Practice Guidelines for Evaluating New Fever in Critically Ill Adult Patients

Naomi P. O'Grady, Philip S. Barie, John G. Bartlett, Thomas Bleck, Glenda Garvey, Judith Jacobi, Peter Linden, Dennis G. Maki, Myung Nam, William Pasculle, Michael D. Pasquale, Debra L. Tribett, and Henry Masur

From the National Institutes of Health, Bethesda, and the Johns Hopkins Hospital and St. Agnes Hospital, Baltimore, Maryland; the New York Hospital, and the Columbia-Presbyterian Medical Center, New York, New York; the University of Virginia, Charlottesville, and Infectious Disease Physicians, Inc., Annandale, Virginia; the Methodist Hospital of Indiana, Indianapolis, Indiana; and the University of Pittsburgh Medical Center, Pittsburgh, and the Lehigh Valley Hospital, Allentown, Pennsylvania

Executive Summary

Objective: The development of practice guidelines for evaluating adult patients who develop new fever in the intensive care unit (ICU) for the purpose of guiding clinical practice.
Participants: A task force of 13 experts in disciplines related to critical care medicine, infectious diseases, and surgery was convened from the membership of the Society of Critical Care Medicine and the Infectious Disease Society of America.
Evidence: The task force members provided personal experience and determined the published literature (articles retrieved with use of MEDLINE or textbooks) from which consensus would be sought. The published literature was reviewed and classified into one of four categories, according to study design and scientific value.
Consensus process: The task force met several times in person and twice monthly by teleconference over a 1-year 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 experts' opinions. 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 an adult patient in the ICU should trigger a careful clinical assessment rather than automatic orders for laboratory and radiological tests. A cost-conscious approach to obtaining diagnostic studies should be undertaken if they are 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 options can be identified.

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These practice guidelines have been developed by a Task Force of the Society of Critical Care Medicine in collaboration with the IDSA and are part of a series of updated and new guidelines from the IDSA that will appear in *CID*.
Reprints or correspondence: Dr. Naomi P. O'Grady, National Institutes of Health, Building 10, Room 7D43, 10 Center Drive MSC 1662, Bethesda, Maryland 20892.

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Introduction

In some intensive care units (ICUs), the measurement of a newly elevated temperature triggers automatic orders for many tests that are time-consuming, costly, and disruptive (table 1). Moreover, the patient may experience discomfort, be exposed to unneeded radiation, or experience considerable blood loss as a result of this testing, which is often repeated several times within 24 hours and daily thereafter. In an era when use 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 Society of Critical Care Medicine (SCCM) and the Infectious Diseases Society of America (IDSA) established a task force to provide practice guidelines for the evaluation of new fever in adult patients in the ICU, with the goal of promoting the rational consumption of resources and promoting an efficient evaluation. These practice guidelines presume that any unexplained temperature elevation merits a clinical assessment by a health care professional that includes a review of the patient's history and a focused physical examination before any laboratory tests or imaging procedures are ordered.

These practice guidelines specifically address how to evaluate 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. If the initial history and physical examination reveal a consolidated lung, a purulent wound, or a phlebetic leg, then diagnosis and treatment of that infectious process should commence: such management is addressed by other practice guidelines aimed specifically at conditions including pneumonia and catheter-related infections. Specific questions addressed in these practice parameters relate to the search for the underlying cause of fever and include the following: What temperature should elicit an evaluation? When are blood cultures warranted? When should intravascular catheters be cultured or removed? When are cultures of respiratory secretions, urine, stool, or CSF warranted? When are radiographic studies warranted?

These practice guidelines do not address fever in children, since the issues for children differ from those for adults and merit discussion in a separate document. In addition, these guidelines do not address an approach to persistent fever after the initial evaluation or an approach to localized infection once the anatomic source of fever has been identified. These issues

Table 1. Typical costs associated with evaluation of fever.

Device or study	Cost ($ U.S.)*
Pulmonary artery flotation catheter	90–135
Central venous catheter	21–62
Antiseptic-coated central venous catheter	31–68
Peripherally inserted catheter	46–80
Infrared ear thermometer	300
Disposable cover	0.12
Electronic oral/rectal thermometer	350
Disposable cover	0.04
Glass thermometer	1.50
Microbiology	
Blood culture (per bottle)	25
Urine culture and sensitivity	19
Gram stain	8
Sputum culture and sensitivity	28
Sputum acid fast stain	37
Wound culture and sensitivity	19
Culture for *Clostridium difficile* toxin	27
Legionella urine antigen	47
Legionella DFA	29
Legionella culture	35
Chemistry	
Complete blood count with differential	3.50
Chemistry panel-24	4
Urinalysis	4
Radiology	
Chest PA and lateral views	75
Head CT scan with contrast	416
Head CT scan without contrast	390
Head CT scan with and without contrast	568
Abdominal CT scan with contrast	650
Abdominal CT scan without contrast	587
Abdominal CT scan with and without contrast	792
Chest CT scan with contrast	651
Chest CT scan without contrast	499

* Charges are representative of hospital and commercial sources in the Washington, D.C., and Pittsburgh areas.

are addressed in other monographs or practice guidelines. The current document also does not address the desirability or selection of empirical vs. specific therapy, since the need for therapy is so dependent on clinical evaluation and the underlying disease. It did not appear to this task force that it would be easy to provide useful therapeutic guidelines that took into account the acuity of illness, the underlying disease process, concurrent drugs (i.e., immunosuppressive agents and antimicrobials), ability to tolerate toxicities, and geographic antibiotic susceptibility differences.

In each ICU, specific policies for evaluating fever must be established; these policies must take into account the type of ICU involved (e.g., medical ICU, surgical ICU, or burn ICU), the specific patient population (e.g., immunosuppressed patients vs. immunocompetent patients or elderly vs. younger adults), recent epidemics (e.g., outbreaks of *Clostridium difficile* diarrhea or vancomycin-resistant *Enterococcus*), or endemic pathogens (e.g., methicillin-resistant *Staphylococcus aureus*). It is hoped that the present guidelines will assist intensivists and consultants by serving as a starting point for developing an effective and cost-conscious approach that is appropriate for their patient populations. The specific recommendations are rated by the strength of evidence, based on the published criteria of the IDSA (tables 2 and 3) [1].

Table 2. Categories reflecting the strength of recommendation.

Category	Definition
A	Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. Should always be offered.
B	Moderate evidence for efficacy—or strong evidence for efficacy, but only limited clinical benefit—supports recommendation for use. Should generally be offered.
C	Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy may not outweigh adverse consequences such as toxicity, drug interactions, or cost of the chemoprophylaxis or alternative approaches. Optional.
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered.
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should never be offered.

Initiating an Evaluation of Fever: Measuring Body Temperature and Defining Fever as a Threshold for Diagnostic Efforts

Definition of Fever

The definition of fever is arbitrary and depends on the purpose for which fever is defined. In some literature, fever is defined as a core temperature of $>38.0°C$ (100.4°F) [2, 3], whereas in other sources, fever is defined as two consecutive temperature elevations to $>38.3°C$ (101°F). Since there is considerable variability in ‘‘normal temperature’’ among healthy adults and since the site and method of measurement can influ-

Table 3. Categories reflecting the quality of evidence for each recommendation.

Grade	Definition
I	Evidence from at least one properly randomized, controlled trial
II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies or dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

ence the recorded number, a variety of arbitrary definitions of fever are acceptable, depending on the desired sensitivity of an indicator of thermal abnormality. The lower the temperature used to define fever, the more sensitive the indicator is for detecting an infectious process but the less specific the indicator will be, i.e., a larger number of patients will be evaluated to detect true infectious disease.

Normal body temperature is generally considered to be 37.0°C (98.6°F). In healthy individuals, this temperature varies by 0.5–1.0°C, according to circadian rhythm and menstrual cycle [4]. With heavy exercise, temperature can rise by 2–3°C. While many biological processes can alter body temperature, a variety of environmental forces in an ICU, such as specialized mattresses, hot lights, air conditioning, cardiopulmonary bypass, peritoneal lavage, dialysis, and continuous hemofiltration, can also alter temperature. Thermoregulatory mechanisms can also be disrupted by drugs (e.g., antipyretics or immunosuppressive agents) or damage to the CNS or the autonomic nervous system. Thus, it is often difficult to determine whether an abnormal temperature reflects a physiological process, the effects of a drug, or an environmental influence.

A wide range of biological processes—some infectious, and many noninfectious—can cause temperature elevation. Some of the noninfectious etiologies can be as life-threatening as infection; these etiologies include adrenal insufficiency, thyroid storm, malignant hyperthermia, or heat stroke. Thus, infection is not the only type of process that causes temperature elevation requiring immediate attention. Conversely, in some patients in an ICU, such as those who have undergone surgery, those with certain neurological pathologies, and those with certain underlying diseases, temperature elevation is so predictable that such elevations should not necessarily trigger a laboratory and radiological evaluation for infection unless specific symptoms and signs suggest that the expected cause of fever is not the etiology. This circumstance clearly requires careful assessment of patients, experience with a given patient population, and clinical judgment.

On the other hand, a substantial proportion of infected patients are not febrile; such patients may be euthermic or hypothermic. These include elderly patients, patients with open abdominal wounds, patients with large burns, patients receiving extracorporeal membrane oxygenation, 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 such as otherwise unexplained hypotension, tachycardia, tachypnea, confusion, rigors, skin lesions, respiratory manifestations, oliguria, lactic acidosis, leukocytosis, leukopenia, 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 all patients with temperatures of ⩾38.3°C to be febrile, warranting special attention to determine if infection is present. Cost-effective treatment of patients in an ICU mandates that infection be considered a possibility regardless of temperature but that laboratory tests for infection should be initiated for febrile patients only if clinical assessment indicates a reasonable possibility that infection might be present.

Site and Technology of Temperature Measurement

Temperature has traditionally been measured orally, rectally, or centrally (by intravascular thermistor) and in the axilla. In an ICU, temperature measurement in the axilla should be discouraged because of its unreliable correlation with core temperature and its poor reproducibility [5–7].

The ideal system for measuring temperature should safely and conveniently provide reliable, reproducible values. 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 against which other devices for measuring core temperature must be compared [5–10]. However, thermistors are not in place in all patients in the ICU. Even when available, these thermistors are not all equal in technical performance. Readings from well-functioning units can be altered by the infusion of large volumes of fluid into the right atrial port. Thermistors in indwelling bladder catheters provide readings that are essentially identical to those provided by thermistors in intravascular sites but are seldom used in most ICUs [5, 6, 9].

Mercury thermometers or electronic probes (intermittent or continuous) have traditionally been used to measure rectal temperatures. Readings from the rectum are often a few tenths of a degree higher than core temperature [5, 7, 10, 11]. Rectal temperature measurement is often perceived by patients as unpleasant and intrusive. Access to the rectum may be limited by a patient's position. Moreover, there is a small risk of trauma or perforation of the rectum that is a particular problem in patients who are neutropenic or coagulopathic or who have recently undergone rectal surgery. Rectal temperature measurements have also been implicated in spreading enteric pathogens such as *Clostridium difficile* or vancomycin-resistant *Enterococcus* nosocomially via the device or the operator [12, 13].

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 [6, 14]. 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 because of intubation or inability of the patient to cooperate.

The 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, and there is a risk of trauma to the tympanic membrane. Infrared ear thermometers are also available for detecting radiant energy from the tym-

panic 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. Readings obtained with tympanic membrane and infrared devices do not always correlate well with those obtained with other measurement devices [5–9], which may be due to poor maintenance or calibration.

Recommendations

1. Temperature is most accurately measured by an intravascular or bladder thermistor, but measurement by electronic probe in the mouth, rectum, or external auditory canal is acceptable in appropriate cases. Axillary measurements should not be used (B, III).
2. Any device used to measure temperature must be maintained and calibrated appropriately by using the manufacturer's guidelines as a reference (B, III).
3. Any device used to measure temperature must be used in a manner that does not facilitate nosocomial spread of pathogens by the instrument or the operator (A, II).
4. Temperature and site of temperature measurement should be recorded in patients' charts (B, III).
5. New onset of temperature $\geqslant$38.3°C is a reasonable trigger for a clinical assessment but not necessarily for a laboratory or radiological evaluation for the presence of infection (B, III).
6. Critical care units could reduce the cost of operation in many instances by eliminating automatic laboratory and radiological tests for patients with new temperature elevations (A, II). Instead, these tests should be ordered on the basis of clinical assessment. However, a clinical and laboratory evaluation for infection may be appropriate for euthermic or hypothermic patients, depending on the 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 performed for patients with new fever, even when the clinical findings do not strongly suggest a noninfectious cause.

Skin Preparation

The site of venipuncture should be cleaned with either 10% povidone iodine or 1%–2% tincture of iodine. The access to an intravascular device and to the stopper on a culture bottle should be cleaned with 70% alcohol [15, 16]. BACTEC bottles (Becton Dickinson, Sparks, MD) and other radiometric bottles should not be swabbed with iodine-containing antiseptics, since these solutions may degrade the stoppers. These bottles should, however, be cleaned with 70% alcohol.

Iodophors must be allowed to dry to provide maximal antiseptic activity and thus to minimize the risk of contamination. They should be removed from the skin with alcohol after blood has been drawn for culture to reduce the likelihood of skin irritation. If a patient is hypersensitive to iodine, two applications of 70% alcohol will provide adequate disinfection.

When blood is to be inoculated into a culture or transport tube, the needle used for venipuncture need not be replaced by a sterile needle. The risk of a needle-stick injury during the switch in needles is currently believed to outweigh the risk of contamination [17].

Blood Volume and Collection System

One blood culture is defined as a sample of blood drawn at a single time at a single site, regardless of the number of bottles or tubes into which the laboratory requires the blood to be injected. In most laboratories, a system of inoculating a ratio of 1 mL of blood per 5 mL of media is used. This often means 5 mL of blood are injected into each of two or three bottles or tubes for routine culture by using different media to maximize the yield of aerobic and anaerobic bacteria and *Candida* species (table 4). The sensitivity of blood culturing is related to many factors, the most important of which is the volume of blood drawn [16, 18–22]. At least 10–15 mL of blood should be drawn for each culture whenever possible.

Many different culture systems can provide excellent results (table 4). Laboratory personnel need to make their own decisions about selecting the optimal routine system on the basis of budgetary constraints, manpower, and the patient population served. Special bottles can be added in special circumstances. The usefulness of antibiotic removal devices in blood culture systems is controversial, although these devices are used routinely in some laboratories. Some studies have shown that, when compared with conventional culture systems, the use of these devices can increase the recovery of aerobic gram-positive cocci, regardless of whether or not patients are receiving antibiotics [23]. These devices do not consistently enhance the recovery of gram-negative bacilli. Considering the varied experiences related to benefit, as well as the substantial additive cost, their use is considered optional.

In general, collection systems for children should not be used for adults because the smaller volume of blood collected will diminish the yield of pathogens for adults [19]. When bacteremia occurs in children, the concentration of organisms is often considerably higher than that in adults. Thus, collection systems for children usually provide a reasonable yield for children but not for adults, regardless of the size of the adult. However, if it is impossible to obtain the minimum volume of blood required for the adult collection system and <5 mL of blood is obtained, it is acceptable to use a pediatric bottle system, so that the ratio of blood to culture medium provides optimal conditions for the growth of microorganisms.

Cultures of Blood for Unusual Pathogens

For special patient populations or in certain geographic areas, it may be appropriate for the evaluation of fever to include

Table 4. Comparison of commonly used blood culture systems for patients with fever.

Method	Rating					Comments
	Aerobes	Anaerobes	Yeast	Fungi	Mycobacteria	
Conventional broth-in-bottle	2	2	1–2	1	1	Slower than automated systems; low blood volume in some brands
Broth-in-bottle (continuous monitoring)	3	2–3	2–3	1	1*, 3†	Continuous system with monitoring speeds time to detection
Lysis-centrifugation (Isolator)	2–3	1	3	3	3	Volume cultured is only 10 mL
Antibiotic removal system (resin bottles)	2–3	1–2	2–3	1	1	Greatest efficacy for *Staphylococci* and yeast

NOTE. 1 = not recommended; 2 = acceptable; 3 = best available method.
* With use of standard blood culture bottles.
† With use of special mycobacterial culture bottles.

cultures for organisms other than routine aerobic and facultatively anaerobic bacteria. Most often these pathogens are sought in patients with specific underlying conditions (i.e., allogeneic transplant recipients or patients with cancer and prolonged neutropenia), or they are sought because of unusual exposures (i.e., to species of *Francisella, Bartonella,* or *Histoplasma*). In such situations, special communication with the microbiology laboratory is required to determine if different culture systems in addition to the routine system are needed or if incubating the routine culture for a longer period would be useful.

Number of Cultures and Sites

No more than three blood samples for culture (10–15 mL each) need to be drawn during the initial 24 hours after the onset of new fever, and in most situations two blood samples are sufficient [17]. Each sample should be drawn by separate venipuncture [24, 25]. There is no evidence that the yield of cultures of blood drawn from an artery is different from the yield from a vein except in unusual situations involving arterial infections. Drawing two blood samples from separate venipuncture sites, 10 minutes apart, at the onset of fever is a logical strategy to help to discern whether the organism recovered in the blood represents a true pathogen (both cultures are often positive) or a contaminant (one culture may be positive, while the other is negative). Unfortunately, this distinction cannot be made unequivocally because true bacteremias can be intermittent [23]. Separating venipunctures by a 10-minute interval, a logical but unsubstantiated recommendation, should not be allowed to result in delaying therapy in critically ill patients. It may be appropriate to shorten this interval for sicker patients.

If venipuncture is difficult to perform and if there is an intravascular device in place, the second blood sample can be drawn from the device at the time that the venipuncture sample is obtained. In most cases, when true bacteremia or fungemia exists, the two samples (one from venipuncture and one drawn through a device) will yield identical results [26]. In the majority of cases of discordant results, the blood drawn through the device will be positive, and the blood drawn by venipuncture will be negative; in such a case the isolate is more likely to be a contaminant than a true pathogen; however, again, clinical judgment rather than specific criteria are needed to interpret the significance of discordant results [24, 27].

There are no data to support the common practice of drawing a sample from each port of multilumen catheters. Common sense must determine which catheter(s) and which lumen(s) are used for drawing sample(s); it is logical to draw blood for culture through the most recently inserted catheter to reduce the risk of contaminating the culture with organisms that colonize the vascular access device.

Labeling

Blood culture bottles should be clearly labeled with the time, date, and anatomic site or catheter lumen from which blood is drawn, as well as any other information that may be appropriate. This procedure is extremely useful for interpreting the significance of the result.

Recommendations

1. Perform a pair of blood cultures after an initial elevation in a patient's temperature is observed. Perform a second pair within the next 24 hours. Additional blood cultures should be performed thereafter when there is a high clinical suspicion of bacteremia or fungemia (B, II).
2. For patients without indwelling vascular catheters in place, obtain two samples of blood from peripheral sites by separate venipunctures after appropriate disinfection of the skin (A, III).
3. For skin preparation, povidone iodine should be allowed to dry for 2 minutes, and tincture of iodine should be allowed to dry for 30 seconds. Alcohol, an acceptable alternative for

iodine-allergic patients, need not be allowed to dry for any minimum amount of time (A, II).

4. The injection port of the blood culture bottles should be wiped with alcohol before blood is injected into the bottles to decrease the risk of contamination (A, III).

5. If blood for culture cannot be obtained from two peripheral sites, draw one peripheral specimen and one specimen from the most recently inserted catheter, if possible (A, II). Cultures of blood obtained through intravascular catheters yield less precise information than cultures of blood obtained by venipuncture.

6. Draw at least 10–15 mL of blood per culture (A, II).

7. After the initial 24-hour period, blood cultures should be ordered on the basis of clinical judgment (A, III).

Intravascular Catheters and Fever

Stable vascular access is essential in the treatment of critically ill patients in the ICU. Most patients will have one or more central venous catheters in place, and they may have arterial catheters as well. An increasing number of patients will have some type of tunneled, surgically implanted, cuffed central venous catheter (e.g., a Hickman catheter) or some type of subcutaneous central venous port (e.g., a Portacath). The variety of such devices is increasing rapidly.

Vascular access devices can cause fever due to localized infection or systemic infection or rarely, because of an allergic reaction. The relative risk of bloodstream infection caused by various intravascular devices ranges widely and depends on the length of time they have been in place as well as the type of device, the patient population, the techniques used in the insertion and manipulation of the device, and the frequency of manipulation [27–31]. The risk has been estimated for various devices, although local experiences vary considerably. The highest risk of fever is now with short-term, noncuffed central venous catheters, with the rate ranging from five to 10 cases per 1,000 catheter-days; the rate is especially high with noncuffed, temporary hemodialysis catheters. In contrast, the risk of bloodstream infection with small, peripheral iv catheters is <0.2 cases per 1,000 catheter-days. With good care, permanent, surgically implanted central venous devices are also associated with a low risk of bloodstream infection; the rate is approximately two cases of bacteremia per 1,000 catheter-days.

Location of Infection

Catheters should be assessed to determine whether infection is present at the site of insertion (often manifested by evidence of inflammation or purulence at the exit site or along the tunnel), at the intravascular site (often manifested by positive blood cultures or thrombosis), or at sites proximal to the catheter (connector sites and ports or the infusate). These distinctions have important therapeutic implications.

It is also important to recognize that infusate (parenteral fluid, blood products, or iv medications) administered through an intravascular device can become contaminated and produce device-related bacteremia, which is more likely to culminate in septic shock than are other catheter-related infections [28]. Contamination of infusate is infrequent. Most nosocomial epidemics of contaminated infusate are caused by gram-negative bacilli that are introduced during manufacture of the infusate (intrinsic contamination) or during its preparation and administration in the hospital (extrinsic contamination) [28, 32].

Diagnosis

Certain clinical, epidemiological, and microbiological findings are very helpful and point toward a vascular catheter as the source of infection [28, 33]. These findings include: (1) bacteremia or fungemia in an immunocompetent patient without underlying diseases; (2) no identifiable local infection; (3) the presence of an intravascular device at the onset of fever; (4) inflammation or purulence at the catheter insertion site or along the tunnel; (5) abrupt onset of infection that is associated with fulminant shock; and (6) multiple blood cultures positive for organisms that might otherwise be disregarded as contaminants, such as staphylococci (especially coagulase-negative staphylococci), *Corynebacterium jeikeium, Bacillus* species, *Candida* species, or *Malassezia* species.

Evaluation

As part of a comprehensive physical examination, catheter access sites should be examined, and any expressible purulence or exudate should be gram stained and cultured. Two peripheral blood samples or one drawn percutaneously and one drawn through the catheter should be obtained. Cultures of blood drawn through the catheter, in combination with cultures of blood drawn percutaneously, may be especially useful if microbial growth can be quantitated. A clinical decision to culture every port of multilumen catheters must be made individually on the basis of clinical suspicion and the patient's ability to tolerate phlebotomy.

A quantitative culture of blood drawn through an infected catheter characteristically shows a marked step-up in the concentration of organisms, usually 10-fold or greater, as compared with a quantitative culture of blood drawn concomitantly from a peripheral vein. Because of the additional expense and expertise necessary for processing, quantitative cultures of catheter-drawn blood are not routinely necessary as part of the usual evaluation of fever. They do, however, provide useful information, especially when catheters are surgically implanted and cannot easily be removed on empirical grounds. A lysis-centrifugation system (Isolator, E. I. DuPont de Nemours and Co., Wilmington, DE) is one system that can be used to perform quantitative cultures [28, 34].

When short catheters (<3 inches) are removed, the entire catheter from just inside the skin surface to the tip should be cultured. Quantitative or semiquantitative cultures should be performed. Ideally, when large centrally placed catheters are removed, both a 2-inch intracutaneous segment and the tip should be cultured in the same container, although it may be difficult to train the staff to send anything other than the terminal portion of the catheter to the microbiology laboratory. When pulmonary artery flotation catheters are cultured, the introducer should be cultured as well [30, 35].

When catheter segments are cultured semiquantitatively on solid media [36–38] or quantitatively in liquid media, the results can improve the sensitivity and specificity for diagnosis of catheter-related infection. If blood cultures are positive, a catheter can be identified as the source if colony counts obtained by semiquantitative cultures are high (>15 cfu). However, in the absence of a positive blood culture, the clinical significance of a positive catheter culture is unknown. High colony counts (>15 cfu) correlate with catheter-related bloodstream infections, although the correlation is modest. The results of gram stains [38] or acridine orange stains [39] of intravascular segments of removed catheters also correlate with the results of semiquantitative or quantitative cultures, but these stains are expensive and time-consuming to perform.

For patients with fever who are in stable condition, it is not necessary to remove or change all indwelling catheters, although such an approach would be the most cautious management strategy. If a patient is in shock or manifests ominous new signs such as peripheral embolization, disseminated intravascular coagulation, or acute respiratory distress syndrome, removal of all intravascular catheters, with reinsertion at new sites, is indicated even if the catheters are cuffed or tunneled devices [40]. In addition, if there is clinical evidence of vascular compromise (i.e., progressive edema of a limb or arterial insufficiency), catheters should be removed. If a radiographic study is performed and there is evidence of a thrombus, clinical judgment is needed to determine if anticoagulation, thrombolysis, or surgical intervention is necessary. Surgical intervention to remove an infected thrombus is rarely performed because medical management usually suffices, but in cases in which septic emboli recur or blood cultures remain positive over many days, such intervention may be appropriate [28, 41, 42].

The occurrence of central-vein septic phlebitis due to a centrally placed catheter is unusual [41, 42]. In patients 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 and/or septic embolization. This syndrome is most often encountered in patients with burns or in other patients in the ICU who develop catheter-related infections that remain unrecognized, permitting microorganisms to proliferate to high levels within intravascular thrombi. The syndrome of intravenous suppuration is now predominantly a complication of the use of central venous catheters, typically those that have been left in place for many days (especially for several days after the onset of catheter-related bloodstream infection) in vulnerable patients [43].

Recommendations

1. Examine patients for the presence of inflammation or purulence at the catheter exit site and along the tunnel, and assess for signs of vascular compromise and evidence of embolic phenomena (A, III).
2. Any pus expressed from the catheter site should be gram stained and cultured (A, III).
3. If there is evidence of a tunnel infection, embolic phenomenon, vascular compromise, or sepsis, the catheter should be removed and cultured, and a new catheter should be inserted at a different site (B, II).
4. Blood for two cultures should be drawn peripherally by venipuncture or, if quantitative cultures can be performed, blood for one culture drawn by venipuncture and blood for at least one culture drawn through the catheter should be obtained (B, II). The proximal port is the logical port from which to draw blood if it is not feasible to draw samples from each port. When short-term, uncuffed central venous catheters are suspected of infection, it is usually more efficient to replace the existing catheter than to draw blood for quantitative cultures (B, III).
5. The catheter tip culture may provide useful information if catheter infection or colonization is suspected. For pulmonary artery flotation catheters, both the introducer tip and the catheter tip should be cultured if catheter-related infection is suspected (C, II).
6. It is not routinely necessary to culture infusate specimens as part of the workup for catheter-related infections unless there is strong epidemiological evidence to do so (B, III).

Pulmonary Infections and ICU-Acquired Pneumonia

In many settings, pneumonia is an easy diagnosis to establish in a febrile patient on the basis of chest radiographs, respiratory secretions, symptoms, and signs. In an ICU, however, it can be difficult to determine whether fever is due to pneumonia when a patient has another noninfectious process that results in abnormal radiographic findings and gas exchange (e.g., congestive heart failure, atelectasis, or acute respiratory distress syndrome). Many patients in the ICU are intubated and sedated or cannot cough or have abnormal secretions for other reasons. Thus, determining whether lower respiratory tract infection is the cause of fever and whether the infectious process is tracheitis, tracheobronchitis, pneumonia, or abscess can be difficult.

Diagnostic Evaluation

Physical examination, chest radiography, and examination of pulmonary secretions comprise the initial evaluation of patients with suspected pneumonia. Chest radiographs, obtained with a

mobile unit while patients are supine or erect, posteroanterior radiographs with lateral views, and CT studies, in that order, provide increasingly useful information. For initial evaluations of fever, chest radiographs obtained with use of a mobile unit are generally adequate. Radiographs should be obtained while patients are in an erect, seated position during deep inspiration, if possible. The absence of infiltrates, masses, or effusions on radiographs does not exclude pneumonia, abscess, or empyema as the cause of fever. Clinical judgment is needed to determine whether the suspicion of infection is high enough to warrant transporting a patient to the radiology suite for a higher resolution study.

Respiratory secretions can be obtained for examination by a variety of techniques including expectoration, saline induction, deep tracheal suctioning, bronchoscopic aspiration, or bronchoscopic or nonbronchoscopic alveolar lavage. Each of these techniques has advantages and disadvantages [44, 45]. For initial evaluation of fever, before it is apparent whether pneumonia is present, examination of an expectorated sputum specimen, as opposed to a more invasively obtained specimen or deep tracheal aspirate, is usually sufficient. Saline should be instilled in a patient's endotracheal tube only when an adequate specimen cannot be obtained by deep suctioning, since there is concern that saline dilutes specimens and could introduce pathogens into the lower airway.

The utility of fiberoptic bronchoscopy is variable depending on the pathogen and the technique. Aspirates from the inner channel of the bronchoscope are subject to contamination by the upper airway flora and are subject to the same limitations as expectorated sputum [46, 47]. Bronchoscopy is impractical for routine use because it is expensive, requires technical expertise that may be difficult to obtain in a timely manner, and is associated with occasional complications. However, bronchoscopy may be especially useful for the detection of selected pathogens such as *Pneumocystis carinii,* cytomegalovirus (CMV), and *Mycobacterium* species and for selected patients, especially those who are immunocompromised.

However pulmonary secretions are acquired for analysis, they should be transported to the laboratory and processed within 2 hours so that any fastidious organisms that may be present, such as *Streptococcus pneumoniae,* do not die. It is important that any expectorated specimen be examined via direct microscopy to determine if the specimen represents saliva (i.e., if the predominant cells are epithelial) or a lower respiratory secretion (i.e., if the predominant cells are leukocytes when a patient is not neutropenic).

If a specimen is of lower respiratory origin, in most situations a gram stain should be performed, and the specimen should be cultured routinely for aerobic bacterial pathogens. In appropriate circumstances it may be desirable to perform other direct tests such as a potassium hydroxide wet mount for detecting fungi, EIA for influenza A virus, an acid fast stain for mycobacteria, a fluorescent antibody stain for *Legionella* species or respiratory syncytial virus (RSV), a urinary antigen test for *Legionella pneumophila,* or an immunofluorescent stain for *P. carinii.* It may also be desirable to culture the specimen for fungi, mycobacteria, *Legionella* species, adenovirus, coxsackie virus, influenza virus, parainfluenza virus, and RSV.

Clinicians need to be aware of the organisms that are virtually always pathogens when they are recovered from respiratory secretions. Though not all-inclusive, the list might include *Legionella* species, *Chlamydia* species, *Mycobacterium tuberculosis,* influenza viruses, RSV, parainfluenza virus, *Strongyloides stercoralis, Toxoplasma gondii, P. carinii, Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis,* and *Cryptococcus neoformans.* Potential bacterial pathogens such as *Pseudomonas aeruginosa,* Enterobacteriaceae, *S. pneumoniae, S. aureus,* and *Haemophilus influenzae* are frequently found 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 or contaminant is facilitated by detection of pathogenic organisms as the dominant flora on direct gram stain and/or their recovery in moderate or heavy concentrations from respiratory secretions. Quantitative cultures of bronchoscopic specimens or other specimens from the lower airways may also facilitate the distinction between colonizing bacteria and pathogens. The use of these quantitative techniques is not considered standard practice for most patients who are being evaluated for respiratory tract infections in the ICU, although this technology may be useful for selected patient populations in settings where the methodology is well standardized. The utility of quantitative cultures for identifying the causative pathogen has been reviewed in other publications [48–50].

It is appropriate to draw blood for cultures in an attempt to identify the cause of pneumonia. Such cultures have low yields, but when respiratory pathogens are identified in blood cultures, the information is highly specific and useful for designing management strategies.

Many febrile patients in the ICU have small amounts of pleural fluid because they have congestive heart failure, hypoalbumenemia, or a postoperative process. It is not necessary to obtain a sample of pleural fluid for culture for every febrile patient. The use of thoracentesis to obtain fluid for stain, culture, and cytology (as well as measurement of pH and levels of protein, glucose, and lactate dehydrogenase) would be especially appropriate if there is enough fluid for safe aspiration and there is either an adjacent pulmonary infiltrate, suspicion of tuberculosis, or possible contamination of the pleural space by surgery, trauma, or a fistula. The fluid should be cultured for aerobic and anaerobic bacteria; culture for fungi or mycobacteria should be performed if epidemiologically appropriate.

Once specimens for culture are obtained and pathogens are cultured in the laboratory, antimicrobial susceptibility tests should be performed on isolates of aerobic and facultative bacteria, including *S. pneumoniae.* Susceptibility testing of an-

aerobic bacteria, fungi, or viruses is not routinely indicated; the utility of these tests in the treatment of individual patients should be discussed with the laboratory personnel if it is believed that the tests could be useful.

Recommendations

If a febrile patient is suspected of having a lower respiratory tract infection on the basis of clinical and/or radiographic assessment, the following steps should be taken:

1. Obtain one sample of lower respiratory tract secretions for direct examination and culture. Expectorated sputum, induced sputum, tracheal secretions, or bronchoscopically obtained material can be used effectively. If pneumonia is documented by physical examination or radiographic evaluation, a decision to perform bronchoscopy or another invasive diagnostic study should be considered according to factors discussed in other references [44–46] (A, II).
2. Respiratory secretions obtained for microbiological evaluation should be transported to the laboratory within 2 hours of collection (A, II).
3. Respiratory secretions that are judged to be appropriate samples in the laboratory should be evaluated by gram stain and cultured for aerobic and facultative bacteria. Additional stains, rapid tests, cultures, and other tests should be performed as epidemiologically appropriate (A, II).
4. A chest imaging study should be obtained. In most cases the most feasible study will be an anteroposterior chest radiograph, obtained with a mobile unit while a patient is in an erect, seated position. Posteroanterior chest radiographs with lateral views or CT scans offer more information and should be obtained when clinically indicated (A, I).
5. Pleural fluid should be obtained for gram stain and routine culture (along 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 (A, II).

Stool Evaluations for Febrile Patients in the ICU

Many patients in the ICU have diarrhea, which is often caused by enteral feedings or drugs. The only common enteric cause of fever among patients in the ICU is *C. difficile,* which should be suspected in any patient with fever and diarrhea who has received an antibacterial agent or chemotherapy within 3 weeks before the onset of the diarrhea [51]. *C. difficile* accounts for 10%–25% of all cases of antibiotic-associated diarrhea and virtually all of the cases of antibiotic-associated pseudomembranous colitis [52]. Other organisms that can cause fever and diarrhea include species of *Salmonella* and *Shigella, Campylobacter jejuni,* species of *Aeromonas* and *Yersinia, Escherichia coli O157:H7, Entamoeba histolytica,* and multiple viruses that are not usually identified by standard techniques. In general, these are community-acquired diseases; only rarely is infectious diarrhea acquired after a patient has been admitted to the ICU. If a patient does not have diarrhea on admission to the hospital and is not infected with HIV, it is unlikely that these organisms are the cause of diarrhea and fever in the ICU [53]. Thus, sending stools for bacterial cultures or for ova and parasite examination should generally be avoided as part of a fever evaluation unless a patient is admitted to the hospital with diarrhea or the patient is infected with HIV.

Presentation

Most patients who have *C. difficile*–associated fever present with diarrhea. (Diarrhea is defined in this document as the passage of two or more stools per day that conform to the container in which they are placed.) However, rare patients, especially those who have undergone surgery, may present with ileus or toxic megacolon without diarrhea as the manifestation of *C. difficile* disease. For these patients the diagnosis of *C. difficile* disease may be difficult to establish because stool specimens are unobtainable [54].

Clinical features that support the diagnosis of *C. difficile* disease are: exposure to a likely inducing agent (cephalosporin, ampicillin, or clindamycin), a systemic inflammatory response that is otherwise unexplained (fever and/or leukocytosis, including a leukemoid reaction), the presence of pseudomembranous colitis on endoscopy, or evidence of colitis, as demonstrated by CT, endoscopy, or a positive fecal leukocyte exam [54, 55].

Evaluation for *C. difficile*

A tissue culture assay for *C. difficile* toxin is the diagnostic ''gold standard,'' although EIA is now used in most laboratories for detection of toxin A alone or toxin A plus toxin B. EIA is slightly less sensitive than the tissue culture assay, but EIA is technically easier to perform and provides an answer within 2–3 hours. The sensitivity of EIA for detecting *C. difficile* toxin is 72% for the first sample and 84% for the second sample, while the sensitivity of the tissue culture toxin assay is 81% for the first sample and 91% for the second sample [55]. Once the diagnosis is made and therapy has begun, repeated toxin assays should not be done to assess response to therapy or used as criteria for discontinuing enteric precautions, as many patients will harbor toxin as carriers without any clinical manifestations of colitis.

The fecal leukocyte examination is sensitive for identifying inflammatory diarrhea, but this test is nonspecific. If fecal leukocytes are demonstrated by use of methylene blue stain, the sensitivity for detecting *C. difficile* is 40%; use of the lactoferrin latex agglutination test increases the sensitivity to 75% [56].

Cultures for *C. difficile* are technically demanding, require 2–3 days for growth, and are not specific for distinguishing between the presence of toxin-positive strains or toxin-negative strains or asymptomatic carriage [55, 57]. Cultures may be

useful in the setting of nosocomial outbreaks when isolates are needed for strain typing for epidemiological purposes [51].

Direct visualization of pseudomembranes is highly specific for the diagnosis of *C. difficile* colitis [58]. One study showed that in terms of sensitivity, only 71% of patients with severe disease had pseudomembranes documented by direct visualization, while only 23% of patients with mild disease were found to have pseudomembranes [59]. Concerns about cost, risk of perforation during examination, and the relative ease of cytotoxin assays have removed flexible sigmoidoscopy and colonoscopy from the forefront of diagnosis. However, a role for direct visualization may exist in cases requiring rapid diagnosis if laboratory results will be delayed or if false-negative assays for *C. difficile* toxin are suspected [51]. Many clinicians, however, would treat such patients empirically rather than perform sigmoidoscopy or colonoscopy.

Evaluation for Other Enteric Pathogens

Patients who have a recent and significant history of travel to developing countries, patients with HIV disease, and patients who have had unusual domestic exposures may require more extensive evaluations. For patients with recent histories of travel, the evaluation should be directed by the most likely pathogens that occur in the area of travel, although the most common cause of traveler's diarrhea, enterotoxigenic *E. coli,* is not detected with the usual laboratory tests. For patients who have traveled to areas where parasitic disease is common, a stool examination for ova and parasites and *Cyclospora, E. histolytica,* and *S. stercoralis* should be performed.

Patients with HIV disease commonly have chronic diarrhea caused by *Salmonella* species, *Microsporidium,* CMV, or perhaps *Mycobacterium avium* complex. Enteric disease due to CMV is usually associated with fever, whereas parasitic disease is a less common source of fever; detection of *Microspordium* requires special stains of the stool or biopsy of the small bowel. The diagnosis of CMV infection should be made endoscopically by means of a biopsy. Fecal leukocyte stains are also helpful; the major conditions associated with fecal leukocytes in this population are CMV infection, salmonellosis, and *C. difficile*–associated colitis.

Recommendations

If a patient at risk for *C. difficile* disease passes more than two stools per day that conform to the container in which they are placed and if clinical evaluation indicates that a laboratory evaluation is necessary, the following steps should be taken:

1. Day 1: send one stool sample for *C. difficile* evaluation (B, II).
2. If the first specimen is negative for *C. difficile,* send an additional sample for *C. difficile* evaluation (B, II).
3. If severe illness is present and rapid tests for *C. difficile* are negative or can't be performed, consider performing flexible sigmoidoscopy (C, III).
4. If severe illness is present, consider empirical therapy with metronidazole while awaiting the results of diagnostic studies. Empirical therapy is generally not recommended if two stool evaluations are negative when a reliable assay has been used. 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 (B, III).
5. Stool cultures for other enteric pathogens are rarely indicated for patients who do not present to the hospital with diarrhea or for patients who are not infected with HIV. Perform stool cultures for other enteric pathogens and examine stools for ova and parasites only if it is epidemiologically appropriate (B, III).

Urinary Tract Infections

Bacteriuria is a very common occurrence in patients in the ICU, especially those with bladder catheters in place. Deciding when bacteria in the urine are actually causing urinary tract disease or fever is a complex challenge.

Etiology

For patients in the ICU, the majority of infections are related to the presence of bladder catheters, although other instrumentation, obstruction of the urethra, bladder, or ureters, and hematogenous spread are also predisposing conditions for or vectors of infection. Gram negative bacilli, *Streptococcus faecalis,* and yeasts are frequent causative organisms [60–62].

Diagnosis

When clinical findings indicate that a laboratory evaluation of fever is appropriate, one specimen of urine should be obtained and evaluated by direct microscopy, gram stain, and quantitative culture.

Urine for culture and urinalysis should not be collected from the drainage bag, since multiplication of bacteria can occur while the urine is in the bag. The catheter should instead be clamped and urine aspirated from the port provided for this purpose. Health care personnel should wear gloves whenever manipulating a urinary device and should scrupulously clean the port with alcohol before collecting specimens. For patients without a Foley catheter in place, a midstream clean-catch urine specimen should be collected. Urine collected for culture should be transported to the laboratory rapidly to prevent the multiplication of bacteria within the receptacle during transit. If the transport of a urine specimen will be delayed longer than ~1 hour, the specimen should be refrigerated. For transport to

a remote laboratory site, the use of a urine preservative device containing boric acid is justified.

The quantity of urinary bacteria that is sufficient to cause a febrile urinary tract infection is unclear. In patients with urinary catheters and low colony counts, bacteria, if present, will increase in quantity over time. It is likely that most febrile catheter-associated urinary tract infections occur with counts $>10^4$ cfu/mL and that pyuria is almost always present in nonneutropenic patients.

Although it is appropriate to collect urine specimens in the investigation of fever, routine monitoring or surveillance cultures of urine contribute little to patient care [63]. The presence of pyuria can help establish the importance of bacteria in a patient's urine. The simplest method of detecting pyuria is the leukocyte esterase dipstick test, which indicates the presence of polymorphonuclear leukocytes in urine. An equally simple method is to perform a gram stain of centrifuged urine sediment, which will demonstrate the presence of inflammatory cells, and usually provide clues to the type of microorganisms present. Urinalysis does not correlate quantitatively with gram stain of urine sediment.

The interpretation of urine culture results for patients in the ICU is often difficult. In the absence of substantial pyuria or concordant blood and urine culture results, there are no clear-cut guidelines for establishing whether a fever is caused by organisms in the urine.

Recommendations

If clinical evaluation indicates that a laboratory workup is necessary, the following steps should be taken:

1. Obtain urine for culture and for determination of the presence of pyuria (B, III).
2. For patients with Foley catheters in place, urine should be collected from the urine port of the catheter and not the drainage bag (B, II).
3. Urine should be transported to the laboratory rapidly to avoid bacterial multiplication (B, II).
4. If transport to the laboratory will be delayed for >1 hour, the specimen should be refrigerated or placed in a preservative (B, II).

Sinusitis

In the ICU the most common risk factor for sinusitis is anatomic compromise of the ostia draining the sinuses, usually due to the presence of a nasotracheal or nasogastric tube, which leads to interference of the normal mucociliary clearance of the sinus cavity [64–66]. Sinusitis is often part of the differential diagnosis of fever, but it is relatively uncommon to document sinusitis as the cause of fever with much degree of certainty. Thus an evaluation for sinusitis is not generally part of the initial evaluation of fever and should be undertaken only after more likely etiologies have been ruled out.

Etiology

The paranasal sinuses are normally sterile. The infectious agents responsible for most cases of sinusitis in the ICU are those nosocomial agents that typically colonize the naso-oropharynx [66–68]. Gram-negative bacilli constitute 60% of bacterial isolates from patients with nosocomial sinusitis, and *P. aeruginosa* is the most common. Gram-positive bacteria comprise one-third of the isolates (*S. aureus* is the most common), whereas fungi comprise the remaining 5%–10% of isolates [65, 66, 68, 69].

Diagnosis of Sinusitis

The presence of two major criteria (cough and purulent nasal discharge) or one major and two minor criteria (periorbital edema, headache, facial pain, tooth pain, earache, sore throat, foul breath, wheezing, or fever) for >7 days suggests the presence of acute bacterial sinusitis [70]. However, even on physical examination in the outpatient setting, sinusitis is difficult to diagnose. The diagnosis of sinusitis in critically ill, intubated patients is even more difficult. Complaints of facial pain and headache can usually be obtained, but purulent nasal discharge is present in only 25% of ICU patients with proven sinusitis [68].

Plain radiographs, ultrasonograms, CT scans, and MRI scans can be obtained to diagnose acute sinusitis. One recent prospective study showed that an assessment consisting of history, nasal endoscopy, and a series of plain sinus radiographs correlated with CT findings in >90% of cases but was dependent on the experience of the clinician in performing rigid nasal endoscopy [71]. The rate of concordance between plain films and CT scans, when reviewed by an experienced radiologist, was 87% in that series.

The finding of sinus opacification or air-fluid levels on a standard radiograph of the sinuses has been found to be sensitive for detecting sinusitis [68, 69, 72–74]. However, these findings are not specific. Practically speaking, it is nearly impossible to obtain an adequate study with plain radiographs by using portable equipment in an ICU. For critically ill patients with occult fever, the diagnostic yield with CT scanning is higher, and it may be performed in conjunction with chest or abdominal scanning as indicated [75].

Other radiological procedures, including ultrasonography and MRI, have been used to diagnose sinusitis [73, 76]. A-mode ultrasonography appears to be as sensitive as conventional procedures (93%) but far less specific, making it useful only as a screening tool [73]. Marked deficiencies in determining bone structures make MRI less useful than CT for the diagnosis of acute sinusitis.

Sinus puncture and aspiration under aseptic conditions, with subsequent microbial analysis, allows a definitive diagnosis of infectious sinusitis. The discordance between radiographic findings and microbiological results makes sampling manda-

tory, and it provides the optimal means for tailoring antibiotic therapy. The disadvantages are that sampling is an invasive procedure (albeit minimally so) and that specimens are susceptible to contamination with normal nasal (or oral) flora if rigorous aseptic technique is not used when they are obtained. Povidone-iodine is used for topical preparation, and intravenous sedation at the bedside is usually sufficient to prevent discomfort [77].

Recommendations

1. If findings on clinical evaluation suggest that sinusitis should be sought as a cause of fever, a CT should be performed to obtain radiological evidence of pathology (B, III).
2. If findings are consistent with sinusitis and it is strongly suspected clinically, patients should undergo puncture and aspiration of the sinuses under sterile conditions (C, III).
3. The aspirate should be gram stained and cultured for aerobic and anaerobic organisms as well as fungi to determine the causative pathogens (B, II).

Postoperative Fever

Fever is a common phenomenon during the initial 48 hours after surgery. It should be remembered that fever in this early postoperative period is usually noninfectious in origin [78], presuming that pulmonary aspiration or unusual breaks in sterile technique did not occur. Considerable money can be wasted in overzealous evaluation of early postoperative fever. However, after >96 hours have elapsed, fever is likely to represent infection.

It is not mandatory to obtain a chest radiograph to evaluate postoperative fever unless the respiratory rate, findings on auscultation, abnormal blood gas determinations, or pulmonary secretions suggest a high probability that a radiograph will be useful. Atelectasis is often considered to be a cause of postoperative fever. A clinician must be alert to the possibility that a patient could have aspirated during the perioperative period or that a community-acquired infection (e.g., influenza A or legionella pneumonia) was incubating before the operation.

Postoperative urinary tract infection is common because of the use of urinary drainage catheters [79]. The duration of catheterization is the most important risk factor for the development of nosocomial cystitis or pyelonephritis. It is not mandatory to perform a urinalysis or culture to evaluate fever during the initial 2–3 postoperative days unless there is reason, based on history or examination, to suspect an infection in the urinary tract.

Fever can be related to a hematoma or infection of the surgical field. Wound infection, except for that due to group A streptococci and clostridia, is rare in the first few days after surgery; infection due to these organisms can develop 1–3 days after surgery. Their presence should be suspected on the basis of inspection of the wound.

Many emergency abdominal operations are performed to control an infection (e.g., peritonitis due to a perforated diverticulum). Even under optimal circumstances (definitive surgical control and timely administration of appropriate broad-spectrum antibiotics), it may take ⩾72 hours for patients with abdominal infections to defervesce. New or persistent fever >4 days after surgery should raise a strong suspicion of persistent pathology or a new complication. The only important exceptions to this rule are the development of erysipelas, clostridial myonecrosis, or toxic shock syndrome due to group A streptococcus or *S. aureus* [80]. 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. When erysipelas or myonecrosis is present, the diagnosis is often suspected by inspection alone, and such patients usually appear toxic. Crush syndrome and tetanus are two other rare complications of traumatic wounds that may cause fever.

Other potentially serious causes of postoperative fever include deep venous thrombosis, suppurative phlebitis, pulmonary embolism, and catheter-related infection. It is important to inspect all previous catheter sites on a patient and immediately evaluate (usually by duplex ultrasonography with color Doppler flow studies) any new swelling of an extremity.

Recommendations

1. Aggressive pulmonary toilet should be instituted for a patient with fever in the early postoperative period; this should include incentive spirometry to reduce the likelihood or extent of atelectasis (B, III). It is not mandatory to obtain a chest radiograph during the initial 72 hours after surgery if fever is the only indication.
2. A urinalysis and culture are not mandatory during the initial 72 hours after surgery if fever is the only indication. Urinalysis and culture should be performed for febrile patients with indwelling bladder catheters in place for >72 hours (B, III).
3. Surgical wounds should be examined daily for signs of infection. They do not need to be cultured if there is no symptom or sign suggesting infection (B, II).
4. The clinician should maintain a high level of suspicion for deep venous thrombosis, superficial thrombophlebitis, and pulmonary embolism, especially if a patient is sedentary, has lower extremity immobility or malignancy, or is taking an oral contraceptive (B, II).

Wound Infections

In the United States, surgical incisions rank second in frequency among nosocomial infection sites [81–83]. Wound infections alone account for ~25% of costs related to the treatment of all nosocomial infections [84, 85]. Nationally, the overall incidence of wound infections is ~3%–6%, a figure

that is based on the total number of infections and operative caseloads sampled from many hospitals [82, 83, 85].

Definitions

For operations in which the body cavity is entered, the surgical wound is subdivided into superficial and deep components. The former consists of the portion of the wound within the skin and subcutaneous tissue above the layer of the fascial closure, and the latter refers to infection of the tissues or spaces at or beneath the fascial layer [86–87]. In most patients a wound infection never escapes the local tissue boundaries. These boundaries are defined deeply by fascia and laterally by skin and subcutaneous fat. In this sense, most wound infections are subcutaneous abscesses.

Superficial incision-site infection is characterized by purulent drainage from the incision or a drain located above the fascial layer. A deep incision-site infection is characterized by either purulent drainage from the deep incision but not from the organ-space component of the surgical site or by a deep incision that dehisces spontaneously [88].

Risk Factors

Classification of wounds by probability of bacterial contamination is the single most important factor in determining the likelihood that a wound infection will develop [89, 90]. Traditionally, surgical wounds have been classified as: class 1 (clean)—no inflammatory focus encountered during surgery; no known breaks in aseptic technique; no entry into the alimentary, urinary, or respiratory tract; wound closed primarily; class 2 (clean-contaminated)—alimentary, urinary, or respiratory tract entered without major spillage; or minor breach of asepsis; class 3 (contaminated)—major break in asepsis; gross spill of alimentary tract contents at any level; entry into any hollow organ containing infected contents; and class 4 (dirty)—acute purulent inflammation found; traumatic wounds requiring surgical repair; feces or devitalized tissue in the field of operation. The validity of this classification scheme is borne out by the results of numerous retrospective and prospective epidemiological studies that demonstrate consistently that wound infections occur with increasing frequency as the class of the wound progresses from clean (1%–3% of infections), to clean-contaminated (4%–5%), to contaminated (6%–15%), to dirty (16%–40%) [80, 89, 91, 92].

With use of data from the National Nosocomial Infections Surveillance System, a system for classifying the risk of surgical wound infection has recently been developed that accounts for wound class, operative procedure, and variations in patients' underlying severity of illness [93]. This risk index score, which ranges from 0 to 3, is the number of risk factors present among the following: (1) an American Society of Anesthesiologists preoperative assessment score of 3, 4, or 5 [94]; (2) an operation classified as contaminated or dirty; and (3) an operation lasting over T hours, where T depends on the operative procedure being performed. This system is a significantly better predictor of surgical wound infection than the traditional wound classification system [93]. In addition, it provides a better means of comparing the risk of surgical wound infection among surgeons, among institutions, and across a broad range of operative procedures.

Microbiology

In clean surgical procedures in which the gastrointestinal, gynecological, or respiratory tracts have not been entered, *S. aureus* from the exogenous environment or patients' skin flora is the usual cause of infection [80, 88, 95]. In all other categories of surgical procedures, the polymicrobial aerobic-anaerobic flora closely resembling the normal endogenous microflora of the surgically resected organ are the most frequently isolated pathogens [95].

Aspirates from infection in and around the oral, rectal, and vulvovaginal regions tend to yield mixed aerobic and anaerobic flora similar to those that are part of the normal microbial flora at the adjacent mucous membrane. Conversely, specimens obtained from areas remote from those sites primarily contain constituents of the microflora endogenous to the skin.

Recommendations

1. Examine the surgical wound for erythema, purulence, or tenderness (B, II).
2. If infection is suspected, the wound should be opened (B, II).
3. Gram stain and cultures should be performed on any expressed pus or material obtained from deep within the wound site (B, II).

CNS Infection

There are numerous noninfectious reasons for both fever and alteration in neurological parameters, including mental status, for patients in the ICU [96]. Conversely, some of these patients with compromised immunity develop CNS conditions, including infection, that can produce fever in the absence of neurological signs or symptoms. Hence, the intensivist needs to maintain a high index of suspicion for CNS infection.

Diagnostic Evaluation

CNS infection rarely causes encephalopathy in the absence of detectable focal abnormalities. However, infection must be considered for any febrile ICU patient—even one without focal findings—because of the inherent limitations of a neurological examination when a patient is critically ill.

Imaging studies and culture of the CSF are the cardinal features of a diagnostic evaluation. Patients with focal neurological findings suggesting disease above the foramen magnum

will generally require imaging studies before lumbar puncture. Performance of CT without contrast media is adequate for excluding the presence of mass lesions or obstructive hydrocephalus, which might contraindicate lumbar puncture. If bacterial meningitis is suspected and 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* infection) should be started after blood cultures are performed. The usual contraindications to lumbar puncture, detected with use of CT, 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 [97]. If findings on physical examination suggest involvement of the spinal cord, a neurologist or neurosurgeon should be consulted because of the potential for spinal cord herniation with an intra-axial mass. The postponement of lumbar puncture until an imaging study has been performed for a patient who is unresponsive and does not have focal findings is a clinical decision.

Patients with suspected brain abscesses should not undergo lumbar puncture because of the risk of herniation; the bacteriologic yield of CSF analysis in this setting is too low to justify the risk [98]. Aspiration of a suspected abscess is the diagnostic procedure of choice. The optimal timing of aspiration is currently debated; if aspiration is delayed, administration of 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, CSF should almost always be obtained for analysis. The site of CSF access for patients with ventriculostomy catheters is straightforward. If a shunt system includes a CSF reservoir, the reservoir should be aspirated; this is also with Ommaya reservoirs. Patients in whom CSF flow to the lumbar subarachnoid space is obstructed may also need to undergo lumbar puncture, since one space may be infected while the other is sterile.

If a patient with a ventriculostomy catheter in place develops stupor or signs of meningitis, the catheter should be removed and the tip cultured. This should probably be performed in a manner analogous to that for intravascular catheters, although evidence is lacking. Often, the catheter will need replacement. The same procedure should be followed for patients with lumbar drains in place.

Tests to be Performed on CSF

Basic tests to be performed on CSF from patients with suspected CNS infection include cell counts, determinations of glucose and protein concentrations, gram stain, and bacterial cultures. Whether testing for cryptococcal antigen, stains and cultures for fungi, acid-fast smears and cultures, cytological examination for neoplasia, or a serological test for syphilis are needed depends on the clinical situation. The precise combination of tests most likely to detect bacterial infection is debated. It should be remembered that the normal protein content of CSF varies with the site from which the specimen was withdrawn: the upper protein content limit for ventricular fluid is usually 15 mg/dL; that for cisternal fluid, 20 mg/dL; and that for lumbar fluid, 45 mg/dL.

Patients with bacterial meningitis typically have a CSF glucose concentration of <35 mg/dL, a CSF/blood glucose ratio of <0.23, a CSF protein concentration of >220 mg/dL, a total WBC count of $>2{,}000/\mu L$, and a neutrophil count of $>1{,}180/\mu L$ [99]. Conversely, in immunologically normal hosts, the presence of a normal opening pressure, <5 WBCs/μL, and a normal CSF protein concentration essentially exclude the diagnosis of meningitis [100]. The applicability of these findings to critically ill, immunocompromised patients is uncertain, and a high index of suspicion for infection should be maintained regardless of cell count and glucose concentration until the results of cultures have been obtained. Lactate and pH measurements may be useful in some circumstances but do not distinguish bacterial meningitis from other forms of the disease.

Recommendations

1. If a patient has unexplained altered consciousness or focal neurological signs and new fever, lumbar puncture should be considered unless the procedure is contraindicated (B, III).
2. For a patient with a new fever and new focal neurological findings suggesting disease above the foramen magnum, an imaging study is usually required before lumbar puncture. If a mass is present, consultation with a neurologist or neurosurgeon is required to determine the optimal diagnostic approach (B, II).
3. When febrile patients have an intracranial device in place, 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 (B, III).
4. CSF should be evaluated by gram stain and culture. Additional tests for tuberculosis, fungal disease, or neoplasia should be performed as dictated by the clinical situation (B, III).

Noninfectious Causes of Fever in the ICU

Although an infectious cause must always be assumed and sought for new fever in critically ill patients, there are certain noninfectious causes that must be considered as well. These noninfectious causes include drug-related fever, fevers related to other therapies, inflammatory states not initiated by infection, certain endocrine emergencies, and a group of miscellaneous causes that must be considered in specific settings.

Drug-Related Fever

Any drug can cause fever due to hypersensitivity [101–105]. In addition, some drugs cause fever by producing local inflammation at the site of administration (e.g., phlebitis, sterile abscesses, or a soft-tissue reaction); amphotericin B, erythromycin, potassium chloride, and cytotoxic chemotherapeutic agents are prime examples [105]. Drugs or their delivery systems (diluent, intravenous fluid, or intravascular delivery devices) may also contain pyrogens or, rarely, microbial contaminants [31]. Some drugs may also stimulate heat production (e.g., thyroxine), limit heat dissipation (e.g., atropine or epinephrine), or alter thermoregulation (e.g., butyrophene tranquilizers, phenothiazines, antihistamines, or antiparkinson drugs) [101].

Among drug categories, fever is most often attributed to antimicrobials (especially β-lactam drugs), antiepileptic drugs (especially phenytoin), antiarrhythmics (especially quinidine and procainamide), and antihypertensives (methyldopa). There is nothing characteristic about the fevers induced by these drugs [100, 101]. Fever does not invariably occur immediately after one of these drugs is administered; it may take days for fever to develop and many more days before it abates. In one series, the lag time between initiating treatment with certain drugs and the onset of fever was a mean of 21 days (median, 8 days) [105]. It often takes 1–3 days for a patient's temperature to return to normal, although it can take >7 days for the temperature to return to normal after the offending agent is removed [102]. Rash occurs in only a small fraction of cases; eosinophilia is also uncommon.

The diagnosis of drug-induced fever is usually established on the basis of a temporal relationship between the fever and initiation and withdrawal of treatment with 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.

Two important syndromes, malignant hyperthermia and neuroleptic malignant syndrome, deserve consideration when a fever is especially high because the results can be devastating if it is left untreated. Malignant hyperthermia is more often identified in the operating room than in the ICU, but onset of this condition can be delayed for as long as 24 hours. It can be caused by succinylcholine and the inhalation anesthetics, of which halothane is the most frequently identified cause. 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, which generates fever and increasing creatinine phosphokinase concentrations.

Though rare, the neuroleptic malignant syndrome, a second hyperthermic syndrome, is more often identified in the ICU than is malignant hyperthermia. It has been strongly associated with antipsychotic neuroleptic medications—phenothiazines, thioxanthines, and butyropherones. Haldoperidol is perhaps most frequently reported to be related to this syndrome in patients in the ICU. Neuroleptic malignant syndrome manifests as muscle rigidity that generates fever as well as increasing creatinine phosphokinase concentrations. However, unlike the situation with malignant hyperthermia which is mediated by calcium dysregulation, the initiator of muscle contraction in the neuroleptic malignant syndrome is central.

It is important to note that withdrawal of certain drugs may be associated with fever, often with associated tachycardia, diaphoresis, and hyperreflexia. Alcohol and 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 obtainable when a patient is admitted to the ICU. Withdrawal and related fever may therefore occur several hours or days after admission.

Fevers Related to Other Therapies

Fever associated with transfusion of blood products, particularly RBCs and platelets, most frequently occurs in patients who have received multiple transfusions. A reaction to transfusion of RBCs may present only as fever, or as fever in the setting of intravascular hemolysis or acute respiratory distress syndrome.

Fever in association with vasodilatation, erythroderma, and occasionally, hypotension, has been associated with the rapid killing of microorganisms, the liberation of biologically active fragments of the lysed organisms, and the resulting action of cytokines—the Jarisch-Herxheimer phenomenon. This reaction has been best described in association with the treatment of syphilis (neonatal or secondary) but may occur during acute treatment of other infections. Fever can also be a feature of tumor lysis syndrome, the result of rapid lysis of a large burden certain tumor cells.

Cytokine-related fever has occurred in association with the infusion of IL-2, granulocyte-macrophage colony-stimulating factor, and on occasion, granulocyte colony-stimulating factor during the treatment of certain malignancies.

Inflammatory States Causing Fever Not Initiated by Infection

Chemically induced thrombophlebitis may be difficult to distinguish from infection of a vein. Certain drugs, when administered peripherally, are highly associated with inflammation of the veins—particularly the penicillins, erythromycin, vancomycin, amphotericin B, potassium chloride supplements, and certain chemotherapeutic agents.

Certain inflammatory processes may cause fever in the absence of infection, particularly pulmonary infarction and the fibroproliferative phase of adult respiratory distress syndrome [106]. In addition, acute or chronic pancreatitis may be associated with fever as well as hemodynamic instability.

Fever (temperature, usually <38.5°C) may be associated with acute myocardial infarction in the first few days. Higher

temperature elevations have been associated with Dressler's syndrome in the later period after myocardial infarction, or after cardiothoracic surgery involving incision of the pericardium (''postpericardiotomy'' syndrome).

Several endocrine emergencies can be associated with fever. Although hormonal measurement may indicate hyperthyroidism in a patient without striking clinical manifestations, a physiological stress such as surgery or a critical illness may precipitate thyroid storm—an acute febrile illness and hyperdynamic state that may be indistinguishable from septic shock.

Acute adrenal insufficiency in patients in the ICU may result when patients receiving chronic exogenous corticosteroids for underlying diseases (e.g., asthma or collagen vascular disease) are inadvertently deprived of supplemental glucocorticoid and mineralocorticoid hormones. This condition may also occur in the setting of acute coagulopathy with hemorrhagic destruction of the adrenal glands, either secondary to aggressive anticoagulation with heparin or coumadin or secondary to disseminated intravascular coagulation associated with septic shock. Acute adrenal insufficiency may present as the abrupt onset of high fever, hypotension, and a hyperdynamic state that, like thyroid storm, will be indistinguishable from septic shock, even by pulmonary artery catheter indices.

Many other noninfectious entities can cause fever in a patient in the ICU. Subarachnoid hemorrhage, gout, fat emboli, and transplant rejection are among the well-recognized causes. Deep venous thrombosis, in association with indwelling catheters or occurring spontaneously may also be associated with fever. The recognition and identification of a noninfectious cause of fever requires the same careful assessment of a patient, including physical examination and review of all drugs, therapies, and the setting, as is necessary for the recognition and identification of an infectious cause of fever.

Recommendations

1. Examine the patient and exclude infectious causes of fever. Pay particular attention to old intravascular catheter sites and old surgical wound sites (B, III).
2. Revisit all new medications and blood products the patient has received. Ideally, if treatment with the suspected drug can be stopped, do so. If not, consider a comparable substitute (B, III).
3. 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 (B, III).

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