericarditis	Myocardial infarction, myocardial/perivalvular abscess, balloon pump syndrome, postpericardiotomy syndrome
Pulmonary	VAP, mediastinitis, tracheobronchitis, empyema	Pulmonary emboli, ARDS, atelectasis (without pneumonia), BOOP, bronchogenic carcinoma without postobstructive pneumonia, systemic lupus erythematosus pneumonitis
Gastrointestinal	Intra-abdominal abscess, cholangitis, cholecystitis, viral hepatitis, peritonitis, diarrhea ( <i>Clostridium difficile</i> )	Pancreatitis, acalculous cholecystitis, ischemia of the bowel, bleeding, cirrhosis, ischemic colitis, irritable bowel syndrome
Urinary tract	Catheter-associated bacteremia, urosepsis, pyelonephritis, cystitis	
Skin/soft tissue	Decubitus ulcers, cellulitis, wound infection	
Bone/joint	Chronic osteomyelitis, septic arthritis	Acute gout
Other	Transient bacteremias, sinusitis	Adrenal insufficiency, phlebitis/thrombophlebitis, neoplastic fever, alcohol/drug withdrawal, delirium tremens, drug fever, fat emboli, deep venous thrombosis, postoperative fever (48 h), fever after transfusions

ARDS acute respiratory distress syndrome, CNS central nervous system, VAP ventilator associated pneumonia, BOOP bronchiolitis obliterans organizing pneumonia

myocardial infarctions), thrombolytic therapy with hemorrhagic complications and administration of antiarrhythmic medication (procainamide, quinidine) [17]. Fever also occurs in deep venous thrombosis without, however, the necessity for routine venography as the initial diagnostic procedure of pyrexia [1].

In neurosurgical ICU patients, the commonest causes of fever include posterior fossa syndrome, drug fever, central causes, IV-line sepsis, meningitis, wound infections and nosocomial pneumonia [18]. Wound infections are caused mainly by the skin flora of the head (group A streptococci, *Staphylococcus aureus*) or by gram-negative pathogens after open-head trauma resulting in low-grade fevers where the diagnosis is simple with the aid of culture materials. Postoperative meningitis is common after open-head trauma procedures characterized by a persistent fever after the initial postoperative period. The diagnosis is made by Gram's stain and cerebrospinal fluid (CSF) culture. Posterior fossa syndrome mimics meningitis, presenting stiff neck, low level of glucose/increased level of protein and predominance of polymorphonuclear leukocytes in CSF. These findings are consequences of blood insertion in CSF, and 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 [18]. Other causes include central fever resistant to antipyretics (intracranial lesion, trauma affecting the brain or hypothalamus) which exceeds 39°C (106°F)

and which is characterized by absence of perspiration, anticonvulsive medications and deep venous thrombosis including fat embolism in trauma patients [18]. Pyrexia in the acute phase after head injury is extremely frequent and deleterious for cerebral perfusion pressure (CCP) affecting intracranial pressure (ICP) [19]. In tense patients antipyretic therapy is poorly effective for controlling body temperature and is correlated with a longer ICU stay [19].

Acalculous cholecystitis is the result of gallbladder ischemia and bile stasis, and is frequently unrecognized as a cause of fever in critically ill patients (estimated incidence of 1.5%) [20]. The diagnosis remains difficult especially in septic patients or in patients recovering from abdominal sepsis because of the non-specific clinical signs (pain in the right upper quadrant, nausea, vomiting, fever) and laboratory workup. The radiologic investigation is performed with (a) ultrasound indicating a wall thickness > 3 mm, intramural lucencies, gallbladder distension, pericholecystic fluid and intramural sludge; (b) CT scanning presenting high sensitivity and specificity; and (c) hepatobiliary scintigraphy which is associated with a high false-positive rate (> 50%) [20]. Acalculous cholecystitis is related to a delayed diagnosis which often progresses to ischemia, gangrene and perforation, indicating the necessity for a high index of suspicion. Percutaneous cholecystostomy is the procedure of choice for the definitive therapy but if the abdominal signs, fever and leukocytosis have not ameliorated open cholecystectomy is recommended [21].

Fever due to drug hypersensitivity reaction or so-called “drug fever” is a non-infectious cause of fever characterized by unknown incidence (3–7% of febrile episodes are attributed to drug reactions but many more cases remain undiagnosed), a temperature range of 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 [1, 22]. The usual scenario in the ICU includes a critically ill patient in whom the infection is resolved and after an initial defervescence in temperature a recurrence of fever is noticed. In this patient if the infection has resolved or has not been detected at other sites, the antibiotics should be stopped. If the patient is clinically stable but the infection has not been resolved the antibiotics should be changed to a combination with the same spectrum of pathogens but without sensitizing potential. The presumed offending agent in suspected drug fever should be withdrawn. Taking into account the difficult diagnosis of drug fever, the clinician has to evaluate non-specific signs or symptoms, to avoid needless therapy and to discontinue with safety the offending medication. A concomitant maculopapular rash makes the diagnosis simple but accompanies the fever in only 5–10% of cases. Rarely present are 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). Drug fever is associated with a lack of appropriate pulse rate response and a relative bradycardia (in the absence of intrinsic conduction defects or beta-blockade) [23]. The medications considered as high risk for drug-fever development are all antibiotics (especially  $\alpha$ -lactams), diuretics,  $\alpha$ -methyldopa, quinidine, hydralazine, procainamide, diphenylhydantoin, antiseizures and stool softeners. Antibiotics with minimal risk for drug-fever development include clindamycin, vancomycin, chloramphenicol, aztreonam, doxycycline erythromycin, imipenem, quinolones and aminoglycosides [1, 23]. After the discontinuation of the offending medication, the fever resolves usually within 72 h but when a rash is present it persists for days or weeks.

Atelectasis is listed as a usual cause of fever in the ICU leading to significantly increased levels of IL-1 and TNF- $\alpha$  of macrophages in the atelectatic lung [24]. Blood transfusions (especially platelet transfusion) indicating an incidence of 0.5% are associated with a febrile response within 30 min to 2 h after the transfusion is begun and last 2–24 h preceded by chills (usually an acute leukocytosis for up to 12 h has been present) [25]. Acute respiratory distress syndrome (ARDS) patients in the late stage of the disease present with pulmonary fibroproliferation, fever and leukocytosis in the absence of infection as a result of the inflammatory-fibrotic process in the airspace of the lungs [26].

In the initial postoperative period the majority of fevers in the ICU are non-infectious (72% of fevers occur in the first 48 h of surgery) caused by the release of endogenous pyrogens into the bloodstream [2]. Postoperative fever warrants a careful evaluation to rule out infection, which is increasingly likely with time. In these patients specific predisposing factors (specific type and site of surgery) and underlying comorbidities leading to certain postoperative infections (pneumonia is most common in patients undergoing upper abdominal or thoracic surgeries, wound infections usually occur in upper abdominal surgery, urinary tract infections are usually associated with lower abdominal procedures) must be taken into account.

Malignant hyperthermia occurs after general anesthesia with depolarizing paralytic agents inducing mutation in the calcium channel of muscle sarcoplasmic reticulum. Malignant neuroleptic syndrome is considered a consequence of blockade of dopamine receptors from antipsychotic drugs inducing muscular rigidity and inhibiting hypothalamic heat-conserving mechanisms and malignant neuroleptic syndrome. Heatstroke is seen more often in patients under psychotropic medication or anticholinergic drugs which inhibit normal heat loss through sweating characterized by a temperature exceeding 41°C [8]. Malignant hyperthermia and malignant neuroleptic syndrome respond to administration of dantrolene and dopamine agonists (bromocriptine) to prevent tissue damage although a diligent and simultaneous search is indicated for an underlying cause of fever. The management of heatstroke includes discontinuation of anticholinergic drugs and external cooling of the body (first with ice baths and later with cooling blankets).

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 infection, nosocomial diarrhea and wound infections [27, 28]. Almost all cases of nosocomial pneumonia developing in the ICU occur in patients under mechanical ventilation. VAP occurs in 25% of mechanically ventilated patients presenting with leukocytosis, purulent tracheal secretions and new or worsening infiltrates on the chest roentgenogram, but it is difficult to differentiate from other conditions characterized by the same symptoms and signs [29]. The most aggressive diagnostic approach for VAP includes bronchoscopy, bronchoalveolar lavage (BAL), semiquantitative mini-BAL and protected specimen brush performance. However, with prior antibiotic therapy these techniques are considered of limited diagnostic value [30]. The intensivist frequently has to differentiate pneumonia from ARDS (acute respiratory distress syndrome) and LVF (left ventricular failure) because of the

same pattern of pulmonary infiltrates. ARDS is characterized in the chest X-ray by the low lung volume and LVF from the immediate and permanent improvement of pulmonary infiltrates after the administration of aggressive therapy.

Gram-negative microorganisms account mainly for nosocomial sinusitis while in 50% of cases isolates are polymicrobial, indicating the pathogens commonly colonize ICU patients. Sinusitis occurs with an incidence of 5% of all nosocomial infections in the ICU characterized by fever and leukocytosis (purulent nasal discharge is often lacking) commonly affecting neurosurgical or trauma patients [22]. The diagnosis is made by CT scan of the sinus, and predisposing factors are considered to be nasotracheal and nasogastric tube placement, nasal packing, facial fractures and steroid administration. Fever is present in a few cases of nosocomial sinusitis and when a CT scan is performed the fever may be attributed to a concomitant infection.

Bloodstream infections (bacteremias) in the absence of an IV-line or catheters in the ICU patient originate from gastrointestinal and genitourinary systems. Catheter related infection/sepsis (a bloodstream infection due to a pathogen that has colonized a vascular device) occurs with an incidence of 10 infections/1,000 catheter days, which increases with the length of time (the catheter in situ), the number of ports and the number of manipulations. The pathogens which commonly colonize/infect the catheters are *Staphylococcus aureus*, coagulase-negative *Staphylococci* followed by enterococci, Gram-negative bacteria and *Candida* species. The management of catheter colonization remains controversial including topical antibiotics and antimicrobial solution administration, subcutaneous tunnelling of catheters and silver-impregnated subcutaneous cuffs. The most effective method to reduce colonization seems to be the antimicrobial bonding of central venous catheters using chlorhexidine gluconate, silver sulfadiazine, minocycline and rifampin [31]. In the case of catheter sepsis the catheter should be changed to a new site and the tip must be cultured (quantitative or semiquantitative). The replacement of the colonized catheter should not be performed by guidewire because of the rapid recolonization.

Intensive care unit patients frequently present with diarrhea of infectious or non-infectious causes. Diarrheas of infectious origin are antibiotic associated and present fever of low grade. The principal pathogen is *Clostridium difficile*. A negative stool culture for *C. difficile* excludes the infectious origin of diarrheas and enteral feeding must be reconsidered because of the high osmolality/flow rate of the enteral solution. In these patients the decreased volume (by one half) of enteral nutrition allows the cessation of diarrheas within 12–24 h [32].

Intra-abdominal infections could be the main cause of ICU admission or a secondary cause after abdominal surgery. Abscess formation is the most common infection and is frequently complicated by acalculous cholecystitis, biliary sepsis and diarrhea due to *C. difficile* [22]. Detection of the infection site is performed by CT scan of the abdomen, ultrasound and nuclear medicine techniques (gallium-67, indium-111 white blood cell scintigraphy). Nuclear medicine techniques are used to detect infections with non-localizing signs. CT scans and ultrasound are used to evaluate focal findings (CT scan is used mainly to detect infections sited in the mid-lower abdomen/peritoneal cavity and ultrasound for evaluation of infections in the pelvis and right upper quadrant of the abdomen) [33].

Fungi (mainly *Candida* spp.) are important opportunistic pathogens in the ICU associated with certain predisposing factors characterized by the difficult diagnosis because of the lack of a laboratory method able to distinguish colonization from infection. The diagnosis of these infections is made by the identification of the fungi from sterile or histologic specimens [34]. During recent years cytomegalovirus (CMV) antigenemia has been proposed as a cause of unexplained prolonged fever in severely ill immunocompetent ICU patients [35]. The significance of CMV detection is unknown because the differentiation between CMV detection and CMV disease represents a diagnostic dilemma, although patients with detectable CMV tend to have a higher morbidity and mortality compared with patients in whom the virus remains undetectable [35].

Intensive care unit-acquired urinary tract infections (UTIs) have an incidence of 9.6/1,000 ICU days, commonly affect women/medical patients and despite the increased morbidity associated with critical illness are not a significant attributable cause of mortality in the ICU [36]. The main pathogens associated with ICU-acquired UTI development are *Escherichia coli* (23%), *Candida albicans* (20%), and *Enterococcus* species (15%) [37]. The management of UTIs includes antibiotic administration after urine culture performance and specific preventive measures (use of a catheter valve instead of a standard drainage system, use of a silver-alloy, hydrogel-coated latex urinary catheter instead of uncoated catheters). The term “asymptomatic bacteriuria” is frequently used to define the colonization of the urinary tract without bacterial invasion and acute inflammatory response. Bacteriuria should be treated with antibiotics only after urinary tract manipulations/surgery, in patients with kidney stones and in patients with obstruction.

### 1.4 Approach to the Febrile Critically Ill Patient and Treatment

The approach to the febrile patient in the ICU includes (a) an overview of the medical record (comorbidities, recent procedures, current medications, indwelling devices), (b) physical examination/review of the chest X-ray and (c) evaluation of fever characteristics (magnitude, duration, relationship to the patient’s pulse rate, temporal relationship to both diagnostic and therapeutic interventions). In the ICU, fever could arise as remittent or intermittent, sustained or appearing at different point times in the course of the patient’s illness, after 48 h from mechanical ventilation initiation (VAP), 5–7 days postoperatively (abscess formation) or at the 10–14th ICU day (fungal infections). The cause of fever varies according to the types of ICU and patient population. In medical ICUs the commonest causes of fever are secondary to myocardial infarction, pulmonary emboli, acute pancreatitis, adrenal insufficiency, gastrointestinal bleeding, central catheter related infections, ventilator associated pneumonia (VAP) or drug reactions. In surgical ICUs are additionally seen wound infections, peritonitis or abscesses. In cases of unknown origin where fever may fluctuate widely within a 24-h period a graph of temperature and pulse rate is used in relation to procedural intervention timing and transfusions.

Critically ill patients often show single spikes of temperature which return to normal without treatment

(are considered to have no clinical significance) related to intervention inducing bacteremia, endotracheal suctioning, urinary catheter placement and transfusion of blood products. The fever related to an invasive procedure or manipulation of an indwelling device with or without transient bacteremia frequently resolves spontaneously, while fever due to underlying chronic diseases, current medical illness or its complications or reactions following drug therapy may be persistent.

In all febrile ICU patients (Fig. 1.2) and before the initiation of any treatment (empiric antibiotic therapy, antipyretic treatment), blood cultures (at least two and no more than three sets obtained by separate needles from different sites) as well as other appropriate cultures must be performed. Bacteremia is an important cause of morbidity and mortality in the ICU leading to fever and chills 1–2 h after the presence of microorganisms in the blood (the initiating event), therefore explaining the frequently negative blood cultures at the time of the temperature spike [38].

In the case of unexplained fever or fever of unknown origin with unexplained leukocytosis, anion gap acidosis, hypotension or persistent tachycardia and tachypnea, the initial evaluation of the patient must focus on ruling out a possible infection (most commonly in the ICU urinary tract infections, pneumonia, phlebitis, wound infection and bacteremia) with the aid of certain laboratory tests including a complete blood count (CBC), urine examination with culture, blood cultures and a chest roentgenogram (especially in patients on mechanical ventilation). In patients with progressive

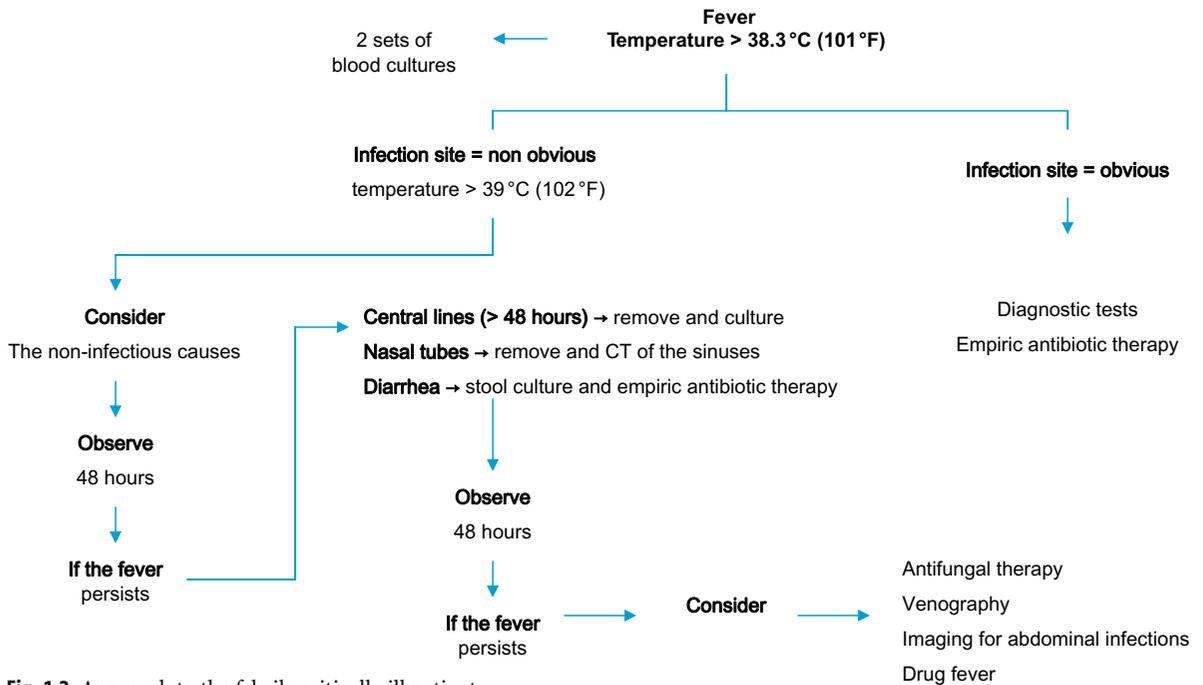


Fig. 1.2. Approach to the febrile critically ill patient

signs of severe sepsis and in all neutropenic patients with fever, broad-spectrum antimicrobial therapy should be started immediately after cultures have been obtained. In patients with no clinically obvious signs of infection all the central lines (placed > 48 h) and the nasal tubes should be removed and cultured (with semi-quantitative or quantitative cultures), while in the case of diarrhea, stool cultures for WBC count and toxin against *C. difficile* should be performed. CT scanning of the abdomen is indicated in patients with abdominal sepsis or with signs of abdominal infection (tenderness, distension, etc.). If fever persists after 48 h despite empiric 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 (antifungal treatment is indicated) and with additional diagnostic tests being performed including venography, blood cultures for eosinophils (drug fever) and abdominal imaging.

For the suppression of fever in the ICU, antipyretic agents (acetaminophen, cyclooxygenase 2, non-steroidal, metamizol, propacetamol) and external cooling methods are used. Antipyretics include agents capable of blocking or reversing the fever's cytokine-mediated rise in core temperature without affecting body temperature in the afebrile state and must be distinguished from hypothermia agents which are able of lowering core temperature even in the absence of fever [39]. External cooling methods include hypothermia blanket placement, the use of which, however, is characterized by certain side effects including large temperature fluctuations, rebound hyperthermia, increased hypermetabolism and elevated oxygen consumption leading to increased epinephrine and norepinephrine levels [40].

Fever is a normal adaptive brain response to circulating cytokines during systemic inflammation and no harm is done by letting it take its natural course [41]. In the ICU fever should be treated in cardiorespiratory patients and neurosurgical individuals and in those patients in whom the temperature exceeds 40 °C (104 °F). Antipyretic therapy must be justified regardless of the metabolic cost (if the fever exceeds its physiological benefit), the result (if the symptomatic relief adversely affects the course of the febrile illness) and the side effects of the antipyretic regimens (in patients with reduced glutathione reserves such as alcoholics, malnourished patients, etc., regular doses of acetaminophen are associated with acute hepatitis).

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