

Evaluation and Workup of Fever in the Hospitalized Patient

Overview of Fever in the Hospitalized Patient

Fever in the hospitalized patient is a common clinical challenge, often indicating an underlying pathology that requires prompt evaluation and management. Fever is defined as a temperature $>38^{\circ}\text{C}$ (100.4°F) and can result from infectious, inflammatory, thrombotic, malignant, or other causes. It may represent a new process or a complication of the patient's hospital course (e.g., nosocomial infection, postoperative fever). Early identification of the cause is critical to prevent progression to severe complications like sepsis, organ failure, or death. This pamphlet provides students with a detailed systematic approach to evaluate fever in the hospital setting, including an expanded differential diagnosis, comprehensive physical exam, labs, diagnostic studies, etiologies, management strategies, and a table distinguishing causes, with clinical scenarios for practical application.

Clinical Presentation

Fever Characteristics:

- **Definition:** Core temperature $>38^{\circ}\text{C}$ (100.4°F); rectal temperature is most accurate in critically ill patients.
- **Patterns:**
 - **Sustained/Continuous:** Fever with minimal variation ($<1^{\circ}\text{C}$); suggests gram-negative bacteremia, typhoid fever, or CNS infections (e.g., meningitis).
 - **Intermittent:** Fever spikes with return to normal between episodes; typical of abscess, endocarditis, or malaria.
 - **Relapsing:** Fever with afebrile periods lasting days; seen in malaria (tertian/quartan fever), brucellosis, or lymphoma (Pel-Ebstein fever in Hodgkin lymphoma).
 - **Remittent:** Daily fever with fluctuations but not returning to normal; common in viral infections or TB.
- **Severity:**
 - **Hyperpyrexia ($>41.5^{\circ}\text{C}$):** Suggests severe infection (e.g., meningitis), drug reaction, or CNS etiology (e.g., neuroleptic malignant syndrome).

- **Fever with hemodynamic instability:** Indicates sepsis, septic shock, or severe systemic inflammation.

Symptoms:

- **Systemic Symptoms:**

- **Chills, rigors:** Common with bacteremia, abscess, or endocarditis.
- **Night sweats, weight loss:** Suggest chronic infections (e.g., TB, endocarditis), malignancy (e.g., lymphoma), or autoimmune diseases (e.g., vasculitis).
- **Fatigue, malaise:** Non-specific; seen in infections, autoimmune, or malignant causes.

- **Localizing Symptoms:**

- **Respiratory:** Cough, dyspnea, chest pain (pneumonia, PE, pleuritis).
- **Abdominal:** Pain, diarrhea, nausea (intra-abdominal infection, C. difficile colitis, malignancy).
- **Genitourinary:** Dysuria, frequency, hematuria (UTI, pyelonephritis).
- **Musculoskeletal:** Joint pain, swelling (septic arthritis, gout), muscle tenderness (rhabdomyolysis, polymyositis).
- **Neurological:** Headache, neck stiffness, altered mental status (meningitis, encephalitis, brain abscess).
- **Skin:** Rash (drug reaction, endocarditis), petechiae (meningococcemia), IV site erythema (thrombophlebitis).

Physical Exam:

- **Vitals:**

- Confirm fever ($>38^{\circ}\text{C}$), assess for tachycardia (HR >100 bpm, suggests infection or hypovolemia), hypotension (sepsis), hypoxia (pneumonia, PE).
- **Relative bradycardia:** Fever with inappropriately low HR (e.g., typhoid fever, Legionella).

- **General Appearance:**

- **Pallor:** Anemia (malignancy, chronic infection).
- **Cachexia:** Weight loss (TB, lymphoma, chronic infection).
- **Diaphoresis:** Bacteremia, malignancy (e.g., lymphoma night sweats).

- **HEENT:**

- **Pharyngeal erythema/exudates:** Streptococcal pharyngitis, mononucleosis.
- **Sinus tenderness:** Sinusitis.
- **Lymphadenopathy:** Cervical (TB, lymphoma), generalized (HIV, lymphoma).
- **Oral ulcers:** Behçet's disease, SLE.

- **Cardiovascular:**

- **Murmur:** Endocarditis (new regurgitant murmur), pericarditis (friction rub).

- **JVD, peripheral edema:** HF as a precipitant or complication.
- **Respiratory:**
 - **Crackles, wheezing:** Pneumonia, aspiration, pulmonary edema.
 - **Pleural rub:** PE, pleuritis (autoimmune, e.g., SLE).
 - **Decreased breath sounds:** Pleural effusion (TB, malignancy).
- **Abdomen:**
 - **Tenderness:** Appendicitis, cholecystitis, diverticulitis.
 - **Organomegaly:** Hepatomegaly (hepatitis, malignancy), splenomegaly (lymphoma, endocarditis).
 - **Rebound tenderness:** Peritonitis (e.g., perforated viscus).
- **Skin:**
 - **Rash:** Maculopapular (drug reaction, viral exanthem), petechiae (meningococcemia, endocarditis), erythema migrans (Lyme disease).
 - **IV site erythema, tenderness:** Thrombophlebitis, CLABSI.
 - **Janeway lesions, Osler nodes:** Endocarditis.
- **Musculoskeletal:**
 - **Joint swelling, erythema, warmth:** Septic arthritis, gout, reactive arthritis.
 - **Muscle tenderness:** Rhabdomyolysis, polymyositis.
- **Neurological:**
 - **Altered mental status:** Encephalitis, meningitis, sepsis.
 - **Neck stiffness, Kernig/Brudzinski signs:** Meningitis.
 - **Focal deficits:** Brain abscess, stroke (as a precipitant or complication).

Systematic Approach to Evaluation

- **Step 1: Confirm Fever and Assess Severity**
 - Measure temperature (rectal preferred in critical illness; $>38^{\circ}\text{C}$ confirms fever).
 - **Check vital signs:** Hypotension (SBP <90 mmHg), tachycardia (HR >100 bpm), hypoxia (SpO₂ $<90\%$) suggest sepsis, severe infection, or PE.
 - **Determine fever pattern:** Sustained, intermittent, relapsing, remittent (guides differential).
 - Assess for systemic inflammatory response syndrome (SIRS): ≥ 2 of: T $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, HR >90 bpm, RR $>20/\text{min}$ or PaCO₂ <32 mmHg, WBC $>12,000/\mu\text{L}$ or $<4,000/\mu\text{L}$.
- **Step 2: Detailed History**
 - **Onset and Duration:**
 - **Acute (<1 week):** Pneumonia, UTI, postoperative fever.
 - **Subacute (1-4 weeks):** Endocarditis, TB, abscess.
 - **Chronic (>4 weeks):** Malignancy (e.g., lymphoma), chronic infections (e.g., TB, brucellosis), autoimmune (e.g., Still's disease).

- **Fever Pattern:**
 - **Sustained:** Typhoid fever, CNS infections.
 - **Intermittent:** Abscess, endocarditis, malaria.
 - **Relapsing:** Malaria, lymphoma, brucellosis.
- **Associated Symptoms:**
 - **Localizing:** Cough (pneumonia), dysuria (UTI), joint pain (septic arthritis).
 - **Systemic:** Night sweats, weight loss (TB, malignancy), fatigue (autoimmune, chronic infection).
- **Risk Factors:**
 - **Hospitalization/Surgery:** Nosocomial infections (VAP, CLABSI), postoperative complications (DVT, atelectasis).
 - **IV Lines/Catheters:** Thrombophlebitis, CLABSI.
 - **Travel:** Malaria (Africa), typhoid fever (South Asia), dengue (tropics).
 - **Immunosuppression:** HIV (opportunistic infections), steroids (PCP, TB), chemotherapy (neutropenic fever).
 - **Drug History:** Antibiotics (e.g., beta-lactams), anticonvulsants (e.g., phenytoin), allopurinol (drug fever).
 - **Social History:** IV drug use (endocarditis), homelessness (TB), animal exposure (brucellosis, Q fever).
 - **Medical History:**
 - **Diabetes:** Increased infection risk (e.g., UTI, soft tissue infections).
 - **Malignancy:** Tumor fever, neutropenic fever.
 - **Autoimmune Disease:** SLE, vasculitis, Still's disease.
 - **Recent Transfusion:** Transfusion reaction.
 - **Prosthetic Devices:** Prosthetic joint infection, pacemaker infection.
- **Step 3: Comprehensive Physical Exam** Perform a thorough exam to identify the source (see above for specific findings).
 - **Focus on localizing signs:** E.g., murmur (endocarditis), joint swelling (septic arthritis), IV site erythema (thrombophlebitis).
 - **Reassess daily:** Fever may unmask new findings (e.g., rash, murmur) as the disease evolves.
- **Step 4: Initial Labs and Diagnostic Studies**
 - **Labs:**
 - **CBC with Differential:** Leukocytosis (bacterial infection), leukopenia (viral, sepsis, typhoid fever), eosinophilia (drug reaction, parasitic infection), anemia (chronic disease, hemolysis).
 - **CMP:** Cr/BUN (AKI in sepsis), LFTs (hepatitis, abscess, malignancy), electrolytes (e.g., hyponatremia in SIADH with malignancy, hypokalemia in adrenal insufficiency).

- **Inflammatory Markers:** ESR, CRP (elevated in infection, autoimmune, malignancy), procalcitonin (elevated in bacterial infection, >0.5 ng/mL suggests sepsis).
 - **Blood Cultures:** 2 sets from separate sites (endocarditis, bacteremia); draw before antibiotics if possible.
 - **Urinalysis/Urine Culture:** Pyuria, bacteriuria (UTI, pyelonephritis).
 - **Lactate:** >2 mmol/L (sepsis, hypoperfusion); >4 mmol/L indicates septic shock.
 - **Coagulation:** INR, D-dimer (DIC in sepsis, DVT/PE).
- **Diagnostic Studies:**
 - **CXR:** Pneumonia (consolidation), TB (cavities, miliary pattern), malignancy (mass, lymphadenopathy), PE (Westermarck sign, rare).
 - **EKG:** Ischemia (MI as precipitant), pericarditis (drug reaction mimic), low voltage (amyloidosis in malignancy).
 - **Urine Studies:** Urinalysis (infection), urine drug screen (cocaine, amphetamines as fever cause).
 - **Other:** Based on suspected source (e.g., CT abdomen for abscess, ECHO for endocarditis).
- **Step 5: Targeted Workup Based on Suspected Etiology**
 - **Infectious:**
 - **Blood/Fluid Cultures:** Blood, sputum (pneumonia), urine (UTI), CSF (meningitis).
 - **Imaging:** CT abdomen/pelvis (abscess, malignancy), CT chest (TB, malignancy), MRI brain (abscess, encephalitis).
 - **Specific Tests:** AFB smear/culture (TB), malaria smear (travel history), HIV test (opportunistic infections), viral serologies (e.g., EBV, CMV).
 - **Thrombophlebitic:**
 - **Doppler US:** DVT, septic thrombophlebitis.
 - **CTPA:** PE (if dyspnea, hypoxia).
 - **Catheter Tip Culture:** If CLABSI suspected.
 - **Autoimmune:**
 - **Autoimmune Panel:** ANA, RF, anti-dsDNA (SLE), ANCA (vasculitis), anti-Ro/La (Sjögren's), ferritin (Still's disease).
 - **Imaging/Biopsy:** CT chest (sarcoidosis), temporal artery biopsy (GCA).
 - **Malignant:**
 - **Imaging:** CT chest/abdomen/pelvis (lymphoma, solid tumors), PET scan (metastases).
 - **Tumor Markers:** LDH, beta-2 microglobulin (lymphoma), CA 19-9 (pancreatic cancer).
 - **Biopsy:** Lymph node, bone marrow (lymphoma, leukemia).

- **Other:**

- **Drug Fever:** Discontinue suspected drug, monitor for resolution (typically 48-72h).
- **Endocrine:** TSH (hyperthyroidism), AM cortisol (adrenal insufficiency).
- **HLH:** Ferritin (>10,000 µg/L), triglycerides, bone marrow biopsy (hemophagocytosis).
- **Transfusion Reaction:** Direct Coombs test, haptoglobin, LDH (hemolysis).

Differential Diagnosis and Etiologies

Infectious Causes:

Nosocomial Infections:

- **Ventilator-Associated Pneumonia (VAP):** Fever, purulent sputum, new infiltrates; common in ICU patients on mechanical ventilation >48h.
- **Central Line-Associated Bloodstream Infection (CLABSI):** Fever, IV site erythema, bacteremia; associated with indwelling catheters.
- **Clostridium difficile Colitis:** Fever, diarrhea, recent antibiotics; toxin PCR positive.
- **Catheter-Associated UTI (CAUTI):** Fever, dysuria, pyuria; common with indwelling Foley catheters.

Community-Acquired Infections:

- **Pneumonia:** Fever, cough, dyspnea; CXR consolidation.
- **Endocarditis:** Fever, murmur, stigmata (e.g., Janeway lesions); blood cultures, ECHO.
- **Meningitis:** Fever, headache, neck stiffness; CSF analysis (cell count, glucose, protein).
- **Intra-Abdominal Infection:** Fever, abdominal pain; CT abdomen (e.g., appendicitis, diverticulitis).
- **Typhoid Fever:** Sustained fever, relative bradycardia, rose spots; blood culture (*Salmonella typhi*).

Opportunistic Infections:

- **Tuberculosis (TB):** Fever, night sweats, weight loss; CXR (cavities), sputum AFB.
- **Pneumocystis Pneumonia (PCP):** Fever, dry cough, hypoxia; HIV/immunosuppressed, CXR (ground-glass opacities).
- **Cryptococcosis:** Fever, headache; HIV/immunosuppressed, CSF cryptococcal antigen.
- **Cytomegalovirus (CMV):** Fever, retinitis, colitis; HIV/immunosuppressed, CMV PCR.

Thrombophlebitic Causes:

- **Deep Vein Thrombosis (DVT)/Pulmonary Embolism (PE):** Fever, leg swelling, dyspnea; Doppler US, CTPA.
- **Septic Thrombophlebitis:** Fever, IV site erythema, bacteremia; culture catheter tip, Doppler US.
- **Superficial Thrombophlebitis:** Fever, erythema along vein; often IV-related, Doppler US.

Autoimmune Causes:

- **Systemic Lupus Erythematosus (SLE):** Fever, rash, joint pain; ANA, anti-dsDNA positive.
- **Vasculitis** (e.g., Giant Cell Arteritis, Polyarteritis Nodosa): Fever, headache (GCA), myalgias; ANCA, temporal artery biopsy.
- **Still's Disease:** Fever, evanescent rash, arthritis; ferritin >3000 µg/L, ESR/CRP elevated.
- **Sarcoidosis:** Fever, hilar lymphadenopathy, erythema nodosum; CXR, ACE levels, biopsy (non-caseating granulomas).

Malignant Causes:

- **Lymphoma (Hodgkin, Non-Hodgkin):** Fever, night sweats, weight loss (B symptoms); lymphadenopathy, CT, biopsy.
- **Leukemia:** Fever, fatigue, bruising; CBC (blasts), bone marrow biopsy.
- **Solid Tumors:** Fever, weight loss; e.g., renal cell carcinoma, hepatocellular carcinoma; CT, tumor markers (e.g., AFP, CA 19-9).
- **Tumor Fever:** Paraneoplastic; often resolves with tumor treatment.

Other Causes:

- **Drug Fever:** Fever, rash; common with beta-lactams, phenytoin, allopurinol; resolves 48-72h after discontinuation.
- **Postoperative Fever:**
 - **Atelectasis:** Day 1-2, fever, decreased breath sounds; CXR, incentive spirometry.
 - **Wound Infection:** Day 3-5, fever, erythema; wound culture, antibiotics.
 - **DVT/PE:** Day 5-7, fever, leg swelling; Doppler US, anticoagulation.
- **Endocrine:**
 - **Hyperthyroidism:** Fever, tachycardia, tremor; TSH ↓, free T4 ↑.

- **Adrenal Insufficiency:** Fever, hypotension, fatigue; AM cortisol ↓, ACTH stimulation test.
- **Miscellaneous:**
 - **Transfusion Reaction:** Fever, chills; direct Coombs test, stop transfusion.
 - **Hemophagocytic Lymphohistiocytosis (HLH):** Fever, splenomegaly, cytopenias; ferritin >10,000 µg/L, bone marrow biopsy.
 - **Neuroleptic Malignant Syndrome (NMS):** Fever, rigidity, altered mental status; CK ↑, stop neuroleptics (e.g., haloperidol).

Table: Distinguishing Causes of Fever in the Hospitalized Patient

Etiology	Clinical Features	Diagnostic Findings	Management
Infectious (Nosocomial)			
VAP	Fever, purulent sputum, hypoxia	CXR (infiltrates), sputum culture (e.g., Pseudomonas)	Antibiotics (piperacillin-tazobactam + vancomycin), respiratory support
CLABSI	Fever, IV site erythema	Blood cultures (e.g., S. aureus), catheter tip culture	Remove catheter, antibiotics (vancomycin)
C. difficile	Fever, diarrhea, recent antibiotics	Stool toxin PCR, leukocytosis	Vancomycin 125 mg PO QID x 10 days
Infectious (Community)			
Pneumonia	Fever, cough, dyspnea	CXR (consolidation), sputum culture	Ceftriaxone 1 g IV daily + azithromycin 500 mg IV daily
Endocarditis	Fever, murmur, Janeway lesions	Blood cultures, ECHO (vegetation)	Vancomycin + gentamicin, ECHO follow-up
Meningitis	Fever, headache, neck stiffness	CSF: ↑ WBC, ↓ glucose, culture	Ceftriaxone 2 g IV q12h + vancomycin, steroids if bacterial
Thrombophlebitic			
DVT/PE	Fever, leg swelling, dyspnea	Doppler US (DVT), CTPA (PE), D-dimer	Heparin 80 units/kg IV bolus, then 18 units/kg/h
Septic Thrombophlebitis	Fever, IV site erythema	Blood cultures, Doppler US	Remove IV line, antibiotics (vancomycin)
Autoimmune			
SLE	Fever, rash, joint pain	ANA +, anti-dsDNA +, low C3/C4	Prednisone 1 mg/kg/day PO, hydroxychloroquine 400 mg PO daily
Still's Disease	Fever, evanescent rash, arthritis	Ferritin >3000 µg/L, ESR/CRP ↑	Anakinra 100 mg SC daily, steroids
Sarcoidosis	Fever, hilar lymphadenopathy	CXR (hilar nodes), ACE levels, biopsy	Prednisone 20-40 mg PO daily

Etiology	Clinical Features	Diagnostic Findings	Management
Malignant			
Lymphoma	Fever, night sweats, weight loss	CT (lymphadenopathy), biopsy (Hodgkin)	Chemotherapy (e.g., ABVD), antipyretics
Solid Tumor	Fever, weight loss, mass	CT (e.g., renal cell carcinoma), tumor markers	Treat tumor (e.g., surgery, chemo), antipyretics
Other			
Drug Fever	Fever, rash, recent drug start	Resolves 48-72h after discontinuation	Stop offending drug (e.g., beta-lactam), acetaminophen
Hyperthyroidism	Fever, tachycardia, tremor	TSH ↓, free T4 ↑	Methimazole 20 mg PO daily, propranolol 40 mg PO TID
HLH	Fever, splenomegaly, cytopenias	Ferritin >10,000 µg/L, bone marrow biopsy	Etoposide, dexamethasone, treat trigger (e.g., infection)

Key Pearls

- **Presentation:** Fever patterns (sustained, intermittent, relapsing), localizing symptoms (cough, dysuria), systemic (weight loss, night sweats).
- **Systematic Approach:** Confirm fever, history/exam, initial labs (CBC, CMP, cultures), targeted workup (imaging, specific tests).
- **Differential Diagnosis:** Infectious (nosocomial, community-acquired), thrombophlebitic (DVT), autoimmune (SLE), malignant (lymphoma), drug fever.
- **Etiologies:** Broad (infectious, autoimmune, malignant, thrombotic), guided by history/exam.
- **Management:** Treat underlying cause (e.g., antibiotics for infection, steroids for autoimmune), supportive care (antipyretics, fluids).
- **Monitoring:** Vitals q4-6h, repeat labs (e.g., cultures, inflammatory markers) to assess response.

References

- **UpToDate:** "Fever in the Hospitalized Patient: Evaluation and Management" (2025). UpToDate Fever
- **IDSA:** "Guidelines for the Management of Fever in Hospitalized Patients" (2024). IDSA Guidelines
- **AAFP:** "Approach to Fever of Unknown Origin" (2023). AAFP Guidelines
- **NEJM:** "Fever in the ICU: Advances in Diagnosis and Management" (2024). NEJM Fever

Case Scenarios

Case 1: A 60-Year-Old Male with Fever and Endocarditis

- Presentation: A 60-year-old male with a history of IV drug use presents with 2 weeks of fever, chills, and fatigue. Exam shows T 38.5°C, BP 110/70 mmHg, HR 100 bpm, new systolic murmur at apex, splinter hemorrhages, Janeway lesions, no rash or joint swelling.
- Labs/Studies: WBC 14,000/ μ L, ESR 80 mm/h, CRP 100 mg/L, blood cultures: *S. aureus* (2/2 sets), ECHO: Mitral valve vegetation, EKG: Normal, CXR normal.
- Diagnosis: Infectious Endocarditis → Subacute fever, murmur, stigmata (splinter hemorrhages, Janeway lesions), positive cultures.
- Management: Admit for treatment. Start vancomycin 15 mg/kg IV q12h + gentamicin 1 mg/kg IV q8h. Consult cardiology: ECHO confirms vegetation, no abscess. Blood cultures clear after 72h. Monitor: Repeat ECHO, renal function (gentamicin nephrotoxicity). Continue antibiotics x 6 weeks. Fever resolves by day 5. Discharge with outpatient IV antibiotics, cardiology follow-up.

Case 2: A 45-Year-Old Female with Fever and DVT

- Presentation A 45-year-old female, postoperative day 7 after hip replacement, presents with fever, left leg swelling, and calf tenderness. Exam shows T 38.2°C, BP 120/80 mmHg, HR 90 bpm, left leg erythema, swelling, tenderness, no respiratory distress.
- Labs/Studies: **WBC 12,000/ μ L, D-dimer elevated, Doppler US:** Left femoral DVT, CXR normal, blood cultures negative, lactate 1.5 mmol/L, urinalysis normal.
- Diagnosis: Deep Vein Thrombosis (Postoperative) → Acute fever, leg swelling, Doppler-confirmed DVT, postoperative state.
- Management: Admit for anticoagulation. Start heparin 80 units/kg IV bolus, then 18 units/kg/h (target aPTT 60-80s). Consult hematology: No PE on CTPA. Antipyretics (acetaminophen 650 mg PO q6h). Monitor: Repeat US, aPTT q6h. Fever resolves by day 3. Transition to apixaban 10 mg PO BID x 7 days, then 5 mg BID. Discharge with hematology follow-up.

Case 3: A 50-Year-Old Male with Fever and Lymphoma

- Presentation: A 50-year-old male presents with 4 weeks of fever, night sweats, 10 kg weight loss, and fatigue. Exam shows T 38°C, BP 115/75 mmHg, HR 85 bpm, cervical lymphadenopathy, hepatosplenomegaly, no rash, normal joints, no murmurs.

- Labs/Studies: WBC 8,000/ μ L, Hgb 10 g/dL, ESR 90 mm/h, CRP 120 mg/L, LDH 600 U/L, CT chest/abdomen: Diffuse lymphadenopathy, lymph node biopsy: Hodgkin lymphoma, blood cultures negative, urinalysis normal.
- Diagnosis: Hodgkin Lymphoma (Tumor Fever) → Chronic fever, night sweats, weight loss, lymphadenopathy, biopsy-confirmed.
- Management: **Admit for oncology workup. Consult hematology:** Staging (Ann Arbor stage III), start ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, dacarbazine). Antipyretics (acetaminophen 650 mg PO q6h). Monitor: CBC, LFTs (chemotherapy toxicity). Fever resolves after first cycle. Discharge with oncology follow-up for continued chemotherapy.

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