

APPROACH TO FEVER



Critically ill patients frequently develop fever during their ICU stay. This is commonly defined as a temperature $\geq 38.3^{\circ}\text{C}$ (101°F) but lower thresholds are frequently used in immunocompromised patients. The priority is differentiating between infectious and non-infectious causes. However, given the prolonged course of fever described in many patients with COVID-19, knowing when to pursue additional work-up in a patient with persistent fever may be especially challenging in this setting.

Differential Diagnosis

Important Infectious Causes of Fever

- Bacteremia
- Central-line infections
- C. difficile colitis
- Intra-abdominal abscess
- Sinusitis
- Urinary tract infection
- Ventilator-associated pneumonia
- Wound or surgical site infection

Non-Infectious Causes of Fever

- Acalculous cholecystitis
- Central fever: TBI/stroke/ICH
- Drug fever
- Endocrine: hyperthyroidism, adrenal insufficiency
- NMS or serotonin syndrome
- Pancreatitis
- Post-operative SIRS
- Transfusion reaction
- Venous thromboembolism
- Withdrawal or overdose

Suggested Work-Up for New or Persistent Fever

1 Consider the characteristics of the fever:

- Is it a true fever?
- Is it new? If not, is it different from recent fevers?
- Have any other clinical features changed?
- Is there a clear cause?

If the fever is new or different, the patient's clinical status has changed, or there is no clear cause → Pursue additional work-up

2 Rule out an obvious source of infection:

- The following work-up should be sent:
 - Blood cultures: Peripheral culture, central line(s)
 - Endotracheal aspirate or sputum sample
 - Examine surgical sites, wounds, and drains with cultures as applicable
 - Urine culture
 - Chest x-ray to look for pneumonia
 - Stool sample for c. difficile if loose stools

If the fever has been persistent or intermittent, you do not need to resend this work-up every time the temperature spikes. Consider resending if the patient's clinical status has otherwise changed or it has been several days since cultures were sent and the source remains unclear.

When should I start antibiotics?

While the infectious work-up is pending, you do not need to start antibiotics in all patients with fever. However, **empiric treatment is warranted if there is a clear infectious source or signs of evolving sepsis** (\downarrow BP, \uparrow HR, new organ dysfunction, elevated lactate).

Reassess any antibiotics that have been started in 48-72hrs. Consider stopping if infectious work-up is negative.

3 If initial infectious work-up is negative and fevers continue without a clear cause, additional investigations should be guided by the clinical situation. Work-up can be carried out in a stepwise fashion, ruling out the most likely aetiologies first:

FOR ALL PATIENTS:

- Review medications and stop any drugs that may be contributing:
 - Common culprits: Antibiotics (beta-lactams), antiepileptics (phenytoin), diuretics, stool softeners
 - If the patient is on antipsychotics or serotonergic agents, ensure there are no features in keeping with serotonin syndrome or neuroleptic malignant syndrome, particularly if fevers are very high ($T \geq 39.0^{\circ}\text{C}$)
 - Rash, eosinophilia, and transaminitis may be clues to a systemic drug reaction
- Send additional bloodwork:
 - Lipase to rule out pancreatitis
 - Liver panel to assess for transaminitis or biliary disease
 - TSH +/- cortisol to look for endocrine causes if other clinical features are consistent
- Review recent medication and substance use:
 - Withdrawal from prescription medications
 - Withdrawal from alcohol or drug misuse

CONSIDER BASED ON THE CLINICAL SITUATION:

- Lower extremity dopplers to rule out DVT +/- CT pulmonary angiogram if other features concerning for PE
- Abdominal ultrasound to rule out acalculous cholecystitis
- Remove old central lines: Take out lines that have been in situ > 1 week, even if cultures are negative
- Rule out occult infection:
 - If concern for infection is high and no other cause for fever can be identified, consider ID consult and additional imaging:
 - CT chest to rule out pneumonia or empyema
 - CT abdomen/pelvis to rule out abscess
 - CT sinuses to rule out sinusitis