Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America

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Objective: **To update the practice parameters for the evaluation of adult patients who develop a new fever in the intensive care unit, for the purpose of guiding clinical practice.**

Participants: **A task force of 11 experts in the disciplines related to critical care medicine and infectious diseases was convened from the membership of the Society of Critical Care Medicine and the Infectious Diseases Society of America. Specialties represented included critical care medicine, surgery, internal medicine, infectious diseases, neurology, and laboratory medicine/microbiology.**

Evidence: **The task force members provided personal experience and determined the published literature (MEDLINE articles, textbooks, etc.) from which consensus was obtained. Published literature was reviewed and classified into one of four categories, according to study design and scientific value.**

Consensus Process: **The task force met twice in person, several times by teleconference, and held multiple e-mail discussions during a 2-yr period to identify the pertinent literature and arrive at consensus recommendations. Consideration was given to the relationship between the weight of scientific evidence and the strength of the recommendation. Draft documents were composed and debated by the task force until consensus was reached by nominal group process.**

Conclusions: **The panel concluded that, because fever can have many infectious and noninfectious etiologies, a new fever in a patient in the intensive care unit should trigger a careful clinical assessment rather than automatic orders for laboratory and radiologic tests. A cost-conscious approach to obtaining cultures and imaging studies should be undertaken if indicated after a clinical evaluation. The goal of such an approach is to determine, in a directed manner, whether infection is present so that additional testing can be avoided and therapeutic decisions can be made. (Crit Care Med 2008; 36:1330–1349)**

Key Words: fever; intensive care unit; critical illness; blood cultures; catheter infection; pneumonia; colitis; sinusitis; surgical site infection; nosocomial infection; temperature measurement; urinary tract infection

In some intensive care units (ICUs), the measurement of a newly elevated temperature triggers an automatic order set that includes many tests that are time consuming, costly, and disruptive to the patient and staff. Moreover, the patient may experience discomfort, be exposed to unneeded radiation, require transport outside the controlled environment of the ICU, or experience considerable blood loss due to this testing, which is often repeated several times within 24 hrs and daily thereafter. In an era when utilization of hospital and patient resources is under intensive scrutiny, it is appropriate to assess how such fevers should be evaluated in a prudent and cost-effective manner.

The American College of Critical Care Medicine of the Society of Critical Care Medicine and the Infectious Diseases Society of America reconvened a Task Force to update practice parameters for the evaluation of a new fever in adult patients (i.e., ≥18 yrs of age) in an ICU (1). The goal of this update is to continue to promote the rational consumption of resources and an efficient evaluation. This guideline presumes that any unexplained temperature elevation merits a clinical assessment by a healthcare professional that includes a review of the patient's history and a focused physical examina-

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The American College of Critical Care Medicine (ACCM), which honors individuals for their achievements and contributions to multidisciplinary critical care medicine, is the consultative body of the Society of Critical Care Medicine (SCCM), which possesses recognized expertise in the practice of critical care. The College has developed administrative guidelines and clinical practice parameters for the critical care practitioner. New guidelines and practice parameters are continually developed, and current ones are systematically reviewed and revised.

This guideline was developed in collaboration with the Infectious Diseases Society of America.

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Dr. Bartlett holds consultancies with HIV-Bristol-Myers, Abbott, Merck, Johnson & Johnson, and Tibotec; and a patent with Gilead.

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Table 1. Society of Critical Care Medicine's rating system for references and recommendations

References
a) Randomized, prospective, controlled investigation
b) Nonrandomized, concurrent, or historical cohort investigation
c) Peer-reviewed, state-of-the-art articles, review articles, editorials, or substantial case series
d) Non–peer-reviewed published opinions, such as textbook statements or official organizational publications
Recommendations
Level 1: Convincingly justifiable on scientific evidence alone
Level 2: Reasonably justifiable by available scientific evidence and strongly supported by expert critical care opinion
Level 3: Adequate scientific evidence is lacking but widely supported by available data and expert critical care opinion

tion before any laboratory tests or imaging procedures are ordered.

This update specifically addresses how to evaluate a new fever in an adult patient already in the ICU who has previously been afebrile and in whom the source of fever is not initially obvious. This update will assist intensivists and consultants as a starting point for developing an effective and cost-conscious approach appropriate for their patient populations. The specific recommendations are rated by the strength of evidence, using the published criteria of the Society of Critical Care Medicine (Table 1).

Initiating a Fever Evaluation: Measuring Body Temperature and Defining Fever as Thresholds for Diagnostic Effort

Definition of Fever. The definition of fever is arbitrary and depends on the purpose for which it is defined. Some literature defines fever as a core temperature of >38.0°C (100.4°F) (2–4), whereas other sources define fever as two consecutive elevations of >38.3°C (101.0°F). In patients who are neutropenic, fever has been defined as a single oral temperature of >38.3°C (101.0°F) in the absence of an obvious environmental cause, or a temperature elevation of >38.0°C (100.4°F) for >1 hr (4). A variety of definitions of fever are acceptable, depending on how sensitive an indicator of thermal abnormality an ICU practitioner wants to utilize. Normal body temperature is generally considered to be 37.0°C (98.6°F) (4, 5). In healthy individuals, this temperature varies by 0.5 to 1.0°C, according to circadian rhythm and menstrual cycle (6). With heavy exercise, temperature can rise by 2 to 3°C (7). Whereas many biological processes can alter body temperature, a variety of environmental forces in an ICU can also alter temperature, such as specialized mattresses, hot lights, air conditioning, cardiopulmonary bypass, peritoneal lavage, dialysis, and continuous hemofiltration (8–10). Thermoregulatory mechanisms can also be disrupted by drugs or by damage to the central or the autonomic nervous systems. Thus, it is often difficult to determine whether an abnormal temperature is a reflection of a physiologic process, a drug, or an environmental influence.

A substantial proportion of infected patients are not febrile: such patients may be euthermic or hypothermic. These patients include the elderly, patients with open abdominal wounds, patients with large burns, patients receiving extracorporeal membrane oxygenation or continuous renal replacement therapy (11), patients with congestive heart failure, end-stage liver disease, or chronic renal failure, and patients taking anti-inflammatory or antipyretic drugs. A patient who is hypothermic or euthermic may have a life-threatening infection. Other symptoms and signs in the absence of fever, such as otherwise unexplained hypotension, tachycardia, tachypnea, confusion, rigors, skin lesions, respiratory manifestations, oliguria, lactic acidosis, leukocytosis, leukopenia, immature neutrophils (i.e., bands) of >10%, or thrombocytopenia, might appropriately mandate a comprehensive search for infection and aggressive, immediate empirical therapy.

As a broad generalization, it is reasonable in many ICUs to consider everyone with a temperature of ≥38.3°C (≥101°F) to be febrile and to warrant special attention to determine whether infection is present. However, a lower threshold may be used for immunocompromised patients because they are not able to manifest a similar fever response as the one seen in immunocompetent patients. Effective management of patients in an ICU mandates that infection be considered in patients regardless of temperature but that laboratory tests to search for infection should be initiated in febrile patients only after a clinical assessment indicates a reasonable possibility that infection might be present.

Site and Technology of Temperature Measurement. The ideal system for measuring temperature should provide reliable, reproducible values safely and conveniently. Any device must be calibrated properly and checked periodically according to the manufacturer's specifications.

Most authorities consider the thermistor of a pulmonary artery catheter to be the standard for measuring core temperature against which other devices must be compared (6, 12–16). Not all patients have such a thermistor in place. Even when available, these thermistors are not all equal in technical performance. Thermistors in indwelling bladder catheters provide essentially identical readings to thermistors in intravascular sites, are less invasive, provide continuous readings, and provide stable measurements, regardless of urine flow rate (12, 13, 16–18). However, bladder thermistor catheters are costly and require a monitor. Esophageal probes placed in the distal third of the esophagus provide readings comparable with thermistors in intravascular sites and with bladder catheters (19). However, confirming accurate placement is difficult because they are not radiopaque. In addition, they are uncomfortable in alert or spontaneously breathing patients. The theoretical risk of an esophageal probe eroding or perforating the esophagus when left in place for extended periods of time makes this probe impractical for use in the critically ill patient.

Rectal temperatures obtained with a mercury thermometer or an electronic probe (intermittent or continuous) are traditional measurement devices. Readings from the rectum are often a few tenths of a degree higher than core temperature (12, 14, 20, 21). The patient often perceives rectal temperature measurement as unpleasant and intrusive. Access to the rectum may be limited by patient position. Moreover, there is a small risk of trauma or perforation to the rectum, which is a particular problem in patients who are neutropenic, coagulopathic, or who have had recent rectal surgery. Rectal temperature measurements have also been implicated in spreading enteric pathogens such as *Clostridium difficile* or vancomycin-resistant enterococci via the device or the operator (22–24).

Oral temperature measurement is safe, convenient, and familiar for alert

and cooperative patients. Mouth breathing, heated gases, and hot or cold fluids can distort the reading (13, 25). Oral probes can damage oral mucosa, especially in patients with abnormal mucosa due to trauma, thermal injury, infection, surgery, cancer, or cytotoxic drugs. In critically ill patients, oral temperatures are often not practical due to intubation or inability of the patient to cooperate.

Tympanic membrane temperature is believed to reflect the temperature of the hypothalamus and, thus, the core body temperature. Direct measurement of the tympanic membrane temperature requires an electronic probe, is painful in awake patients, and risks trauma to the tympanic membrane. Infrared ear thermometry is also available to detect radiant energy from the tympanic membrane and ear canal through an otoscopic probe. These devices are not accurate if inflammation of the auditory canal or tympanic membrane is present or if there is obstruction of the external canal. Tympanic membrane and infrared devices do not always agree with other measurement devices. Multiple studies have shown consistently poor agreement between measurements made by infrared ear devices and those made by pulmonary artery catheters (12–16, 18, 26).

Infrared thermometry measurement technology used in tympanic membrane thermometers has been adapted to a noninvasive temporal artery thermometer (27). Because the temporal artery has a high arterial perfusion rate that remains unchanged under most conditions, measurement of temperature via skin areas perfused by the temporal artery provide an easy, noninvasive estimate of the core temperature (28). Environmental temperature and sweating have been associated with unreliable temperature measurements compared with rectal and esophageal temperature (29), and the temporal artery thermometer provides similar accuracy to axillary measurements that are not recommended (27).

The chemical dot thermometer is a single-use, flexible polystyrene plastic strip with 50 heat-sensitive dots (temperature sensors) applied to the forehead; each dot represents a temperature increment of 0.1°C over a range of 35.5–40.4°C; the last dot to turn blue constitutes the body temperature (30). Lack of agreement between measurements made using this device and pulmonary artery catheters limits their usefulness in critically ill patients (26).

Table 2. Accuracy of methods used for measuring temperature (6, 12–16)

Most accurate
Pulmonary artery thermistor
Urinary bladder catheter thermistor
Esophageal probe
Rectal probe
Other acceptable methods in order of accuracy
Oral probe
Infrared ear thermometry
Other methods less desirable
Temporal artery thermometer
Axillary thermometer
Chemical dot

Recommendations for Measuring Temperature

1. Choose the most accurate and reliable method to measure temperature based on the clinical circumstances of the patient. Temperature is most accurately measured by an intravascular, esophageal, or bladder thermistor, followed by rectal, oral, and tympanic membrane measurements, in that order (Table 2). Axillary measurements, temporal artery estimates, and chemical dot thermometers should not be used in the ICU (level 2). Rectal thermometers should be avoided in neutropenic patients (level 2).
2. Any device used to measure temperature must be maintained and calibrated appropriately, using the manufacturer's guidelines as a reference (level 2).
3. Any device used to measure temperature must be used in a manner that does not facilitate spread of pathogens by the instrument or the operator (level 2).
4. The site of temperature measurement should be recorded with the temperature in the chart (level 1).
5. A new onset of temperature of ≥38.3°C is a reasonable trigger for a clinical assessment but not necessarily a laboratory or radiologic evaluation for infection (level 3).
6. A new onset of temperature of <36.0°C in the absence of a known cause of hypothermia (e.g., hypothyroidism, cooling blanket, etc.) is a reasonable trigger for a clinical assessment but not necessarily a laboratory or radiologic evaluation for infection (level 3).
7. Critical care units could reduce the cost of fever evaluations by eliminating automatic laboratory and radiologic tests for patients with new temperature elevation (level 2). Instead, these tests should be ordered based on clinical assessment. A clinical and laboratory evaluation for infection, conversely, may be appropriate in euthermic or hypothermic patients, depending on clinical presentation.

Blood Cultures

Because the information provided by a positive blood culture can have such important prognostic and therapeutic implications, blood cultures should be obtained in patients with a new fever when clinical evaluation does not strongly suggest a noninfectious cause.

Skin Preparation. The site of venipuncture should be cleaned with either 2% chlorhexidine gluconate in 70% isopropyl alcohol (2% alcoholic chlorhexidine), or 1–2% tincture of iodine (iodine in alcohol). Povidone iodine (10%), although acceptable, is a less efficient agent. The access to an intravascular device and to the stopper on all blood culture bottles should be cleaned with 70–90% alcohol (31, 32). Most blood culture bottles should not be swabbed with iodine-containing antiseptics because these solutions may degrade the stoppers. Chlorhexidine and tincture of iodine are equally effective for cleaning the site of venipuncture and more effective than aqueous povidone iodine in reducing the rate of blood culture contamination (33–36). Iodophors (aqueous iodine solutions) must be allowed to dry 1.5–2 mins to provide maximal antiseptic activity and thus to minimize the risk of contamination (37). Both alcoholic chlorhexidine and tincture of iodine have an alcohol base, so they dry more rapidly (~30 secs) than iodophors. This reduces the time required for phlebotomy.

When blood is to be inoculated into a culture or transport tube, the needle used for venipuncture should not be replaced by a sterile needle. The risk of a needle stick injury during the switch in needles is currently thought to outweigh the risk of contamination (37, 38).

Blood Volume and Collection System. One blood culture is defined as a sample of 20–30 mL of blood drawn at a single time from a single site, regardless of how many bottles or tubes the laboratory may use to process the specimen. The sensitivity of blood cultures for detection of true bacteremia or fungemia is related to many factors, the most important being obtaining the cultures before the initia-

Table 3. Blood culture systems

Method	Aerobes	Anaerobes	Yeast	Fungi	Mycobacteria	Comments
Conventional broth-in-bottle	++	++	+/++	+	+	Slower than automated systems
Broth-in-bottle with continuous monitoring	+++	++/+++	++/+++	+	+[a], +++[b]	Speeds time to detection compared with intermittent monitoring
Lysis-centrifugation (Isolator[c])	++/+++	+	+++	+++	+++	Volume cultured is 10 mL
Antibiotic removal systems (resin bottles)	++	+/++	++	+	+	Greatest yield on staphylococci and yeast compared with conventional systems

+, not recommended; ++, acceptable; +++, best available method.
[a]Using standard blood culture bottles; [b]using special mycobacterial bottles; [c]Isolator (Inverness Medical Innovations, Waltham, MA).

tion of anti-infective therapy and the volume of blood drawn (32, 39–44). The full amount of blood recommended for each bottle should be drawn (37). The volumes required for blood cultures are typically determined by laboratories based on the various media used and on recommendations of the manufacturer of the blood culture instrument employed (37). A variety of commercial blood culture systems can provide excellent results (Table 3). Laboratories need to make their own decisions about the best system, considering their budget, their manpower, and the patient population they serve. Special media or blood culture systems can be added in designated circumstances. The utility of antibiotic removal devices in blood culture systems is controversial, although some laboratories still use them routinely. Some studies have shown that, when compared with conventional culture systems, these devices can enhance the recovery of staphylococci and yeasts, regardless of whether the patient is receiving antibiotics (37, 45, 46); they do not seem to enhance the recovery of Gram-negative bacilli. Considering varying experiences related to benefit, and the substantial additive costs and increased number of contaminants (37, 47), their use is considered optional.

In general, commercial pediatric collection systems should not be used for adults: the smaller volume of blood sampled will diminish the yield of pathogens for adults (42). If it is not possible to secure the recommended volume of blood required for the adult collection system and <5 mL of blood is obtained, it is acceptable to inject the entire amount into the aerobic blood culture bottle.

Cultures of Blood for Unusual Pathogens. In special patient populations or in special geographic areas, it may be appropriate in the evaluation of fever to include special media or special blood culture systems for organisms other than common aerobic and anaerobic bacteria. For example, cultures containing resins or lytic agents may be helpful in isolating yeast, and lysis-centrifugation may be useful for isolating *Bartonella* species, dimorphic fungi, *Mycobacterium avium*, and *Mycobacterium tuberculosis*. Most often, these pathogens are sought in patients with specific underlying diseases (solid organ transplant and stem cell transplant recipients or patients with prolonged granulocytopenia), or they are sought because of epidemiologic circumstances (*Francisella*, *Bartonella*, or *Histoplasma*). In such situations, communication with the microbiology laboratory is essential to determine whether special culture systems, in addition to routine blood cultures, are needed or if incubating the routine culture for a longer period of time would be useful.

Number of Cultures and Sites. Recent data suggest that the cumulative yield of pathogens is optimized when three to four blood cultures with adequate volume (20–30 mL each) are drawn within the first 24 hrs of suspected bacteremia or fungemia (39, 48). Each culture should be drawn by separate venipuncture or through a separate intravascular device but not through multiple ports of the same intravascular catheter (49, 50). Ideally, blood cultures should not be drawn through nonintact or infected skin (e.g., burns). There is no evidence that the yield of cultures drawn from an artery is different from the yield of cultures drawn from a vein. If the patient has limited access for venipuncture, it is acceptable to draw blood cultures from separate intravascular devices. However, this may increase the number of contaminated blood cultures.

In most cases of true bacteremia/fungemia, when organisms are detected, all specimens, whether drawn through a catheter or through a venipuncture, will yield positive results (51). In the majority of cases of discordant results, the culture drawn through the device will be positive and the culture drawn by venipuncture will be negative; in such instances, the positive culture may represent a contaminant or a catheter-related infection, but clinical judgment rather than any rigid criteria is needed to interpret the significance of discordant results (50, 52, 53).

Drawing three to four blood cultures with appropriate volume from separate sites of access within the first 24 hrs of the onset of fever is the most effective way to discern whether an organism found in blood culture represents a true pathogen (multiple cultures are often positive), a contaminant (only one of multiple blood cultures is positive for an organism commonly found on skin and clinical correlation does not support infection), or a bacteremia/fungemia from an infected catheter (one culture from the source catheter is positive, often with a positive catheter tip, and other cultures are not) (32, 37, 54). Clinical judgment must determine which catheter(s) and which lumen(s) are used for drawing the culture(s). Clinical data that might determine drawing blood cultures from certain catheters include catheter dwell time (carefully inserted catheters that have been in place for <3 days are less likely to be infected than longer-dwelling catheters), conditions of insertion (emergency vs. routine), and local signs of inflammation. Many experts would use the distal port of a catheter to obtain blood cultures. If all blood cultures are obtained from catheters, the blood culture replacing the venipuncture should be obtained from the most recently inserted catheter. Blood cultures should not be obtained via a peripherally inserted venous catheter at the time of insertion as this leads to an unacceptably high rate of contamination (55). Finally, separating blood cultures by defined, spaced intervals (such as every 10 mins) has not been shown to enhance microbial recovery, is not practical, and may

lead to a delay in therapy in critically ill patients (56).

Labeling. Blood cultures should be clearly labeled with the exact time, date, and anatomic site or catheter lumen from which blood is drawn and also include other information (concomitant antimicrobial therapy) that may be appropriate. This labeling is extremely useful for interpreting the significance of the result (see section on catheter-related infections below).

Recommendations for Obtaining Blood Cultures

1. Obtain three to four blood cultures within the first 24 hrs of the onset of fever. Every effort must be made to draw the first cultures before the initiation of antimicrobial therapy. They can be drawn consecutively or simultaneously, unless there is suspicion of an endovascular infection, in which case separate venipunctures by timed intervals can be drawn to demonstrate continuous bacteremia (level 2).
2. Additional blood cultures should be drawn thereafter only when there is clinical suspicion of continuing or recurrent bacteremia or fungemia or for test of cure, 48–96 hrs after initiation of appropriate therapy for bacteremia/fungemia. Additional cultures should not be drawn as a single specimen but should always be paired (level 2).
3. For patients without an indwelling vascular catheter, obtain at least two blood cultures using strict aseptic technique from peripheral sites by separate venipunctures after appropriate disinfection of the skin (level 2).
4. For cutaneous disinfection, 2% chlorhexidine gluconate in 70% isopropyl alcohol is the preferred skin antiseptic, but tincture of iodine is equally effective. Both require ≥30 secs of drying time before proceeding with the culture procedure. Povidone iodine is an acceptable alternative, but it must be allowed to dry for >2 mins (level 1).
5. The injection port of the blood culture bottles should be wiped with 70–90% alcohol before injecting the blood sample into the bottle to reduce the risk of introduced contamination (level 3).
6. If the patient has an intravascular catheter, one blood culture should be drawn by venipuncture and at least one culture should be drawn through an intravascular catheter. Obtaining blood cultures exclusively through intravascular catheters yields slightly less precise information than information obtained when at least one culture is drawn by venipuncture (level 2).
7. Label the blood culture with the exact time, date, and anatomic site from which it was taken (level 2).
8. Draw 20–30 mL of blood per culture (level 2).
9. Paired blood cultures provide more useful information than single blood cultures. Single blood cultures are not recommended, except in neonates (level 2).
10. Once blood cultures have been obtained after the onset of new fever, additional blood cultures should be ordered based on clinical suspicion of continuous or recurrent bacteremia or fungemia (level 2).

Intravascular Devices and Fever

Stable vascular access is essential to the management of the critically ill patient. Most patients will have at least one central venous catheter, and many may have an arterial catheter as well. An increasing number of patients will have some type of tunneled, cuffed central venous catheter or some type of subcutaneous central venous port.

The relative risk of bloodstream infection caused by various intravascular devices ranges widely, depending on the length of the device, the type of device, the patient population, the techniques used in insertion, the frequency of manipulation, and the time they have been in place (57, 58). The highest risk is with short-term, noncuffed central venous catheters, in the range of 2–5 per 1,000 catheter days, and is especially high with noncuffed temporary hemodialysis catheters. Arterial catheters used for hemodynamic monitoring and peripherally inserted central venous catheters used in hospitalized patients seem to have a risk of catheter-related bloodstream infection (2–3 per 1,000 catheter days) similar to conventional subclavian, internal jugular, or femoral short-term, noncuffed central venous catheters. In contrast, the risk of bloodstream infection with small, peripheral intravenous catheters is <0.1 cases per 1,000 catheter days. With good care, surgically implanted ports are associated with a much lower risk of bacteremia/fungemia than temporary percutaneous catheters, approximating 0.2–1 per 1,000 catheter days (57).

Location of Infection. All intravascular devices need to be assessed daily, to determine whether they are still needed and whether there are signs of local infection at the site of insertion (manifested by inflammation or purulence at the exit site or along the tunnel), or systemically (manifested by positive blood cultures or thrombosis).

It is important to recognize that contaminated hubs are common portals of entry for organisms colonizing the endoluminal surface of the catheter (59, 60). In addition, infusate (parenteral fluid, blood products, or intravenous medications) administered through an intravascular device can become contaminated and produce device-related bacteremia or fungemia, which is more likely to culminate in septic shock than are other catheter-related infections.

Diagnosis. Patients with abrupt onset of signs and symptoms of sepsis without risk factors for nosocomial infection (e.g., young, immunocompetent), especially without any local site of infection, should prompt suspicion of infection of an intravascular device. Difficulty drawing or infusing through the catheter may point to the catheter as a source of infection. The presence of inflammation, with or without purulence, at the insertion site, though absent in most cases (61), when combined with signs and symptoms of sepsis, has been shown to be predictive of device-related bacteremia. Finally, recovery of certain microorganisms in multiple blood cultures, such as staphylococci, *Corynebacterium jeikeium*, *Bacillus* species, atypical mycobacteria, *Candida*, or *Malassezia* species, strongly suggest infection of an intravascular device.

Evaluation. As part of the comprehensive physical examination, the access site should be examined at least daily, and any expressible purulence or exudate should be Gram stained and cultured. A minimum of two peripheral blood cultures, or one culture drawn percutaneously and one drawn through the catheter, should be obtained. Standard blood cultures drawn through intravascular devices provide excellent sensitivity for diagnosis of bloodstream infection (62, 63).

Removal and culture of the catheter has historically been the gold standard for the diagnosis of catheter-related bloodstream infection, particularly with short-term catheters. Studies have demonstrated the reliability of semiquantita-

Table 4. Common pathogens and diagnostic tests available

Pathogen	Staining and Rapid Detection Methods	Culture Methods	Other Tests
Legionella	Urinary antigen (serogroup 1 only)	Selective media and nonselective BCYE agar	
Nocardia	Gram stain Modified acid-fast	BCYE agar	Nucleic acid amplification tests for species identification
Mycobacterium tuberculosis	Acid-fast stain Fluorochrome stain Nucleic acid amplification tests	Culture in liquid and solid media	Nucleic acid amplification tests
Mycobacterium avium complex	Acid-fast stain	As above	Nucleic acid tests (direct) for culture identification
Mycobacterium species	Acid-fast stain	As above	Nucleic acid tests (direct) for culture identification
Rhodococcus equi	Gram stain	Routine media	Nucleic acid tests (direct) for culture identification
Pneumocystis jiroveci	Fluorescent-labeled antibody Grocott stain Giemsa stain Gomori stain Toluidine blue		
Aspergillus species	KOH wet mount	Fungal-selective media	Serum ELISA for detection of galactomannan or 1-3β—glucan
Other mycelia	Calcofluor white		
Zygomycosis	Silver stains		
Herpes simplex	Direct fluorescent antibody Wright or Giemsa stain for intranuclear inclusions or multinucleated giant cells	Viral culture	BAL cytology for inclusion bodies Nucleic acid amplification tests
Cytomegalovirus	Shell vial Antigen detection Nucleic acid amplification tests	Viral culture (very slow growth)	BAL cytology for inclusions Blood assay for antigenemia CMV viral load
Human herpesvirus 6, 7	Nucleic acid amplification tests	Viral culture	
Adenovirus	Rapid antigen detection	Viral culture	Nucleic acid amplification tests
Influenza A/B	Direct fluorescent antibody Enzyme immunoassay Rapid antigen detection kit RT-PCR	Viral culture	
Respiratory syncytial virus	Enzyme immunoassay Nucleic acid amplification tests	Viral culture	
Strongyloides	Wet mount		Serum ELISA
Toxoplasma gondii	Giemsa stain		

BAL, bronchoalveolar lavage; BYCE, buffered charcoal yeast extract; CMV, cytomegalovirus; ELISA, enzyme-linked immunosorbent assay; RT-PCR, reverse transcription-polymerase chain reaction.

tive or quantitative catheter tip culture methods for the diagnosis of catheter-related bacteremia (64, 65) (Table 4). The diagnosis of catheter-related bloodstream infection is completed when a colonized catheter is associated with concomitant bloodstream infection with the identical organism, with no other plausible source. Gram-negative stain (66) or acridine orange stain (67) of intravascular segments of removed catheters also correlates with semiquantitative or quantitative cultures but are technically challenging, time consuming, and expensive to perform and thus are offered by few hospitals.

Some ICU clinicians routinely culture central venous catheters on removal, regardless of whether there is fever or any other reason to suspect catheter sepsis. Because up to 20% of removed central venous catheters are colonized at removal, most unassociated with local infection or bacteremia/fungemia, this practice adds to microbiology laboratory expense and can lead to unnecessary therapies if interpreted inappropriately. The predictive value of a positive catheter culture is very low when there is a low pretest probability of catheter sepsis (65), and catheters removed from ICU patients should only be cultured if there is strong clinical suspicion of catheter sepsis (68).

Cultures of catheters obviously require their removal, which presents a disadvantage in patients with long-term central venous devices. Prospective studies have shown that only 25–45% of episodes of sepsis in patients with long-term devices represent true device-related bloodstream infection (69). Thus, it would seem that development of methods for detecting device-related bloodstream infection that do not require removal of the device would be of great value. Although exit site swabs are not sensitive for detecting catheter-related infection, a negative catheter exit site swab culture has a high negative predictive value and may reduce the proportion of unnecessary catheter withdrawals (70, 71).

Blood cultures drawn through the catheter in combination with blood cultures drawn percutaneously may be especially useful for detecting catheter-related bloodstream infection. Microbial growth can be quantitated using a quantitative blood culture system, or by using the differential time to positivity for pe-

ripheral vs. catheter blood cultures drawn simultaneously. If both sets of cultures are positive for the same organism and the set drawn through the catheter becomes positive ≥120 mins earlier than the culture drawn peripherally, this is highly suggestive of catheter-related bloodstream infection. This method is less sensitive but as specific as quantitative culture.

A quantitative blood culture drawn through an infected catheter characteristically shows a marked step-up in concentration of organisms, usually ten-fold or greater, as compared with a quantitative blood culture drawn concomitantly from a peripheral vein. Due to the additional expense and expertise necessary for processing, quantitative cultures of catheter-drawn blood are not routinely performed as part of the usual evaluation of fever. They can, however, provide useful information, especially for surgically implanted catheters that cannot easily be removed.

For patients with fever alone who are not septic (i.e., temperature of >38°C or <36°C, white blood cell count of >12,000 cells/mm^3 or <4,000 cells/mm^3, heart rate of >90 beats/min, respiratory rate of >20 breaths/min, or $Paco_2$ of <32 [3]), there is usually no need to remove or change all indwelling catheters immediately, although such an approach would be the most cautious management strategy and might be desirable in a patient with a prosthetic heart valve or a fresh arterial graft (68). If patients have sepsis or septic shock refractory to vasopressors, peripheral embolization, disseminated intravascular coagulation, or acute respiratory distress syndrome, removal of all intravascular catheters and reinsertion at new sites is indicated, even if the catheters are cuffed or tunneled devices (72). If there is clinical evidence of vascular compromise (i.e., signs of occlusive venous thrombosis or arterial insufficiency), the catheter should be removed. If a radiographic study is performed and there is evidence of thrombosis, clinical judgment is needed to determine whether anticoagulation, thrombolysis, or surgical interventions are necessary.

Septic phlebitis of a central vein due to a centrally placed catheter is unusual (73, 74). With suppurative phlebitis, bloodstream infection characteristically persists after the catheter has been removed, producing a clinical picture of overwhelming sepsis with high-grade bacteremia or fungemia or with septic embolization. This syndrome is most often encountered in burn patients or other ICU patients who develop catheter-related infection that goes unrecognized, permitting microorganisms to proliferate to high levels within an intravascular thrombus (73–75). In patients with persistent bacteremia with *Staphylococcus aureus* or persistent fungemia, echocardiography is appropriate to assess for endocarditis and guide further therapy (68).

Recommendations for Management of Intravascular Catheters

1. Examine the patient at least daily for inflammation or purulence at the exit site or along the tunnel, and assess the patient for signs of venous thrombosis or evidence of embolic phenomena (level 2).
2. Any expressed purulence from the insertion site should be Gram stained and cultured (level 2).
3. If there is evidence of a tunnel infection, embolic phenomenon, vascular compromise, or septic shock, the catheter should be removed and cultured and a new catheter inserted at a different site (level 2).
4. With short-term temporary catheters—peripheral venous catheters, noncuffed central venous catheters, or arterial catheters—if catheter-related sepsis (i.e., source of the infection is a colonized catheter) is considered likely, the suspect catheter or catheters should be removed and a catheter segment cultured. Blood cultures should be obtained as well. With all short-term catheters, a 5- to 7-cm intracutaneous segment should be cultured to document the source of bacteremia; with short peripheral venous or arterial catheters, the tip should be cultured; with longer central venous catheters, the intracutaneous segment and tip should be cultured; and with pulmonary artery catheters, the introducer and the pulmonary artery catheter should be cultured (level 1).
5. At least two blood cultures should be obtained. At least one blood culture should be obtained peripherally by venipuncture. One specimen should be obtained from the suspected catheter (level 1). If a quantitative culture system is available, it should be used to diagnose the catheter as the source of bacteremia/fungemia. Alternatively, differential time to positivity can be used if both blood cultures are positive for the same organism. The distal port is the logical port from which to draw cultures. When short-term, uncuffed central venous catheters are suspected of infection, it is usually more efficient to remove the existing catheter and replace it than to draw quantitative cultures (level 2).
6. Do not routinely culture all catheters removed from ICU patients. Culture only those catheters suspected of being the source of infection (level 2).
7. It is not necessary to routinely culture infusate specimens as part of the evaluation for catheter-related infections, unless there is clinical suspicion for infected infusate or blood products (level 2).

Pulmonary Infections and ICU-Acquired Pneumonia

Pneumonia is the second most common cause of infection acquired in the ICU and a ubiquitous cause of fever, with the majority of cases occurring in mechanically ventilated patients (76, 77). In an ICU, it can be difficult to determine whether fever is due to pneumonia when patients commonly have other noninfectious processes producing abnormal chest radiographs and gas exchange (i.e., congestive heart failure, atelectasis, acute respiratory distress syndrome). Many patients in an ICU are intubated and sedated, cannot cough, and have other reasons for abnormal secretions. In addition, immunocompromised patients, such as solid organ transplant recipients, may have severe pneumonia without fever, cough, sputum production, or leukocytosis (78, 79).

Diagnostic Evaluation. Physical examination, chest radiograph, and examination of pulmonary secretions comprise the initial evaluation. For initial fever evaluations, portable chest radiographs are generally adequate. All radiographs should be performed in an erect sitting position, during deep inspiration if possible. Among all radiographic signs in ICU patients, unilateral air bronchograms have been shown to have the best predictive value for pneumonia; however, no single radiographic finding is highly predictive (80–82). The absence of infiltrates, masses, or effusions does not exclude pneumonia, abscess, or empyema as a cause of fever. Clinical judgment is needed to determine whether the suspicion of infection is high enough to warrant transporting the patient to the radi-

ology suite for a higher resolution study such as computerized tomographic (CT) imaging. Such studies are particularly sensitive for demonstrating parenchymal or pleural disease in the posterior-inferior lung bases (83, 84), although there is only a fair correlation with a diagnosis of pneumonia in complex patients (85). CT imaging is also valuable in immunocompromised patients, in whom small nodular or cavitary lesions are more prevalent and difficult to detect by standard chest radiographs (86, 87). Respiratory secretions can be obtained for examination by a variety of techniques. Expectoration, nasopharyngeal washing, saline induction, deep tracheal suctioning, bronchoscopic protected specimen brush samples or aspiration, or bronchoscopic or nonbronchoscopic (mini-BAL) bronchoalveolar lavage are the principle diagnostic options. Each of these techniques has advantages and disadvantages (77, 88). For initial evaluation of fever in the nonintubated patient, before it is apparent whether pneumonia is present, evaluation of an expectorated sputum, nasotracheal or endotracheal aspirate, as opposed to a more invasively obtained specimen, is usually sufficient. In the intubated patient, saline should be instilled in the endotracheal tube only if an adequate specimen cannot be obtained by deep suctioning in the absence of saline. There is concern that saline dilutes the specimen and could introduce pathogens present in the tube biofilm or upper airway into the lower airway.

The utility of fiberoptic bronchoscopy is variable and depends on the patient populations, causative organism, and current and previous use of antibiotics. Aspirates from the inner channel of the bronchoscope are characteristically contaminated by upper respiratory flora (89, 90). If bronchoscopic sampling is not immediately available, nonbronchoscopic sampling (mini-BAL) can reliably obtain lower respiratory secretions for microscopic evaluation (88, 91). Bronchoscopy, however, may be especially useful for the detection of selected pathogens such as *Pneumocystis jiroveci*, *Aspergillus* and other filamentous fungi, *Nocardia*, *Legionella*, cytomegalovirus (CMV), and *Mycobacterium* species (92, 93).

When pulmonary secretions are acquired for analysis, the specimen should be transported to the laboratory and processed within 2 hrs so that fastidious organisms such as *Streptococcus pneumoniae* remain viable (94). For any expectorated specimen, it is important for the laboratory to perform direct microscopy on the specimen to determine whether it represents saliva (i.e., if the predominant cells are squamous epithelial) or lower respiratory secretions (i.e., if the predominant cells are leukocytes, assuming the patient is nonneutropenic).

If the specimen is of lower respiratory origin, in most situations, a Gram-negative stain should be performed, and the specimen should be cultured for routine aerobic bacterial pathogens. In appropriate circumstances, principally defined by the host category, rapidity of clinical presentation, and radiographic features, it may be desirable to perform other direct tests, such as a potassium hydroxide with calcofluor stain for fungus, an enzyme-immunoassay, or direct fluorescent antibody tests for respiratory viruses and *P. jiroveci*, and an acid-fast stain for mycobacteria. It may also be desirable to culture the specimen for fungi, mycobacteria, *Legionella*, and respiratory viruses. Urinary antigen tests are currently available for *Legionella pneumophila* type 1 and *S. pneumoniae*. Some laboratories have developed and verified nucleic acid amplification tests for some of these pathogens. However, there are currently no assays approved by the Food and Drug Administration, except those available for *M. tuberculosis*. The use of such assays must be driven by institution-specific expertise and in consultation with clinicians. Because local and referral center testing methods may vary across different centers, the most common laboratory technique options for each pathogen are summarized in Table 4.

Clinicians need to be aware of the organisms that are virtually always pathogens when recovered from respiratory secretions. Although not all-inclusive, these organisms might include *Legionella*, *Chlamydia*, *M. tuberculosis*, *Rhodococcus equi*, influenza virus, respiratory syncytial virus, parainfluenza virus, *Strongyloides*, *Toxoplasma gondii*, *P. jiroveci*, *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, and *Cryptococcus neoformans*. Conversely, isolation of enterococci, viridans streptococci, coagulase-negative staphylococci, and *Candida* species (93, 95, 96) should rarely if ever be considered the cause of respiratory dysfunction. Potential bacterial pathogens such as *Pseudomonas aeruginosa*, Enterobacteriaceae, *S. pneumoniae*, *S. aureus*, and *Haemophilus influenzae* are frequently encountered in respiratory specimens and may represent contaminants that colonize the upper airways, or they may be true pathogens of pneumonia. The distinction between pathogen and colonizer is facilitated by detection of pathogenic organisms as the dominant flora on direct Gram-negative stain or their recovery in respiratory secretions in moderate or heavy growth. Quantitative cultures of bronchoscopic or other specimens from lower airways may also facilitate the distinction between colonizing bacteria and pathogens. The use of these quantitative techniques has been shown to increase the specificity of the diagnosis of healthcare-associated pneumonia in some studies but requires bronchoscopic expertise, considerable labor by the microbiology department, and well-standardized methodology (88).

Clinical interpretation of quantitative cultures is likely to be hampered by previous antibiotic administration, which may lower the observed quantitative inoculum after 24 hrs of ongoing antibiotic therapy and up to 72 hrs after cessation of antibiotics (97, 98). The utility of quantitative cultures to identify the causative pathogen has been reviewed elsewhere (99–101).

It is appropriate to draw blood cultures to attempt to identify the cause of pneumonia. Blood tests other than cultures may also yield the etiology of pneumonia, especially in immunocompromised patients: a) antigenemia for CMV in non–human immunodeficiency virus-infected patients, histoplasmosis, and cryptococcosis; b) polymerase chain reaction for CMV, varicella-zoster virus, human herpes virus-6, and adenovirus; and c) galactomannan and beta-D-glucan for aspergillosis and *Candida* may be useful as supportive evidence of infections but may be most useful to exclude invasive fungal infection, given their high negative predictive value.

Many febrile patients in an ICU have small amounts of pleural fluid due to congestive heart failure, hypoalbuminemia, or postoperative processes. It is not necessary to obtain a sample of such fluid for culture in every febrile patient. Thoracentesis to obtain fluid for stain, culture, and cytology (and for measurement of pH, protein, glucose, and lactate dehydrogenase) would be especially appropriate if there is enough fluid to aspirate safely using ultrasound guidance and if there is either an adjacent pulmonary infiltrate, suspicion of tuberculosis, or possible contamination of the pleural space

by surgery, trauma, or a fistula (102, 103). The fluid should be cultured for aerobic and anaerobic bacteria. Cultures for fungi and mycobacteria should be performed as epidemiologically appropriate.

Once cultures are obtained and the laboratory grows pathogens, antimicrobial susceptibility tests should be performed on isolates of aerobic and facultative bacteria, including *S. pneumoniae*. Susceptibility tests should be performed and interpreted using the most recent criteria published by the Clinical and Laboratory Standards Institute. Susceptibility tests for anaerobic bacteria, fungi, or viruses are not routinely indicated.

Recommendations for Evaluation of Pulmonary Infections. If a febrile patient is suspected of having a lower respiratory tract infection by clinical or radiographic assessment:

1. A chest imaging study should be obtained. In most cases, an upright portable anteroposterior chest radiograph is the most feasible study to obtain. Posterior-anterior chest radiographs with lateral view or CT scan offer more information and should be obtained when clinically indicated, especially to rule out opportunistic infections in immunocompromised patients (level 1).
2. Obtain one sample of lower respiratory tract secretions for direct examination and culture before initiation of or change in antibiotics. Expectorated sputum, induced sputum, tracheal secretions, or bronchoscopic or nonbronchoscopic alveolar lavage material can be used effectively. If pneumonia is documented by physical examination and radiographic evaluation, a decision to employ bronchoscopy or other invasive diagnostic approaches should be considered based on an individual basis and the availability of local expertise (level 2).
3. Respiratory secretions obtained for microbiological evaluation should be transported to the laboratory and processed in <2 hrs (level 2).
4. Respiratory secretions that are judged to be appropriate samples by the laboratory should be evaluated by Gram-negative stain and cultured for routine aerobic and facultative bacteria. Additional stains, rapid tests, cultures, and other tests should be performed as epidemiologically appropriate (level 2).
5. Quantitative cultures can provide useful information in certain patient populations when assessed in experienced laboratories; however, quantitative cultures have not yet been sufficiently standardized nor have they been shown to alter outcome for this technique to be considered part of routine evaluation (level 2).
6. Pleural fluid should be obtained with ultrasound guidance for Gram-negative stain and routine culture (with other studies as clinically indicated) if there is an adjacent infiltrate or another reason to suspect infection and the fluid can be safely aspirated (level 2).

Stool Evaluation in the Febrile Patient in the ICU

Many patients in the ICU have diarrhea, which is often caused by enteral feedings or drugs. By far the most common enteric cause of fever in the ICU is *Clostridium difficile*, 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 the diarrhea (104, 105). *C. difficile* accounts for 10–25% of all cases of antibiotic-associated diarrhea and virtually all of the cases of antibiotic-associated pseudomembranous colitis (106). Other organisms that can cause fever and diarrhea include *Salmonella*, *Shigella*, *Campylobacter jejuni*, *Aeromonas*, *Yersinia*, *Escherichia coli*, *Entamoeba histolytica*, and multiple viruses that are not usually identified by standard techniques. In general, these are community-acquired diseases and only rarely cause infectious diarrhea acquired after a patient has been admitted to the ICU. If the patient was not initially admitted to the hospital with diarrhea and is not infected with HIV, it is unlikely that these organisms would produce diarrhea and fever in the ICU. Thus, sending stools for bacterial cultures or ova and parasite examination should generally be avoided as part of a fever evaluation unless the patient was admitted to the hospital with diarrhea, is infected with HIV, or is a part of an outbreak evaluation.

Presentation. Most patients with *C. difficile* as the cause for their fever present with diarrhea. (Diarrhea is defined in this document as more than two stools per day that conform to the container in which they are placed.) However, some patients, especially those who are postoperative, may present with ileus or toxic megacolon or leukocytosis without diarrhea as the manifestation of *C. difficile* disease. In these patients, the diagnosis of *C. difficile* disease may be difficult to establish because stool specimens are not accessible (107). *C. difficile*–associated diarrhea may occur with any antibacterial agent, but the most common causes are clindamycin, cephalosporins, and fluoroquinolones (108). Other clinical clues are fever, toxic megacolon, leukocytosis (especially with a leukemoid reaction), and hypoalbuminemia (109).

Evaluation for C. difficile. Testing algorithms differ markedly among institutions. The most sensitive and specific test most laboratories can perform to establish this diagnosis is the tissue culture assay (110, 111). Disadvantages with this test are the 24- to 48-hr delay in results, lack of experience with tissue culture techniques in many laboratories, and cost. As a result, most laboratories now use enzyme immunoassay (EIA) tests, which are commercially available, provide results within minutes to hours, and are technically easy to perform. They are less sensitive than the tissue culture assay and consequently may require two to three repeat tests to document disease (112). The EIA for toxin A is available, but 2–3% of stains produce only toxin B, so the EIA for toxin A and B is preferred (113). Once toxin is demonstrated, there is no utility in follow-up assays to demonstrate cure, as patients may shed toxin long after they are clinically cured. A two-step algorithm that screens samples for glutamate dehydrogenase, the *C. difficile* common antigen, followed by testing only positives for toxin has been demonstrated to have high negative predictive value (114, 115).

Cultures for *C. difficile* are technically demanding, require 2 to 3 days for growth, and are not specific in distinguishing toxin-positive strains, toxin-negative strains, and asymptomatic carriage (112, 116). Cultures may be useful in the setting of nosocomial outbreaks when isolates are needed for strain typing for epidemiologic purposes (105). The NAP1 strain has been epidemic in many hospitals in the United States, Canada, and Europe; it is associated with serious complications (toxic megacolon, leukemoid reactions, sepsis, and death) and is often refractory to standard therapy (108, 117, 118). There are strain differences in virulence, which may be important to recognize for epidemiologic purposes (119). However, the methods to identify specific strains are not generally avail-

able, and strain identification does not alter management of individual patients.

Direct visualization of pseudomembranes is nearly diagnostic for *C. difficile* colitis (120). Most diagnoses by visualization come from proctoscopic evaluation rather than more extensive lower gastrointestinal evaluation. In terms of sensitivity, in patients with severe disease, only 71% of patients had pseudomembranes documented by direct visualization, whereas pseudomembranes were present in only 23% of patients with mild disease (121). Concerns about cost, risk of perforation during the examination, and the relative ease of cytotoxin assays have removed flexible sigmoidoscopy and colonoscopy from routine use for diagnosis. However, a role for direct visualization may exist in cases requiring rapid diagnosis if laboratory results will be delayed or if false-negative *C. difficile* toxin assays are suspected (105). Many clinicians would treat such patients empirically rather than perform sigmoidoscopy or colonoscopy.

Evaluation for Other Enteric Pathogens. Infection with *Klebsiella oxytoca* should be considered in patients with antibiotic-associated colitis who are negative for *C. difficile* (122). Patients who have a recent and significant travel history to developing countries, patients with HIV disease, and patients with unusual domestic exposures may require a more extensive evaluation. Patients with a recent travel history should have their evaluation directed by the most likely pathogens that occur in their area of travel, although the most common cause of travelers' diarrhea, enterotoxigenic *E. coli*, is not detected with the usual laboratory tests. Patients who have traveled to areas where parasitic disease is common should have their stool evaluated by stool ova and parasite examination for other organisms such as *Cyclospora*, *E. histolytica*, and *Strongyloides*. Norovirus should be considered in the setting of employee illness, patients with a travel history, or when multiple patients on a particular hospital unit are having fever, vomiting, and diarrhea.

Patients with HIV disease and CD4 $<100/\mu L$ often have chronic diarrhea caused by *Salmonella*, *Microsporidium*, CMV, or *M. avium* complex. *Microsporidium* detection requires special stains of the stool or small bowel biopsy. The diagnosis of CMV should be made endoscopically by means of a biopsy. CMV colitis should be highly suspected in the solid organ transplant recipient with fever and diarrhea, particularly in the recipient who received an allograft from a donor with positive CMV serology. Acute neutropenic enterocolitis or typhlitis caused by enteric Gram-negative bacilli (i.e., *Pseudomonas* species) or anaerobes (i.e., *Clostridium septicum*) should be sought in cancer or stem cell transplant recipients by imaging studies or endoscopy.

Recommendations for Evaluation of the Gastrointestinal Tract. If more than two stools per day conform to the container in which they are placed in a patient at risk for *C. difficile* and if clinical evaluation indicates that a laboratory evaluation is necessary:

1. Send one stool sample for *C. difficile* common antigen, EIA for toxin A and B, or tissue culture assay (level 2).
2. If the first specimen for *C. difficile* is negative and testing is performed by an EIA method, send an additional sample for *C. difficile* EIA evaluation. A second specimen is not necessary if the common antigen test was negative (level 2).
3. If severe illness is present and rapid tests for *C. difficile* are negative or unavailable, consider flexible sigmoidoscopy (level 3).
4. If severe illness is present, consider empirical therapy with vancomycin while awaiting diagnostic studies. Empirical therapy is not generally recommended if two stool evaluations are negative using a reliable assay. Although it may be more cost-effective than making the diagnosis, the empirical use of antibiotics, especially vancomycin, is discouraged because of the risk of producing resistant pathogens (level 2).
5. Stool cultures for other enteric pathogens are rarely indicated in a patient who did not present to the hospital with diarrhea or in patients who are not HIV infected. Send stool cultures for other enteric pathogens and examine for ova and parasites only if epidemiologically appropriate or evaluating an immunocompromised host (level 2).
6. Test stool for norovirus if the clinical and epidemiologic setting is appropriate. Testing for norovirus is usually only available in state laboratories and is usually performed in outbreak settings. Obtain consultation with infection control and public health authorities (level 3).

Urinary Tract Infection

Catheter-associated bacteriuria or candiduria usually represents colonization, is rarely symptomatic, and is rarely the cause of fever or secondary bloodstream infection (123), even in immunocompromised patients (124), unless there is urinary tract obstruction, the patient has had recent urologic manipulation or surgery, or is granulocytopenic (125, 126). The traditional clinical signs and symptoms (dysuria, urgency, pelvic or flank pain, fever or chills), that correlate well with significant bacteriuria in noncatheterized patients are rarely reported in ICU patients with documented catheter-associated bacteriuria or candiduria of $>10^5$ colony-forming units (cfu)/mL (123, 124).

Etiology. In the ICU, the majority of urinary tract infections are related to urinary catheters and are caused by multiresistant nosocomial Gram-negative bacilli other than *E. coli*, *Enterococcus* species, and yeasts (123, 127, 128).

Diagnosis. When clinical evaluation indicates the urinary tract is a source of fever, a specimen of urine should be obtained and evaluated by direct microscopy, Gram-negative stain, and quantitative culture.

The specimen should not be collected from the drainage bag because multiplication of bacteria to high levels can occur while the urine is in the bag (129). Rather, a specimen of urine should be aspirated from the catheter sampling port. Healthcare personnel should wear clean gloves whenever manipulating a urinary device and should scrupulously clean the port with 70–90% alcohol before collecting the specimen. For patients without a catheter in place, a conventional midstream clean-catch urine specimen should be obtained. Urine collected for culture should be transported to the laboratory and processed promptly to prevent the multiplication of insignificant numbers of microorganisms to high levels within the receptacle, which might lead to the misdiagnosis of infection. If the transport of urine will be delayed longer than approximately 1 hr, the specimen should be refrigerated. For transport to a remote laboratory site, the use of a urine preservative device containing boric acid is recommended (130).

In contrast to community-acquired urinary tract infections, where pyuria is highly predictive of significant bacteriuria, pyuria may be absent in patients

with catheter-associated urinary tract infection and, even if present, is not reliably predictive of infection or associated with symptoms referable to the urinary tract (123).

The concentration of urinary bacteria or yeast needed to cause symptomatic urinary tract infection or fever is unclear. Whereas it is clear that counts of $>10^3$ cfu/mL represent true bacteriuria or candiduria in catheterized patients (131), there are no data to show that higher counts are more likely to represent symptomatic infection than lower ones. Gram-negative stain of a centrifuged urinary specimen, however, will show microorganisms most of the time if infection is present (132) and can provide valuable information to the clinician selecting empirical antimicrobial therapy for suspected urosepsis.

Although it is appropriate to collect urinary specimens in the investigation of fever, routine monitoring or "surveillance" cultures of urine contribute little to patient management (133). The rapid dipstick tests, which detect leukocyte esterase and nitrite, are unreliable tests in the setting of catheter-related urinary tract infection. The leukocyte esterase test correlates with significant pyuria, which may or may not be present in a catheter-related urinary tract infection. The nitrite test corresponds to Enterobacteriaceae, which convert nitrate to nitrite. In the setting of active bacteriuria caused by *Enterococcus* species, *Candida* species, and coagulase-positive *Staphylococcus* species, it is not reliable and is not recommended for use in patients with urinary catheters in place (134, 135).

Recommendations for Evaluation of the Urinary Tract

1. For patients at high risk for urinary tract infection (kidney transplant patients, granulocytopenic patients, or patients with recent urologic surgery or obstruction), if clinical evaluation suggests a patient may have symptomatic urinary tract infection, a laboratory evaluation is necessary. Obtain urine for microscopic exam, Gram-negative stain, and culture (level 2).
2. Patients who have urinary catheters in place should have urine collected from the sampling port of the catheter and not from the drainage bag (level 2).
3. Urine should be transported to the laboratory and processed within 1 hr to avoid bacterial multiplication. If transport to the laboratory will be delayed for >1 hr, the specimen should be refrigerated. Alternatively, a preservative could be used but is less preferable to refrigeration (level 2).
4. Cultures from catheterized patients showing $>10^3$ cfu/mL represent true bacteriuria or candiduria, but neither higher counts nor the presence of pyuria alone are of much value in determining if the catheter-associated bacteriuria or candiduria is the cause of a patient's fever; in most cases, it is not the cause of fever (level 1).
5. Gram stains of centrifuged urine will reliably show the infecting organisms and can aid in the selection of antiinfective therapy if catheter-associated urosepsis is suspected (level 1).
6. Rapid dipstick tests are not recommended for patients with urinary catheters in the analysis of possible catheter-associated infection (level 1).

Sinusitis

In the ICU setting, nosocomial sinusitis is a closed-space infection that is infrequent and may be clinically occult but, when it occurs, can have serious consequences (136). Whereas sinusitis is often part of the differential diagnosis of fever, the prevalence is low in comparison with other nosocomial infections in the ICU, and the diagnosis can be difficult to document convincingly.

Etiology. The most common risk factor for sinusitis is anatomic obstruction of the ostia draining the facial sinuses, especially the maxillary sinuses. Transnasal intubations of the stomach and especially of the trachea are the leading risk factors, with transnasal intubation of the airway carrying a prevalence of sinusitis estimated to be 33% after 7 days of intubation. Maxillofacial trauma, with obstruction of drainage by retained blood clots, is another clear risk factor. The paranasal sinuses are normally sterile, but bacterial overgrowth occurs when drainage is impeded. The etiological agents responsible for most cases of nosocomial sinusitis are those that colonize the naso-oropharynx (137–139), which occur at high frequency among hospitalized patients, and especially among critically ill patients. Gram-negative bacilli (particularly *P. aeruginosa*) constitute 60% of bacteria isolated from nosocomial sinusitis, whereas Gram-positive cocci (typically *S. aureus* and coagulase-negative staphylococci) comprise one third of isolates and fungi the remaining 5–10% (138–141). Infections are often polymicrobial.

Diagnosis of Sinusitis. Either two major criteria (cough, purulent nasal discharge) or one major and two minor criteria (headache or earache, facial or tooth pain, fever, malodorous breath, sore throat, wheezing) suggest acute bacterial sinusitis in outpatients when these manifestations have been present for ≥7 days (142). A diagnostic challenge even among outpatients, the diagnosis of sinusitis in critically ill, intubated patients is even more difficult. Complaints of facial pain or headache may be impossible to elicit, and purulent nasal discharge is present in only 25% of proved cases of sinusitis (139).

Acute sinusitis can be suggested by plain radiographs, ultrasound, CT, or magnetic resonance imaging (143). Sinus opacification by plain radiography is sensitive but nonspecific for the diagnosis (139, 141, 144, 145). A combination of nasal endoscopy and plain radiography can increase accuracy but depends on the skill of the endoscopist (146). However, obtaining good-quality plain sinus radiographs is a practical impossibility using portable equipment in the ICU. CT scanning provides better sensitivity than plain radiography alone (147, 148).

Microbial analysis of fluid obtained by minimally invasive sinus puncture and aspiration under antiseptic conditions is definitive for the diagnosis of infectious sinusitis. In addition, tissue biopsy may need to be performed to rule out invasive fungal sinusitis in the immunocompromised patient. Although less well studied, endoscopically guided middle meatal tissue culture has been shown to be a safe alternative for septic patients who are not candidates for antral puncture, such as patients with coagulopathies (149). Sampling is mandatory because of the discordant accuracy between radiographic and microbiological testing, whereas pathogen identification and susceptibility testing permit focused, narrow-spectrum antimicrobial therapy. However, specimen collection is susceptible to contamination by bacteria colonizing the overlying mucosa if rigorous antisepsis is not practiced when obtaining the specimen.

Recommendations for Evaluation of the Sinuses

1. If clinical evaluation suggests that sinusitis may be a cause of fever, a CT scan of the facial sinuses should be obtained (level 2).
2. If the patient has not responded to

empirical therapy, puncture and aspiration of the involved sinuses under antiseptic conditions should be performed (level 2).
3. Aspirated fluid should be sent for Gram-negative stain and culture for aerobic and anaerobic bacteria and fungi to determine the causative pathogen and its antimicrobial susceptibility (level 1).

Postoperative Fever

Fever is a common phenomenon during the initial 48 hrs after surgery. It can be useful to remember that fever in this early postoperative period is usually noninfectious in origin (150), presuming that unusual breaks in sterile technique or pulmonary aspiration did not occur. Considerable money can be wasted in overzealous evaluation of early postoperative fever. However, once a patient is >96 hrs postoperative, fever is likely to represent infection.

A chest radiograph is not mandatory for evaluation of postoperative fever unless respiratory rate, auscultation, abnormal blood gas, or pulmonary secretions suggest a high probability of utility. Atelectasis is often considered to be a cause of postoperative fever, although this should be a diagnosis of exclusion. The clinician must be alert to the possibility that the patient could have aspirated during the perioperative period or that the patient was incubating a community-acquired process, for instance, influenza A or *Legionella* pneumonia, before the operation.

Urinary tract infection is common postoperatively because of the use of urinary drainage catheters (151). The duration of catheterization is the most important risk factor for the development of nosocomial cystitis or pyelonephritis. A urinalysis or culture is not mandatory to evaluate fever during the initial 2 to 3 days postoperatively unless there is reason by history or examination to suspect an infection at this site.

Fever can be related to hematoma or infection of the surgical field. Wound infection is rare in the first few days after operation, except for group A streptococcal infections and clostridial infections, which can develop 1–3 days after surgery. These causes should be suspected on the basis of inspection of the wound.

Many emergency abdominal operations are performed for control of an infection (e.g., peritonitis due to perforated diverticulitis). Even under optimal circumstances (definitive surgical source control and timely administration of appropriate broad-spectrum antibiotics), it may take ≥72 hrs for such patients to defervesce. New or persistent fever >4 days after surgery should raise a strong suspicion of persistent pathology or a new complication. Thus, it is mandatory to remove the surgical dressing to inspect the wound. Swabbing the wound for culture is rarely helpful if clinical assessment reveals no symptoms or signs suggesting infection (152). When erysipelas or myonecrosis is present, the diagnosis is often suspected by inspection alone, and such patients are usually "toxic" appearing. Muscle compression injury (either direct trauma or as a result of compartment syndrome) and tetanus are two other rare complications of traumatic wounds that may cause fever. Toxic shock may accompany infection with group A β-hemolytic streptococci or *S. aureus*.

Other potentially serious causes of postoperative fever include deep venous thrombosis, suppurative phlebitis, pulmonary embolism (153–156), drug-induced fever, anesthesia-induced malignant hyperthermia, acute allograft rejection, and catheter-related infection.

Recommendations for Evaluation of Fever Within 72 Hours of Surgery

1. A chest radiograph is not mandatory during the initial 72 hrs postoperatively if fever is the only indication (level 3).
2. A urinalysis and culture are not mandatory during the initial 72 hrs postoperatively if fever is the only indication. Urinalysis and culture should be performed for those febrile patients having indwelling bladder catheters for >72 hrs (level 3).
3. Surgical wounds should be examined daily for infection. They should not be cultured if there is no symptom or sign suggesting infection (see below) (level 2).
4. A high level of suspicion should be maintained for deep venous thrombosis, superficial thrombophlebitis, and pulmonary embolism, especially in patients who are sedentary, have lower limb immobility, have a malignant neoplasm, or are taking an oral contraceptive (level 2).

Surgical Site Infections

Surgical site infections alone account for approximately 25% of overall costs related to treatment of nosocomial infections. The rate of surgical site infection is approximately 3%, based on infections and operative case loads sampled from many hospitals (157, 158). This varies based on the degree of contamination of the incision, the medical comorbidity of the patient (e.g., diabetes mellitus and obesity increase the risk), whether surgery is prolonged or an emergency, and whether antimicrobial prophylaxis is administered correctly (e.g., appropriate narrow spectrum of activity, administration just before incision, and discontinuation within 24 hrs [48 hrs for cardiac surgery]), if indicated (152).

Microbiology. In clean surgical procedures, *S. aureus* from the patient's skin flora or the exogenous environment is the most common cause of surgical site infection (159, 160). However, Gram-negative bacilli may be causative for surgical site infections of clean infra-inguinal operations. For all other categories of procedures, the indigenous polymicrobial aerobic-anaerobic flora of the organ or tissue being operated on are the most common pathogens of surgical site infection. Infections of contaminated operations of perioral, perirectal, and vulvovaginal tissues yield bacteria that are similar to the normal microbial flora of the adjacent mucous membrane. Infections of areas remote from those sites are caused primarily by indigenous skin microflora, especially if no body cavity has been entered. Rarely, necrotizing incisional surgical site infection (superficial or deep) may be caused by group A *Streptococcus* or *Clostridium* species, which, if identified or suspected, carries the same diagnostic and therapeutic urgency as other manifestations of necrotizing soft-tissue infection.

Although patients commonly receive antibiotics when surgical site infection is first diagnosed, there is little or no evidence supporting this practice. Studies of subcutaneous abscesses found no benefit for antibiotic therapy when combined with drainage (161, 162). A trial of antibiotic administration for surgical site infections found no clinical benefit associated with this treatment (163). A common practice endorsed by most experts is to open all infected wounds (152).

Recommendations for Evaluation of Surgical Site Infection

1. Examine the surgical incision at least once daily for erythema, purulence, or

tenderness as part of the fever evaluation (level 2).
2. If there is suspicion of infection, the incision should be opened and cultured (level 2).
3. Gram-negative stain and cultures should be obtained from any expressed purulence obtained from levels within the incision consistent with a deep incisional or organ/space surgical site infection. Tissue biopsies or aspirates are preferable to swabs (level 3).
4. Drainage from superficial surgical site infections may not require Gram-negative stain and culture because incision, drainage, and local care may be sufficient treatment and antibiotic therapy may not be required. Superficial swab cultures are likely to be contaminated with commensal skin flora and are not recommended (level 2).
5. Standard guidelines should be used to define burn wound infection (level 3).

Central Nervous System Infection

A prospective study of fever in neurocritical care patients indicates that although fever occurs in about 25% of such patients, almost half are noninfectious in etiology (164). Hence, the intensivist needs to maintain a high index of suspicion for central nervous system infection.

Diagnostic Evaluation. Central nervous system infection rarely causes encephalopathy without focal abnormalities on neurologic examination. However, in any febrile ICU patient, even without focal findings, infection must be considered because of the inherent limitations of the neurologic examination in critically ill patients. However, the yield of lumbar puncture in patients without immune compromise or central nervous system instrumentation who develop mental status changes in the ICU may be low (165).

Imaging studies and culture of the cerebrospinal fluid are the cardinal features of a diagnostic evaluation. Patients with focal neurologic findings suggesting disease above the foramen magnum will generally require an imaging study before a lumbar puncture. A noncontrast CT scan is adequate to exclude mass lesions or obstructive hydrocephalus, which might contraindicate a lumbar puncture. If bacterial meningitis is suspected and the lumbar puncture is delayed for any reason, including an imaging study, then appropriate empirical antibiotic therapy for meningitis due to rapidly fatal etiologies (such as *S. pneumoniae*) should be started after blood cultures are obtained. The usual contraindications to lumbar puncture detected by CT scanning include lateral shift of midline structures, loss of the suprachiasmatic and basilar cisterns, obliteration of the fourth ventricle, or obliteration of the superior cerebellar and quadrigeminal plate cisterns with sparing of the ambient cisterns (166). If the physical examination suggests involvement of the spinal cord, consultation with a neurologist or neurosurgeon should be obtained because of the potential for spinal cord herniation with an intra-axial mass. Whether to postpone a lumbar puncture for an imaging study in a patient who is unresponsive without focal findings is a clinical decision.

Patients with suspected brain abscesses should not undergo a lumbar puncture until the degree of cerebral edema and intracranial hypertension are determined (167). Aspiration of the suspected abscess is the diagnostic procedure of choice. The optimal timing of aspiration is currently debated; if it is delayed, empirical antibiotic therapy should be considered.

Patients with Intracranial Devices. When a patient with an intracranial device, such as a ventriculostomy catheter or a ventriculoperitoneal shunt, becomes febrile, cerebrospinal fluid (CSF) should almost always be obtained for analysis. The site of CSF access in the patient with a ventriculostomy is straightforward. The patient with a shunt system that includes a CSF reservoir should have the reservoir aspirated; this is also the case for patients with Ommaya reservoirs. Patients in whom CSF flow to the lumbar subarachnoid space is obstructed may also need a lumbar puncture because one space may be infected while the other is sterile. In patients with ventriculostomies who develop stupor or signs of meningitis, the catheter should be removed and the tip cultured.

Tests to Be Performed on CSF. Basic tests to be performed on CSF from patients with suspected central nervous system infection include cell counts and differential, glucose and protein concentrations, Gram-negative stain, and bacterial cultures. Whether to perform cryptococcal antigen testing, fungal staining and cultures, acid-fast bacillus smears and cultures, cytologic examination for neoplasia, polymerase chain reaction tests, or a serologic test for syphilis depends on the clinical situation. The immunocompromised patient may require additional tests such as polymerase chain reaction for herpes simplex virus, CMV, Epstein-Barr virus, human herpes virus-6, JC virus, West Nile virus, adenovirus, and enterovirus. The precise combination of tests with the greatest likelihood of detecting bacterial infection depends on the patient population. The normal protein content of CSF varies with the site from which it was withdrawn; ventricular fluid usually has an upper protein content limit of 15 mg/dL, cisternal fluid of 20 mg/dL, and lumbar fluid of 45 mg/dL.

Patients with bacterial meningitis typically have a CSF glucose of <35 mg/dL, a CSF-blood glucose ratio of <0.23, a CSF protein level concentration of >220 mg/dL, $>2{,}000$ total white blood cells/μL, or $>1{,}180$ neutrophils/μL (168). Conversely, in immunologically normal hosts, the presence of a normal opening pressure, <5 white blood cells/μL, and a normal CSF protein concentration essentially exclude meningitis (169). The applicability of these findings to the critically ill immunocompromised patient is uncertain, and a high index of suspicion for infection should be maintained, regardless of cell count and glucose concentration, until cultures are final. CSF lactate measurements may be useful in neurosurgical patients to distinguish infection from postoperative aseptic meningitis (170, 171).

Recommendations for Evaluation of Central Nervous System Infections

1. If altered consciousness or focal neurologic signs are unexplained, lumbar puncture should be considered in any patient with a new fever, unless there is a contraindication to lumbar puncture (level 3).
2. For a patient with a new fever and new focal neurologic findings suggesting disease above the foramen magnum, an imaging study is usually required before lumbar puncture. If a mass is present, neurology/neurosurgery consultation is required to determine the optimal diagnostic approach (level 2).
3. In febrile patients with an intracranial device, CSF should be obtained for analysis from the CSF reservoir. If CSF flow to the subarachnoid space is obstructed, it may be prudent to also obtain CSF from the lumbar space (level 3).
4. In patients with ventriculostomies who develop stupor or signs of meningitis, the catheter should be removed and the tip cultured (level 3).
5. CSF should be evaluated by Gram-negative stain and culture, glucose,

protein, and cell count with differential. Additional tests for tuberculosis, viral and fungal disease, neoplasia, etc., should be performed as dictated by the clinical situation (level 2).

Other Considerations

Mononucleosis syndrome after blood transfusion has been broadly recognized as a cause of hectic fever in postsurgical patients for more than four decades. Infection may be caused by transmission of CMV by way of transfused white blood cells in the blood product or from reactivation of CMV by transfusion-induced antigenic stimulation (172). The spectrum of disease related to posttransfusion CMV ranges from asymptomatic conversion to a self-limited mononucleosis syndrome. In symptomatic patients, symptoms usually begin 1 month after transfusion. The classic features of mononucleosis are usually absent. Rather, patients develop high fever, which often leads to empirical antimicrobial therapy for sepsis. This syndrome should be suspected when patients with spiking fevers do not respond to antimicrobial therapy or when cultures for bacterial pathogens are negative. Immunocompetent patients with this syndrome lack clinical toxicity, despite daily fever as high as 40°C. The presence of pancytopenia with atypical lymphocytosis and mild elevations of liver function tests may also be clues to this entity (173, 174). In contrast, immunocompromised patients can develop serious consequences, including fatal disseminated disease or diffuse interstitial pneumonia, especially in the setting of primary infection (seronegative patient transfused with seropositive blood). In general, transplant services attempt to administer screened, filtered, or leukocyte-reduced blood components to this group of seriously ill patients to prevent CMV disease. This has substantially reduced but not completely eliminated the risk of this infection. Diagnosis can be made by using quantitative molecular nucleic acid amplification tests to measure serum viral load.

Silent sources of infection, including but not limited to otitis media, decubitus ulcers at the sacrum or the back or the head, perineal or perianal abscesses, and undetected retained tampons need to be carefully ruled out. The recognition and identification of these other less common infectious causes of fever require a careful history and physical examination, including the examination of all devices, drains, and hardware on a daily basis.

Use of Adjunctive Markers for the Evaluation of Fever. Several biomarkers have been investigated for their utility in rapidly discriminating true infection from other inflammatory processes causing fever. Several generations of serum procalcitonin assays with variable cutoff points have been examined (175–180). A more sensitive serum procalcitonin assay is now approved for the early detection of bacterial infections and sepsis in patients during the first day of ICU admission. Procalcitonin level elevations of >0.5 ng/mL occur within 2–3 hrs of onset, with higher levels observed along the continuum from systemic inflammatory response syndrome (0.6–2.0 ng/mL), severe sepsis (2–10 ng/mL), and septic shock (>10 ng/mL). Most importantly, viral infections, recent surgery, and chronic inflammatory states are not associated with an increment in procalcitonin levels.

Traditional endotoxin detection systems, such as the chromogenic limulus lysate assay, have been hampered by contamination concerns, cumbersome techniques, and variable sensitivity, with inconsistent correlation to the presence of true Gram-negative infection (181, 182). However, kinetic luminometric anti-assay (endotoxin activity assay) uses an antibody to the conserved lipid A component of endotoxin to form an antibody-antigen complex capable of stimulating a detectable host neutrophil respiratory burst in an *ex vivo* assay (183). In a multicenter ICU study, the endotoxin activity assay demonstrated a high negative predictive value (98.6%) for Gram-negative infection (184).

Tumor necrosis factor-α, interleukin-6, C-reactive protein, and triggering receptor expressed on myeloid cells-1 (TREM-1) have been tested as methods to discriminate true infection from other inflammatory states but have not yet been validated.

Recommendation for Using Biomarkers to Determine the Cause of Fever

1. Serum procalcitonin levels and endotoxin activity assay can be employed as an adjunctive diagnostic tool for discriminating infection as the cause for fever or sepsis presentations (level 2).

Noninfectious Causes of Fever in the ICU

Drug-Related Fever. Any drug can cause fever due to hypersensitivity (185–187). Hypersensitivity reactions may manifest as fever alone to life-threatening hypersensitivity, such as those that have been associated with abacavir and nevirapine. In addition, some drugs cause fever by producing local inflammation at the site of administration (phlebitis, sterile abscesses, or soft-tissue reaction): amphotericin B, erythromycin, potassium chloride, sulfonamides, and cytotoxic chemotherapies are prime examples. Drugs or their delivery systems (diluent, intravenous fluid, or intravascular delivery devices) may also contain pyrogens or, rarely, microbial contaminants (188). Some drugs may also stimulate heat production (e.g., thyroxine), limit heat dissipation (e.g., atropine or epinephrine), or alter thermoregulation (e.g., butyrophenone tranquilizers, phenothiazines, antihistamines, or antiparkinson drugs).

Among drug categories, fever is most often attributed to antimicrobials (especially β-lactam drugs), anti-epileptic drugs (especially phenytoin), antiarrhythmics (especially quinidine and procainamide), and antihypertensives (methyldopa). There is nothing characteristic about the fevers induced by these drugs (186). Fevers do not invariably occur immediately after drug administration: it may be days after administration that fever occurs and many more days before the fever abates. In one series, the lag time between initiating a drug and fever was a mean of 21 days (median, 8). Fever often took 1 to 3 days to return to normal but can take >7 days to return to normal after removing the offending agent (189). Rash occurs in a small fraction of cases. Eosinophilia is also uncommon.

The diagnosis of drug-induced fever is usually established by temporal relationship of the fever to starting and stopping the drug. Patients can be rechallenged with the drug to confirm the diagnosis, but this is rarely done unless the drug in question is essential and alternatives are not available. Patients who had anaphylaxis or toxic epidermal necrolysis as a result of drug exposure should not be rechallenged.

Two important syndromes, malignant hyperthermia and neuroleptic malignant syndrome, deserve consideration when fever is especially high because the results can be devastating if left untreated (190, 191). Malignant hyperthermia is more often identified in the operating room than in the ICU, but onset can be delayed for as long as 24 hrs, especially if the patient is on steroids. It can be caused

by succinylcholine and the inhalation anesthetics, of which halothane is the most frequently identified. This hyperthermic syndrome is believed to be a genetically determined response mediated by a dysregulation of cytoplasmic calcium control in skeletal muscle. The result of this calcium dysregulation is intense muscle contraction, generating fever and increasing creatinine phosphokinase concentrations.

The neuroleptic malignant syndrome is rare but more often identified in the ICU than malignant hyperthermia. It has been strongly associated with antipsychotic neuroleptic medications—phenothiazines, thioxanthenes, and butyrophenones (190, 192). In the ICU, haloperidol is perhaps the most frequently reported drug. It manifests as muscle rigidity, generating fever and increasing creatinine phosphokinase concentrations. However, unlike malignant hyperthermia, the initiator of muscle contraction is central.

The serotonin syndrome may be confused with neuroleptic malignant syndrome, but it is a distinct entity (193). The mechanism is related to excessive stimulation of the 5-HT1A–receptor and is increasingly seen with the popularity of serotonin reuptake inhibitors in the treatment of various psychiatric disorders. The serotonin syndrome may be exacerbated with concomitant use of linezolid (194).

Importantly, withdrawal of certain drugs may be associated with fever, often with associated tachycardia, diaphoresis, and hyperreflexia. Alcohol, opiates (including methadone), barbiturates, and benzodiazepines have all been associated with this febrile syndrome. It is important to recognize that a history of use of these drugs may not be available when the patient is admitted to the ICU. Withdrawal and related fever may therefore occur several hours or days after admission. Fever related to other therapies and inflammatory states are listed in Table 5.

Recommendations for Recognizing Noninfectious Causes of Fever

1. Consider all new medications and blood products the patient has received. Ideally, if the suspected drug can be stopped, do so. If the drug cannot be stopped, consider a comparable substitute (level 2).
2. Fever induced by drugs may take several days to resolve. Establishing a temporal relationship between fever and the offending agent may be helpful in establishing the diagnosis (level 3).

Table 5. Fever related to other therapies and noninfectious inflammatory states

Acalculous cholecystitis
Acute myocardial infarction
Adrenal insufficiency
Blood product transfusion
Cytokine-related fever
Dressler syndrome (pericardial injury syndrome)
Drug fever
Fat emboli
Fibroproliferative phase of acute respiratory distress syndrome
Gout
Heterotopic ossification
Immune reconstitution inflammatory syndrome
Intracranial bleed
Jarisch-Herxheimer reaction
Pancreatitis
Pulmonary infarction
Pneumonitis without infection
Stroke
Thyroid storm
Transplant rejection
Tumor lysis syndrome
Venous thrombosis

Considerations for Empiric Therapy During Diagnostics

Initiation of therapy may be necessary for unstable or high-risk patients while the diagnostic evaluation is ongoing, and certainly before the results of cultures are available. Usually, this entails antimicrobial therapy, but treatment may also have to be considered for noninfectious causes of fever as well.

If an infectious cause of fever is suspected, empirical antimicrobial therapy may be urgent. Delay of effective antimicrobial therapy has been associated with increased mortality from infection and sepsis (195–201). Antibiotic therapy should begin within 1 hr after the diagnosis of sepsis is considered (202). The choice of regimen depends on the suspected infectious etiology, whether the infection is community-, healthcare-, or hospital-onset, and whether the patient is immunocompromised. If drug-resistant pathogens are suspected, initial broad-spectrum empirical antimicrobial therapy directed against both resistant Gram-positive cocci (including methicillin-resistant *S. aureus*) and Gram-negative bacilli is indicated. This may require several agents to ensure that resistant pathogens are covered. In addition, empirical antifungal coverage may be appropriate in selected patients.

Recommendations for Empiric Therapy of Fever

1. When clinical evaluation suggests that infection is the cause of fever, consideration should be given to administering empirical antimicrobial therapy as soon as possible after cultures are obtained, especially if the patient is seriously ill or deteriorating (level 1).
2. Initial empirical antibiotic therapy should be directed against likely pathogens, as suggested by the suspected source of infection, the patient risk for infection by multidrug-resistant pathogens, and local knowledge of antimicrobial susceptibility patterns (level 1).

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