Fever of Unknown Origin: the Hospitalized Patient

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Objectives

• To develop a systematic approach to fever in the hospitalized patient

• When to suspect noninfectious causes of fever in the hospitalized patient

• To learn when empiric antimicrobial therapy is (and is not) necessary in the hospitalized patient
# Categories of FUO

<table>
<thead>
<tr>
<th>Feature</th>
<th>Nosocomial</th>
<th>Neutropenic</th>
<th>HIV-associated</th>
<th>Classic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s situation</td>
<td>Hospitalized, acute care, no infection when admitted</td>
<td>Neutrophil count &lt;500/µL or expected to reach that level in 1-2 days</td>
<td>Confirmed HIV-positive</td>
<td>All others with fevers for ≥3 weeks</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>3 days b</td>
<td>3 days b</td>
<td>3 days b (or 4 weeks as outpatient)</td>
<td>3 days b or 3 outpatient visits</td>
</tr>
</tbody>
</table>

aAll require temperatures of ≥38.3°C (101°F) on several occasions.
bIncludes at least 2 days’ incubation of microbiology cultures.

Frequency of Etiologic Categories of FUO

- Infections: 36%
- Neoplasia: 24%
- Conn tiss dis: 21%
- Undiagnosed: 13%
- Misc: 6%

Etiologies of FUO over time

Adapted from: Mourad O, Palda V, Detsky AS. Arch Intern Med 2003; 163:545.
Fever in the ICU

- Frequency of fever in ICU has been variably quoted between 26% and 44%
  
  Intensive Care Med 2004; 30:811–816
  Intensive Care Med 1999; 25:668–673
  Crit Care Med 2008;36:1531-1535

- Presence of high grade fever at admission or during ICU stay is associated with poor outcome
  
  Crit Care Med 2008;36:1531-1535
# Causes of FUO

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<tbody>
<tr>
<td>Healthcare-associated infections</td>
<td>Infections:</td>
<td>Primary HIV</td>
<td>Infections connective tissue disease malignancies</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td>Bacterial</td>
<td>Mycobacteria</td>
<td></td>
</tr>
<tr>
<td>Drug fever</td>
<td>Fungal (eg, candidiasis, aspergillosis)</td>
<td>Cytomegalovirus, lymphoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Viral (eg, herpes simplex virus)</td>
<td>Toxoplasma</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Cryptococcus</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Immune reconstitution inflammatory sd (IRIS)</td>
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</table>

Case 1

A 52 year old woman with a history depression and recurrent UTIs was brought in by her daughter in January for altered mental status and agitation. She takes paroxetine. On admission, she is confused, disoriented, and agitated.

Physical Exam: Temp: 38.3°C, HR 110 bpm, BP 150/80. She disoriented but can follow commands. She also has hyperreflexia, particularly of the lower extremities.

Labs: CBC with differential, creatinine, liver enzymes, and UA are normal. A head CT is normal. CSF: 2 WBCs, 0 RBCs, glucose 60, protein 21
Case 1

Which of the following would be the best next step in management?

A. Obtain urine cultures
B. Obtain urine cultures and start levofloxacin
C. Start IV acyclovir
D. Obtain NP swab for influenza/RSV
E. Stop paroxetine and observe
Serotonin Syndrome

- Hyperreflexia (greater in lower extremities)
- Tremor (greater in lower extremities)
- Clonus (greater in lower extremities)
- Increased bowel sounds; may have diarrhea
- Autonomic instability; often hypertensive
- Agitation
- Diaphoresis
- Tachycardia
- Mydriasis

Fever Evaluation: Take a history

- Verify fevers and establish pattern
- Localizing symptoms?
- Workplace?
- Pets?
- Recent travel?
- History of connective tissue disease?
- History of cancer or immunosuppression?
- Medications?
- Drug use?
- Familial fever syndromes?
Drug Fever

• 3-7% of fevers on an inpatient medical service are drug reactions
• Usually in 2nd week of drug administration
• Looks “inappropriately well” for degree of fever
  • fever usually 102º to 104º
  • relative bradycardia
  • 5-10% have rash
• May be associated with leukocytosis and eosinophilia

Ann Intern Med 1987; 106:728–733
Common Causes of Drug Fever

- Antibiotics
  - Penicillins
  - Cephalosporins
  - Sulfonamides
  - Amphotericin B
- Sleep medications

- Antiepileptics
  - Sulfa-containing laxatives
  - Antidepressants
  - Antiarrhythmics
  - NSAIDs
Neuroleptic Malignant Syndromes

• Confusion, hyperthermia, muscle stiffness, autonomic instability

• Drugs implicated: phenothiazines, thioxanthines, butyrphenones--antipsychotics, tranquilizers, and antiemetics

• In the ICU, haloperidol is the most common offending drug

• Dantrolene or bromocriptine, a dopamine agonist, effective in uncontrolled studies
Less Common Causes of Drug Fever

- Other antibiotics
  - Aminoglycosides
  - Tetracyclines
  - Erythromycins
  - Chloramphenicol
  - Vancomycin
  - Carbapenems
  - Quinolones

- Diuretics
- Antihypertensives
- Digoxin
- Steroids
- Diphenhydramine
- Aspirin
- Vitamins
Fever Evaluation: Physical Examination
Evaluation of FUO: Skin

Mucous membranes, Teeth, Wounds
Evaluation of FUO: Head

- Sinus tenderness
- Temporal arteries (older patients)
Evaluation of FUO: Neck

Lymphadenopathy,
Thyromegaly,
Nuchal rigidity
Evaluation of FUO: Chest

Crackles
Murmur
(Osler’s nodes, Janeway lesions, conjunctival hemorrhages)
Evaluation of FUO: Abdomen

- Splenomegaly
- Hepatomegaly
- Abdominal masses
- Diarrhea (C. diff)
Evaluation of FUO: Rectal

Sacral decubitus, Prostatitis, Perirectal abscess in neutropenia
Evaluation of FUO: Extremities

Phlebitis, Deep Vein Thrombosis (DVT)
Evaluation of FUO: Lines!

Central lines, Foley catheter, NG tube, Thrombophlebitis
Case 2

A 69 year old man underwent a 3 vessel CABG (LIMA to LAD, SVG to OM, SVG to PDA). He is extubated overnight and on post-operative day 1 you are paged by the nurse for a temperature of 38.3 degrees.

On physical examination he is sitting upright with unlabored breathing. His pulse is 101 bpm and BP is 105/68, O2 sat 96% on RA. His sternotomy site and IV lines appear to be clean, dry and intact.

AM Labs show a WBC 12.5, otherwise electrolytes and creatinine are normal.
Case 2

What is the best next step in management for this patient’s fever?

A. Obtain blood cultures
B. Obtain blood cultures, urine cultures and CXR
C. Start IV piperacillin/tazobactam
D. B and C
E. Observe for 24-48 hours
Approach to the febrile patient in the ICU

- 50% of fevers in the ICU are noninfectious in origin, with $T \leq 38.3^\circ C$
- In CCUs, noninfectious causes include:
  - Myocardial infarction
  - Dressler’s syndrome
  - Thromboembolism
  - Thrombolytic therapy with hemorrhagic complications
  - Antiarrhythmics
  - DVT/PE
Fever Within 72 Hours of Surgery

- CXR is not mandatory during the initial 72 hrs postoperatively if fever is the only indication.
- A urinalysis and urine culture are not mandatory except in those with indwelling bladder catheters for 72 hrs.
- Surgical wounds should be examined daily for infection - should not be cultured if there is no symptom or sign suggesting infection.
- High level of suspicion for DVT, superficial thrombophlebitis, and pulmonary embolism.
Case 3

A 62 year old woman undergoes a cholecystectomy for symptomatic cholelithiasis. Her postoperative course is complicated by an ileus requiring placement of an NG tube for decompression. On hospital day 3 she develops fever to 38.9 and WBC of 16. She continues to spike on hospital day 4. Blood cultures, UA and CXR are negative. She spikes again on hospital day 5. A CT scan of the abdomen and pelvis shows usual postoperative changes but no fluid collection.
Physical examination otherwise reveals normal vital signs and benign abdominal examination. She still has the NG tube in place. Peripheral IV sites and her wounds are clean, dry and intact without signs of infection.

Which if the following is the most appropriate next step?

A. Obtain a CT scan of the chest with contrast
B. Obtain a repeat CT scan of the abdomen/pelvis
C. Obtain a CT scan of the sinuses
D. Obtain bilateral lower extremity US
E. Start caspofungin
# Infections in the ICU

<table>
<thead>
<tr>
<th>Common</th>
<th>Less common</th>
</tr>
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<tbody>
<tr>
<td>Ventilator-associated pneumonia</td>
<td>Intra-abdominal infection</td>
</tr>
<tr>
<td>Bloodstream infections</td>
<td><em>C. difficile</em></td>
</tr>
<tr>
<td>Catheter-associated BSI</td>
<td>Sinusitis</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>Cellulitis</td>
</tr>
<tr>
<td></td>
<td>Empyema</td>
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<tr>
<td></td>
<td>Endocarditis</td>
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<tr>
<td></td>
<td>Meningitis</td>
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<tr>
<td></td>
<td>Myonecrosis</td>
</tr>
<tr>
<td></td>
<td>Necrotizing fasciitis</td>
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<tr>
<td></td>
<td>Suppurative thrombophlebitis</td>
</tr>
<tr>
<td></td>
<td>Catheter-associated urinary tract</td>
</tr>
<tr>
<td></td>
<td>infection</td>
</tr>
<tr>
<td></td>
<td>Fungal infection</td>
</tr>
</tbody>
</table>
Approach to the febrile patient in the ICU

Fever (temperature >38.3°C or 101°F)

2 Sets of blood cultures, urine and sputum cultures

Infection site
Non-obvious

Consider Non-infectious causes
Observe 48 hours
If the fever persists

Central lines (>48 hours) → remove and culture
Nasal tubes → remove, CT of the sinuses
Diarrhea → stool culture and empiric antibiotic therapy
Observe 48 hours
If the fever persists

Antifungal therapy
Venography
Imaging for abdominal infections

Infection site
Diagnostic tests Empiric antibiotic therapy

Dimopoulos G, Falagas ME. Inf Dis Clin N Am. 2009
<table>
<thead>
<tr>
<th>Test</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cultures</td>
<td>Bacteremia (catheter related and others)</td>
</tr>
<tr>
<td>CVC tip culture</td>
<td>For CRBSI</td>
</tr>
<tr>
<td>Chest X ray</td>
<td>For VAP</td>
</tr>
<tr>
<td>ET/NBAL/BAL quantitative culture</td>
<td>Will guide adjusting empiric antibiotics</td>
</tr>
<tr>
<td>CT PNS</td>
<td>Needs to be followed by drainage and cultures</td>
</tr>
<tr>
<td>CT abdomen</td>
<td>For abdominal sepsis &gt; acalculous cholecystitis</td>
</tr>
<tr>
<td>USG abdomen</td>
<td>For acalculous cholecystitis &gt; abdominal sepsis</td>
</tr>
<tr>
<td>Cl.difficle toxin assay</td>
<td>Less sensitive than cytotoxic assay</td>
</tr>
<tr>
<td>Fungal cultures</td>
<td>Prolonged ICU stay, multiple ABx, TPN</td>
</tr>
<tr>
<td>Microbiological, Serological test for viral, fungal and bacteria</td>
<td>As epidemiological features guide</td>
</tr>
</tbody>
</table>
Nosocomial Sinusitis

• Accounts for about 5% of nosocomial ICU infections

• Gram-negative bacilli cause most cases in intubated patients

• Microbiology:
  • *Pseudomonas* - 60%
  • *S. aureus* and CNS - 33%
  • Polymicrobial infection in up to 50%
Nosocomial Sinusitis

- Purulent nasal discharge often lacking
- Common in trauma and neurosurgical units

Treatment
- Removal of all nasal tubes
- Needle drainage (maxillary sinus)
- Surgical drainage (ethmoid and sphenoid sinuses)
- Antimicrobials
Intra-abdominal Infections

• Suspect intra-abdominal abscess in patients with prolonged post-operative fever after abdominal surgery

• Splenic or hepatic abscesses may complicate other intra-abdominal infections (cholecystitis, appendicitis) causing prolonged fevers

• Acalculous cholecystitis and subsequent biliary sepsis may complicate post-operative period
Acalculous cholecystitis

- 0.2 to 1.5% of patients in ICU
- Gallbladder ischemia & cholestasis with bile salt inspissation associated with parenteral nutrition and PEEP
- Bacterial invasion is a secondary process
- Diagnosis: CT, US or hepatobiliary scintigraphy
- Treatment:
  - Percutaneous cholecystostomy is procedure of choice
  - Surgical drainage as salvage procedure
Intra-abdominal Infections

• Suspect antibiotic-associated colitis due to *Clostridium difficile* in patients on broad-spectrum antibiotics

• Pseudomonas and *C. septicum* in neutropenic patients
Common question:

My patient is crumping despite being on broad spectrum antibiotics…should I start an antifungal?

• Depends:
  • Who is the host?
  • What are their risk factors for disseminated candidiasis?
  • What else are they at risk for (MRSA, VRE, pseudomonas)?
  • Is there a problem of source control with another infection?
Fungal infections in the ICU

• EPIC study - 17% of nosocomial ICU infections were due to fungi

• *Candida* species cause the majority of fungal infections in the ICU (~85%)

• Others - usually in immunocompromised hosts
  • Aspergillus
  • Mucor
  • Fusarium
  • Cryptococcus
Risk factors for candidemia/disseminated candidiasis

- Prolonged use of antibacterials
- Central venous catheters
- Hyperalimentation
- Surgery (especially that which transects the gut wall)
- Prolonged ICU stay
- Colonization by *Candida* of multiple nonsterile sites
Candidemia/disseminated candidiasis: Diagnosis

• Candidemia = pretty straight forward
  • Gold standard = positive blood cultures

• Disseminated candidiasis
  • Gold standard = histologic evidence and/or positive culture from internal organ tissue
  • Does NOT usually involve candidemia
  • Very hard to diagnose and based on high index of suspicion
Case 4

A 32 year old man with diffuse large B-cell lymphoma is admitted to the hospital with undifferentiated fever for 7 days after chemotherapy with R-CHOP. He has not recently received any antimicrobials.

BP: 120/82, P 86, T: 39.1°C, O₂ sat: 98% RA
Skin: Right chest tunneled central venous catheter without erythema, warmth, or tenderness
ENT: No mucositis
Heart/Lungs/Abdomen: unremarkable
Absolute neutrophil count: undetectable
CXR: normal
Blood and urine cultures are pending
Case 4

Which of the following is the best empiric antimicrobial regimen?

A. IV Vancomycin
B. IV Cefepime
C. IV Cefepime and PO Levofloxacin
D. IV Ceftazidime + IV Vancomycin
E. No antimicrobials needed at this time
Neutropenic fever

- High risk patients:
  - ANC ≤ 100
  - ≥ 7 days

- Organisms
  - Gram negatives (especially *Pseudomonas*)
  - Viridans group strep (especially with mucositis)
Neutropenic fever

• When to add empiric Vancomycin?
  • Hemodynamic compromise
  • Pneumonia
  • Skin/soft tissue infection
  • Overt central line infection
  • Severe mucositis
  • Prior antimicrobial use

• When to “double cover” for Pseudomonas?
  • Septic shock
Empiric antimicrobials

Withhold antimicrobials in patients with FUO until the cause is found.

Exceptions:

- Neutropenic fever
- Unstable hospitalized patient
Take Home Points

• Fever in hospitalized patients can have many infectious and noninfectious etiologies: H&P is crucial

• “Routine fever work-up” is not cost-effective

• If initial evaluation shows no infection, antibiotics should be withheld except in neutropenic and unstable patients