

DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

FEVER ASSESSMENT

SUMMARY

The onset of fever in a patient in the ICU is a moment of opportunity for the physician. Appropriate evaluation of fever and institution of early, goal directed therapy where indicated is associated with a clear survival benefit for patients who are septic, experiencing endocrine emergencies or other causes of temperature dysregulation. A “shotgun” approach to fever evaluation, however, may lead to unnecessary diagnostic tests and procedures, confusing or inconclusive data, and significant expense. It may also expose the patient to unnecessary discomfort, risk and even inappropriate therapies.

RECOMMENDATIONS

- **Level 1**
 - None
- **Level 2**
 - Core body temperature measurements (such as from an intravascular or urinary catheter) should be used whenever possible. Axillary and tympanic temperatures are unreliable.
 - Two peripheral blood cultures should be obtained in the presence of a new fever (when clinical evaluation does not strongly suggest a non-infectious cause). If a central venous catheter is present, an additional culture should be drawn from the indwelling catheter.
 - Intravascular catheters should not be routinely cultured during catheter guidewire exchange unless catheter-related infection is suspected. When indicated, the intracutaneous segment (as opposed to the catheter tip) should be sent for semi quantitative culture.
 - Pulmonary secretions should be sent for Gram stain and culture only when a pulmonary etiology for the patient's fever is strongly suspected.
 - Urine should be collected by “clean catch” or from the sampling port of the urinary catheter.
 - If infection is suspected, surgical wounds should be opened with Gram stain and culture obtained from deep within the wound site. Cultures of the skin overlying a wound should not be performed.
 - If there is sufficient clinical suspicion, a CT scan of the sinuses should be obtained.
 - Evaluation for *Clostridium difficile* infection should begin with a *C. difficile* toxin enzyme immunoassay test. If this test is negative, a second test should be performed.
- **Level 3**
 - Fever is defined as a temperature elevation of greater than 38.3°C (101°F)
 - New onset of fever should result in a careful physical examination and clinical assessment of the patient rather than automatic orders for costly radiologic and laboratory tests.
 - Chest radiographs, urinalysis, or culture are not indicated in the first 72-96 hours post-operatively unless history and clinical findings suggest a high probability of utility.
 - The patient with postoperative fever should receive aggressive pulmonary toilet and careful evaluation of all operative wounds.
 - Noninfectious causes of fever should be carefully investigated.
 - If fever is accompanied by altered consciousness or focal neurologic deficits, lumbar puncture or evaluation of CSF from an indwelling ventriculostomy should be considered.

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

INTRODUCTION

Fever, a common problem in both the intensive care unit (ICU) and on the patient ward, is defined as an elevation in core body temperature. The Society of Critical Care Medicine (SCCM) defines fever as a **temperature elevation of greater than 38.3°C (101°F)** (1). The incidence of fever during a typical ICU stay has been reported to vary between 5-70% (Class II) (2,3). Fever represents the body's response to injury, inflammation, and infection. Temperature elevation has been shown to both enhance immune response and suppress certain bacterial species (1). Although it is widely agreed that fever has adaptive advantages as a response to infection, it is also clear that fever has deleterious effects (3). In an evaluation of fever in critically ill surgical patients published in 2004, Barie et al found that fever is associated with a higher incidence of organ failure and death and that peak temperature is a powerful predictor of mortality (Class II) (4). In certain patient groups, however, fever is a predictable aspect of their hospital course and diagnostic evaluation is not indicated; the empiric treatment of such temperature elevations may actually be detrimental. The presence of fever commonly leads to performance of diagnostic tests and procedures as well as institution of therapies that significantly increase patient care costs and expose the patient to unnecessary risks and discomfort. Prophylactic broad-spectrum antibiotic therapy is also commonly instituted placing the patient at risk for both drug reactions and development of resistant bacterial species. Fever should lead to a careful physical evaluation and clinical assessment of the patient rather than automatic orders for costly laboratory and radiologic studies that are commonly associated with a low diagnostic yield (Level 3) (1,3).

LITERATURE REVIEW

Review Articles

In 1998, SCCM created a task force to establish guidelines for evaluating new fever in critically ill patients. O'Grady et al performed an extensive review of the literature regarding many aspects of fever evaluation (1). It is a well referenced and very practical document and is cited often throughout this guideline. Dr. Marik's review article from 2000 entitled "Fever in the ICU" includes a more basic science review of fever and its causes as well as an algorithmic approach to the assessment on fever (3).

Measuring Temperature

The first step in evaluating fever is to accurately assess temperature. The gold standard for temperature monitoring is central core temperature measurement using an intravascular device such as a pulmonary artery (PA) catheter thermistor. This invasive methodology has obvious disadvantages and impracticalities for some patients. Though the optimal method for measuring temperature is still debated, it is clear that the site and method of measurement should be recorded along with the measurement itself (Level 3) (1). Moran et al compared PA thermistor, axillary, tympanic membrane, and urinary bladder thermistor temperature assessments in 110 patients in a tertiary university-based hospital setting (5). The authors found that tympanic membrane measurements showed only modest correlation with PA ($r=0.77$), urinary ($r=0.69$), and axillary ($r=0.76$) temperatures. The average difference between PA and urinary temperature was small at -0.05 , with a good correlation ($p=0.92$). This paper adds to a growing body of evidence that questions tympanic membrane measurements and suggests that urinary bladder temperature monitoring is the preferred alternative when PA catheter monitoring is not indicated and Foley catheter placement is indicated (Class II) (5).

Evaluation of the Patient

With the new onset of fever, a detailed search for possible etiologies should be performed. In addition to a careful physical examination and thorough review of the patient's medical record, this should include:

Review of:

- Patient's injuries
- Previous cultures
- Prior antibiotic therapies
- All medications (to rule out drug-related fever)
- Recent chest radiograph (if available)

Examination of:

- Pulmonary secretions
- All intravascular catheter insertion sites
- All drainage tubes and their output
- All wounds
- All extremities for swelling

Infectious vs. Non-infectious Causes of Fever

The initial goal in fever assessment should be to identify when an infectious vs. a non-infectious cause of fever is present. Some common non-infectious causes for fever are listed below. Many of these are diagnoses of exclusion and many patients will have risk factors for both infectious and non-infectious etiology of their fever. Unless there is strong evidence that the fever is non-infectious in nature, diagnostic tests to evaluate for a source of infection, chosen based on the clinical circumstances, should be initiated. Assuming the absence of pulmonary aspiration or breaks in sterile technique, the development of fever within the first 72-96 hours postoperatively is usually non-infectious in origin (1).

Non-Infectious Causes of Fever

- Alcohol / drug withdrawal
- Postoperative fever
- Post transfusion fever
- Drug fever
- Cerebral infarction
- Adrenal insufficiency
- Myocardial infarction
- Pancreatitis
- Acalculous cholecystitis
- Ischemic bowel
- Aspiration pneumonitis
- ARDS
- Subarachnoid hemorrhage
- Fat emboli
- Transplant rejection
- Deep venous thrombosis
- Pulmonary emboli
- Gout / pseudogout
- Hematoma / Solid organ injury
- Cirrhosis (without primary peritonitis)
- GI bleed
- Thrombophlebitis
- IV contrast reaction
- Neoplastic fevers
- Decubitus ulcers

Blood Cultures

Blood cultures should be obtained in patients with a new fever when clinical evaluation does not strongly suggest a non-infectious cause (Level 2) (1,3). Two peripheral blood cultures should be drawn after the initial temperature elevation. If a central venous catheter is present and considered to be a potential source of infection, a blood culture drawn through the catheter should also be sent. Following this, further blood cultures should be obtained based on clinical judgment rather than automatically with each temperature elevation (Level 2). Obtaining blood cultures more than every 24 hours is rarely helpful (1).

Martinez and colleagues retrospectively reviewed the sensitivity and specificity of blood cultures drawn through a central venous or arterial catheter in comparison to those obtained from peripheral venipuncture (6). Sensitivity and specificity were determined using true bacteremia as the primary outcome measure. Paired blood cultures were used for analysis. No difference in sensitivity was identified. Specificity, however, was significantly less for cultures obtained from indwelling catheters compared to peripheral venipunctures (95% vs. 98%; $p=0.002$). The positive predictive value of cultures obtained through a central venous line was significantly lower than that of peripheral venipuncture (61% vs. 82%; $p=0.045$) (Class III). Cultures should not be drawn from indwelling vascular catheters unless performed at the time of line placement or as part of the evaluation for intravascular catheter-related infection (Level 2) (1,3,7).

Intravascular Catheters

Intravascular catheters are a major source of nosocomial blood stream infections. Intravascular catheters should NOT be routinely cultured unless catheter-related infection is suspected. In a patient with a new fever and no other obvious source, it is reasonable to suspect catheter-related bloodstream infection. While negative blood cultures from a central line can help to exclude catheter related bloodstream infection (CRBSI), positive blood cultures drawn from the catheter may indicate either infection or colonization (7). One approach is to change the suspect line over a guidewire in which case the intracutaneous segment (as opposed to the catheter tip) should be sent for semi-quantitative culture (Class II) (8). If the culture returns with more than 15 colony forming units (CFU) of a specific pathogen, the catheter should be considered infected and removed with a new central venous catheter inserted at a new site. Quantitative blood cultures, drawn peripherally and from the central catheter, are another approach to diagnosis of CRBSI. If the colony count obtained from the central venous catheter is 5-fold

greater than that from the peripheral culture, the catheter should be considered infected (7). Intravascular catheter insertion sites should be cultured and Gram stained ONLY when there is expressible purulence or exudate from around the catheter (Level 2) (1).

There has been a recent surge of work evaluating the maintenance of central venous catheters and prevention and management of CRBSI. These issues are addressed in greater detail in the "Central Venous Catheter" guideline and the "Selection of Central Venous Catheter in the Surgical Patient" guideline. A thorough discussion of the subject is also available in a 2001 consensus guideline by Mermel et al (7).

Pulmonary Infections

Chest radiographs and respiratory cultures are not indicated in the first 72- 96 hours post-operatively unless respiratory rate, auscultation, abnormal blood gas results, or pulmonary secretions suggest a high probability of utility (Level 3) (1,3). The patient with postoperative fever should receive aggressive pulmonary toilet (Level 3). Pulmonary secretions should be sent for Gram stain and culture only when a pulmonary etiology for the patient's fever is strongly suspected. An expectorated or suctioned specimen is adequate for initial evaluation (Level 2) (1). The quality of the sputum sample should be considered in the evaluation of the culture results. Specimens that demonstrate a preponderance of epithelial cells on initial Gram stain are not suitable and should be discarded (1). Saline should be instilled only when adequate specimens cannot be otherwise obtained. Bronchoscopy and bronchoalveolar lavage should be considered when initial sputum evaluations are nondiagnostic or in the presence of a discrete lobar infiltrate (Level 2) (1). A chest imaging study (plain radiograph or chest computed tomography if clinically indicated) should be obtained whenever a pulmonary etiology for fever is suspected (Level 3) (1). Pleural fluid should be obtained for evaluation only when there is an adjacent infiltrate or other reason to suspect infection and the fluid can be safely aspirated (Level 2) (1,3).

Urinary Tract Infections

Urinalysis or culture is not indicated in the first 72-96 hours postoperatively unless there is reason to suspect infection (i.e., break in sterile technique) (Level 3) (1). Asymptomatic bacteruria is very common, especially in patients with indwelling urinary catheters. This typically implies colonization as opposed to true urinary tract infection with antibiotic therapy being indicated only for the latter. When a patient becomes febrile without another obvious source, a urine specimen should be collected by "clean catch" or from the sampling port of the urinary catheter, not from the collecting bag. Interpretation of urine culture in ICU patients may be difficult. If there is concordance of an organism in blood and urine cultures, fever can be attributed to a urinary tract infection (1). Gram-negative bacilli, *Enterococci faecalis*, and yeast are the most common organisms encountered (1). Patients with more than 10⁵ CFU on quantitative urinary culture are usually treated with antibiotics based on work done by Platt et al in the 1980's that demonstrated an increased mortality in these patients (Class II) (9). However, this level of bacteruria may occur in up to 30% of catheterized, hospitalized patients (Class II) (3). The significance of more than 10⁵ CFU remains unclear as does the significance of pyuria in the specimen (1,3).

Wound Evaluation

Surgical and superficial wounds should be inspected daily for signs of infection (Level 3) (1). Superficial wound cultures are rarely indicated unless there is evidence of purulence or suspicious drainage. If infection is suspected, the wound should be opened and Gram stain and cultures should be performed from deep within the wound site (Level 2). Cultures of the skin overlying a wound should not be performed. In post-operative patients or trauma patients, evaluation of the surgical field or deep tissue wounds may be warranted based on clinical suspicion. Plain radiographs, CT, and ultrasound all have a role in evaluation of these patients based on clinical evaluation (Level 3).

Sinusitis

Sinusitis is most commonly caused by obstruction of the ostia draining the sinuses due to a nasotracheal or nasogastric tube. The evaluation of sinusitis is generally not part of the initial evaluation for fever and should be undertaken after the more likely etiologies for fever have been ruled out. Only 25% of ICU patients with sinusitis will have purulent nasal discharge (1). Gram-negative bacilli represent 60% of the bacterial isolates in nosocomial sinusitis with *Pseudomonas aeruginosa* being most common (1). Gram-

positive bacteria comprise one-third of the isolates with *Staphylococcus aureus* being most common. Fungi comprise the remaining 5-10% of isolates. If there is sufficient clinical suspicion, a CT scan of the sinuses should be obtained (Level 2).

Clostridium difficile and Enteric Pathogens

Clostridium difficile colitis is the most common cause of diarrhea-related fever. The majority of patients infected with *C. difficile* are asymptomatic with only one-third developing diarrhea (3). It should be suspected in any patient with fever, diarrhea, and a history of receiving antibacterial agents within the three weeks prior to the onset of diarrhea. The sensitivity of testing stool specimens for *C. difficile* colitis via the enzyme immunoassay test for *C. difficile* toxin is 72% for the first sample and 84% for the second sample. As a result, evaluation for *C. difficile* infection should begin with a *C. difficile* toxin enzyme immunoassay test (Level 2). If this test is negative, a second test should be performed (Level 2). Although direct visualization of pseudomembranes via endoscopy is highly specific, the sensitivity is only 23% for patients with mild disease and there is a risk for perforation of the colon during the procedure (Level 2) (3). The empiric administration of metronidazole or oral vancomycin is discouraged due to the risk of producing resistant pathogens (Level II). If severe illness is present, empiric metronidazole therapy may be considered while awaiting diagnostic studies. Stool evaluation for ova, parasites, and other pathogens should be performed only if the patient has recently traveled to an endemic area, was admitted to the hospital for diarrhea, or the patient is HIV infected (Level 2) (3).

Evaluation of the CNS

If fever is accompanied by altered consciousness or focal neurologic deficits, lumbar puncture (unless contraindicated) or evaluation of CSF from an indwelling ventriculostomy should be considered (Level 3). Gram stain and culture should be performed with further investigation for tuberculosis, fungal disease, neoplasm, etc... as indicated by the clinical situation (1).

Candida and Fungal Infections

Candida is part of the normal intestinal flora of some 30% of healthy people (3). Antibiotic therapy increases the incidence to about 70% and most ICU patients probably become colonized. Though not all colonized patients become infected, Candida species and fungal infections are important opportunistic pathogens in the ICU population. Infection can be assessed from histologic evaluation of specimens or identification from sterile specimens. Tracheal aspirates (especially in neutropenic patients) and Candida found in specimens from indwelling urinary catheters likely represent colonization rather than infection (Level 2) (3).

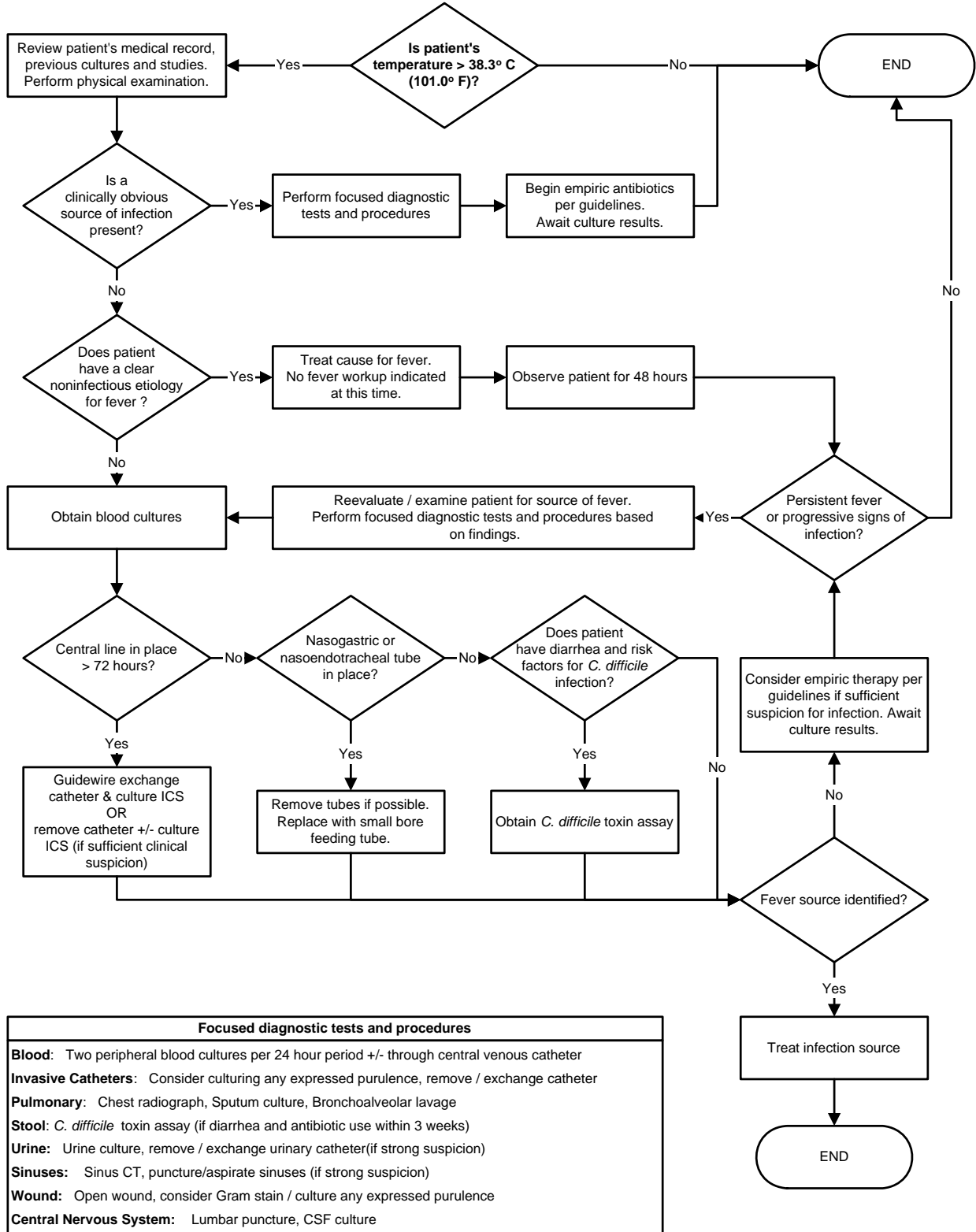
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APPENDIX 1: CULTURE TECHNIQUES (1)

- **Blood**
 - Indication: Blood cultures should be obtained in patients with a new fever when clinical evaluation does not strongly suggest a noninfectious cause.
 - Technique:
 - ❑ The site of venipuncture should be prepped with 10% povidone iodine, 70% alcohol, or equivalent antiseptic (iodophors must dry to provide maximal antiseptic activity) (Level I).
 - ❑ At least 10-15 mL of blood should be drawn from a separate site for each culture (Level II).
 - ❑ The injection port should be wiped with alcohol prior to injection (Level III).
 - ❑ Needles should NOT be switched prior to inoculating blood culture bottles. The risk of needle stick injury during the switch in needles is currently felt to outweigh the risk of contamination.
 - ❑ A pair of blood cultures should be drawn after the initial temperature elevation. Following this, further blood cultures should be obtained based on clinical judgment rather than automatically with each temperature elevation (Level II).
 - ❑ Cultures should not be drawn from indwelling vascular catheters unless performed at the time of line placement (Level III).
- **Intravascular catheters**
 - Indication: Intravascular catheters should be cultured when catheter-related infection is strongly suspected (Level II).
 - Technique:
 - ❑ See Invasive Catheter Guidelines
- **Pulmonary Secretions**
 - Indication: Pulmonary secretions should be cultured when a febrile patient is suspected of having a lower respiratory tract infection by clinical and/or radiographic assessment (Level II).
 - Technique:
 - ❑ Expecterated sputum should be sterilely collected from nonintubated patients (Level II).
 - ❑ Deep tracheal aspirates should be obtained without use of saline in intubated patients. Saline should be instilled only when adequate specimens cannot otherwise be obtained. (Level II).
 - ❑ Bronchoalveolar lavage should be considered when a discrete lobar infiltrate is present on chest radiograph or when tracheal aspirate cultures have not been helpful (Level II).
 - ❑ Sputum samples should be transported to the microbiology laboratory and processed within 2 hours from the time of collection (Level II).
- **Urine**
 - Indication: Urine cultures should be sent in the presence of fever and sufficient clinical suspicion.
 - Technique:
 - ❑ A midstream clean catch specimen should be sent in patients without a Foley catheter.
 - ❑ Aspiration of urine from the sampling port of the urinary collecting tubing should be performed in patients with a Foley catheter. Meticulous cleansing of the aspiration port should be performed.
 - ❑ Specimens should be sent to the microbiology laboratory for processing within 1 hour or the specimen should be refrigerated (Level II).
- **Wound**
 - Indication: Wound cultures should be sent in the presence of fever, purulent drainage or sufficient clinical suspicion.
 - Technique:
 - ❑ Wounds that are suspected of being infected should be opened (Level II).
 - ❑ Gram stain and cultures that are sent should be from deep within the wound site (Level II).
- **Stool**
 - Indication: Stool should be sent for *C. difficile* toxin assay in any patient with fever, diarrhea, and a history of antibiotic administration with the previous 3 weeks. Stool for ova and parasites should be sent only if the patient has recently traveled to an endemic area, was admitted to the hospital for diarrhea, or the patient is HIV infected (Level II).
 - Technique:
 - ❑ Day 1: Send one stool sample for *C. difficile* toxin assay (Level II).
 - ❑ Day 2: If the first specimen is negative, send an additional sample for *C. difficile* toxin assay

FEVER ASSESSMENT GUIDELINES



Focused diagnostic tests and procedures

Blood: Two peripheral blood cultures per 24 hour period +/- through central venous catheter

Invasive Catheters: Consider culturing any expressed purulence, remove / exchange catheter

Pulmonary: Chest radiograph, Sputum culture, Bronchoalveolar lavage

Stool: *C. difficile* toxin assay (if diarrhea and antibiotic use within 3 weeks)

Urine: Urine culture, remove / exchange urinary catheter (if strong suspicion)

Sinuses: Sinus CT, puncture/aspirate sinuses (if strong suspicion)

Wound: Open wound, consider Gram stain / culture any expressed purulence

Central Nervous System: Lumbar puncture, CSF culture