Approach to new fever or rigors in the ICU patient
December 18, 2016 by Josh Farkas

definition & classification of fever
Fever is a bedrock concept in medicine, yet its precise definition remains a bit elusive. The Infectious Disease Society of America defined fever in the ICU as a temperature above 38.3/101.3°C (18379262). This is generally a useful rule of thumb. However, a lower threshold for fever (>38/100.4) may be appropriate in some patients:
- Immunocompromised patients (e.g. neutropenic)
- Elderly patients

18379262
Patients on scheduled acetaminophen or NSAIDs

Precise temperatures may vary, depending on the site and the technique of measurement. Ideally, core temperature should be measured (e.g., rectal or esophageal temperature). However, in practice this is not routinely performed.

Once patients have been in the ICU for a few days, their fever curve may be more informative than any single measurement. A consistent trend over multiple time-points may be more likely to reflect a true event. Alternatively, a one-time fever spike which is below 38.9\(/102\) and immediately disappears is less likely to represent infection. 

(23878765 [https://pubmed.ncbi.nlm.nih.gov/23878765/])

This chapter explores new-onset fevers which occur after a couple days in the ICU, suggesting that the fever results from a process acquired \textit{within} the hospital. For patients who develop fevers shortly after ICU admission, the differential diagnosis will be broader (with a greater focus on community-acquired infection).

ICU-acquired fever should ideally be better defined. Based on definitions of ventilator-associated pneumonia, a fever arising >48 hours after hospital admission might be more likely to have been acquired within the hospital.

\textbf{recognition of neutropenic fever}

- Neutropenia is defined as absolute neutrophil count <500, or between 500-1000 and falling.
  - Absolute neutrophil count = (WBC)(% bands + % neutrophils).
- Fever in the context of neutropenia is defined as a temperature above >38/100.4 for an hour, or a single measurement above 38.3/101.
- Neutropenic fever is critical to recognize, because these patients require empiric broad-spectrum antibiotics.

\textbf{recognition of hyperthermia}

- Hyperthermia is defined as elevated temperature resulting from extreme \textit{heat generation}, rather than from an alteration of the hypothalamic set point.
- Hyperthermia is suggested by the following clinical features:
  - Extreme temperature elevation (temperatures above roughly \(~41/105.8\)).
  - Skin may be hot and dry (but not always!).
  - Antipyretics are ineffective.
- Hyperthermia has its own differential diagnosis and requires specific treatment.
- More on the critical distinction between \textit{fever} versus \textit{hyperthermia}.
appreciation of spontaneous rigors as a fever-equivalent

- Rigors are shaking chills, which which can be very dramatic. They represent an aggressive attempt by the hypothalamus to rapidly increase body temperature. A rigor will often precede development of a fever.
- Rigors are closely linked to bacteremia. Although not supported by evidence specific to the ICU environment, it's logical to investigate a patient with new-onset rigors in the same fashion as a patient with new-onset fever. Overall, evidence linking rigors to bacteremia is probably more persuasive than evidence linking fever to bacteremia.

common causes of fever in the ICU patient

infections (causing ~50% of fever in ICU)

- Pneumonia
- Clostridioides difficile
- Intravascular catheter infection
- Surgical site infection
- Urinary tract infection following the removal of a Foley catheter
- Metastatic or local complications from known infection (e.g., empyema, spinal abscess following endocarditis)
- Less often
  - Acalculous cholecystitis
  - Cellulitis, including infected decubitus ulceration
  - Spontaneous bacterial peritonitis (SBP)
  - Urinary tract infection in a patient with a functioning Foley catheter (rare)

noninfectious

- Procedure-related
  - Hemodialysis
  - Bronchoscopy
  - Febrile transfusion reaction (within 6 hours of transfusion)
  - Benign post-operative fever (post-operative day #1-3)
- Medication-related
  - Drug fever (more on this below)
  - Medication-induced hyperthermia (serotonin syndrome, neuroleptic malignant syndrome, malignant hyperthermia)
- Sterile pulmonary inflammation (ARDS, aspiration pneumonitis)
- Pulmonary embolism (usually low-grade fever, <39/102)

https://emcrit.org/ibcc/passage/fevervshyper/
- Neurogenic fever (more on this below #neurogenic_fever).
- Disorders which seldom arise in the ICU (yet may remain possible)
  - Pancreatitis
  - Thyroid storm or adrenal insufficiency
  - Rheumatologic disorders (vasculitis, gout flare)
  - Malignancy (especially lymphoma, hepatocellular carcinoma, renal cell carcinoma)

**evaluation**

- Physical examination as above.
- Chest X-ray if the patient is intubated or has respiratory symptoms.
- Blood cultures:
  - Two sets of peripheral blood cultures at different sites (each set contains an anaerobic bottle and an aerobic bottle).
  - Additionally, any line in place >48-72 hours should be cultured. ([18379262](https://pubmed.ncbi.nlm.nih.gov/18379262/))

**Urine culture should usually be avoided**

- Why avoid urinalysis and urine culture?
  - These are frequently positive in elderly patients, or anyone with a prolonged Foley catheter.
  - In patients with a Foley catheter, it's extremely unusual for urinary tract infection to be a cause of fever in the absence of urological manipulations, neutropenia, or Foley dysfunction. ([23878765](https://pubmed.ncbi.nlm.nih.gov/23878765/), [18379262](https://pubmed.ncbi.nlm.nih.gov/18379262/))
  - Routinely obtaining urinalysis and urine culture will lead to overdiagnosis of urinary tract infections.
- Bladder ultrasound to exclude Foley catheter dysfunction
  - Obstruction of the Foley catheter causing inadequate drainage of urine may cause ascending urinary tract infection.
  - For an ICU patient with a Foley catheter, the best way to evaluate for urinary tract infection may be bladder ultrasound to exclude Foley dysfunction (the presence of a significant volume of urine in the bladder indicates inadequate drainage).
- **Indications** to obtain a urinalysis and urine culture:
  - (1) Patient who lacks a Foley catheter and has signs/symptoms of urinary tract infection.
  - (2) Neutropenia.
  - (3) Structural urologic abnormality (e.g., recent surgery or urological procedure, or status post renal transplant)
  - More information in the chapter on catheter-associated urinary tract infection here (REF).

**Tracheal aspirate cultures should usually be avoided**

[https://emcrit.org/?attachment_id=475965](https://emcrit.org/?attachment_id=475965)
Tracheal aspirate cultures will often be positive among patients with structural lung disease (i.e., COPD) or prolonged intubation (often with scary bacteria such as Pseudomonas). However, in the absence of other features of infection, this reflects only colonization and should not affect management. Cultures should be obtained only if there is a clinical suspicion of a ventilator-associated pneumonia.

other testing based on clinical scenario

- Clostridioides difficile testing is indicated for patients with diarrhea.
- Abdominal imaging is indicated for patients with abdominal pain or recent abdominal instrumentation. CT scan of the abdomen/pelvis is often most useful as a survey study, but right upper-quadrant ultrasonography may be useful if there is localizing pain in the right upper quadrant.
- If there are clinical features suggestive of venous thromboembolic disease, DVT ultrasonography or CT angiography of the chest may be warranted.
- Lumbar puncture is indicated if there is a reason to suspect meningitis (e.g., recent craniotomy or external ventricular drain). However, if an external ventricular drain is in place, fluid may be removed directly from the drain to avoid the risk of lumbar puncture.
- Paracentesis should be considered in the context of ascites, to exclude spontaneous bacterial peritonitis (SBP).

management

indications for empiric antibiotics

- Fever itself isn't an indication for antibiotics.
  - (They're antibiotics, not anti-pyretics.)
- Antibiotics may be indicated in the following situations:
  - (a) Neutropenic fever
  - (b) Septic shock (e.g., hypotension, tachycardia, oliguria, delirium, tachypnea). More on sepsis here.
  - (c) High index of suspicion for specific infection (e.g., Clostridioides difficile or ventilator associated pneumonia). In many situations antibiotic initiation for a specific focus of infection is appropriate, while awaiting additional diagnostic information (e.g., culture results).

antipyretic therapy

- Whether fever is a beneficial, adaptive response to infection remains controversial.
- Most fevers don't require treatment. Following the fever curve without antipyretic therapy may provide superior diagnostic information (e.g., a low-grade fever which is transient and self-resolving is less concerning for infection).
- Potential indications for acetaminophen are:
  - Neurologic injury (e.g., stroke, anoxic brain injury).
  - Severe fever (e.g. over roughly >40C/104F).
  - Fever that seems to be worsening the patient's clinical condition:
    - Altered mental status (fever can cause delirium)
    - Hemodynamic instability or acute myocardial ischemia (tachycardia may exacerbate both of these)
    - Multiple sclerosis patients (fever may cause acute deterioration – known as Uhthoff Phenomenon)

central venous catheter removal

- Fever alone isn't necessarily an indication to remove a central venous catheter. However, central venous catheter removal should be considered for lines in place >72 hours.
- If the patient is unstable and manifests features of sepsis (e.g., hemodynamic instability), line removal may be more strongly considered.
- More on this in the chapter on catheter-related bloodstream infection.

drug fever

commonly implicated drugs

https://emcrit.org/ibcc/fever/
Antimicrobials (most common class)
- Penicillins, cephalosporins, piperacillin, carbapenems
- Aminoglycosides, fluoroquinolones
- Vancomycin, daptomycin, linezolid (rare)
- Clindamycin
- Tetracyclines, macrolides
- Isoniazid (INH), rifampin
- Sulfonamides, nitrofurantoin, pentamidine
- Antiretrovirals
- Amphotericin B

Cardiac/renal
- Antihypertensives: Captopril, hydralazine, nifedipine
- Digoxin (rare)
- Sulfonamides, diuretics (e.g., furosemide)
- Antiarrhythmics: Propranolol, quinidine

Anti-epileptic agents
- Phenytoin
- Carbamazepine

Immunologics
- Interferon
- Azathioprine

Miscellaneous
- Salicylates, NSAIDs
- Allopurinol
- Heparin (but not low molecular-weight heparins)
- Metoclopramide
- Steroids
- Colace

epidemiology
- Exact numbers are hard to track, but drug fever may occur in up to ~10% of admitted patients. (8698996)
- Risk factors for drug fever:
  - Sensitivities to multiple medications
  - Polypharmacy
  - HIV infection
  - Cystic fibrosis

clinical findings
- Fever may occur to any degree, most commonly the temperature is ~102-104°F (~38.8-40°C).
- Patients can be asymptomatic or may look profoundly ill (e.g., with rigors, myalgias, and hypotension).
  - One clue suggesting drug fever may be that a patient looks “inappropriately well” compared to the degree of fever (23878765)
- Rash is seen only in ~20% of patients (usually a maculopapular central rash, which may involve palms and soles).
- Timing of drug fever is variable. This frequently begins 1-2 weeks after starting a medication, but may emerge after months or years. Upon drug re-challenge, fever may develop within hours.

laboratory abnormalities
- Leukocytosis with left shift may occur in 18% of patients.
Eosinophilia is seen only in ~18% of patients. If present, consider also whether the patient could have DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms).

**diagnosis & treatment**

- Definitive diagnosis is often impossible (as drug fever is largely a diagnosis of exclusion).
- After discontinuing the offending agent, fever should resolve within 4 days if no rash is present. However, sometimes resolution may take a week.

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**neurogenic fever**

**pathophysiology**

- Neurogenic fever (a.k.a. “central fever”) appears to represent a hypothalamic disorder, resulting in an elevation of the hypothalamus’s target temperature for the body (the “set point”).

**causes**

- Subarachnoid hemorrhage
- Intracranial hemorrhage with ventricular extension
- Traumatic brain injury

**clues supporting a neurogenic fever**

- Occurrence within 72 hours of admission.
- Poor response to antipyretics (<10% will defervesce).
- Presence of subarachnoid or intra-ventricular blood.
- Fever usually isn’t associated with diaphoresis or tachycardia.
- Longer duration of fever.

**diagnosis of a neurogenic fever**

- Ultimately this is largely a diagnosis of exclusion.
- Neurogenic fever may be likely if:
  - (a) A reasonably exhaustive evaluation fails to identify an alternative explanation for the fever.
  - (b) Clinical features of the fever are consistent with neurogenic fever (as above).

**management**

- Neurogenic fever is often resistant to antipyretics.
- Reduction in temperature usually requires physical cooling (e.g., with a cooling blanket or physical temperature control device).
  - These patients often have neurologic injury, so treatment of the fever may be important to limit secondary neurologic injury.

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**summary box**
Failure to recognize neutropenic fever as a separate entity that requires immediate treatment.
Approach to new fever or rigors in the ICU patient - EMCrit Project

- Routinely ordering urinalysis and sputum cultures (for most patients, this will only lead to false-positive results and unnecessary antibiotic therapy).
- Failure to recognize a rigor as a fever-equivalent which requires investigation.
- Excessive administration of antibiotics "just to be safe" in situations where they are not indicated.
- Not performing an adequate physical examination when evaluating a patient with fever.

References:


The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.