



Fever of Unknown Origin (FUO)

Tina Mathew, PGY-1 Pharmacy Resident

Preceptor: Linda Johnson, PharmD, BCIDP

Learning objectives

Define FUO

Outline the
causes for FUO
origin

Describe the
workup of a
patient with a
FUO

Summarize the
treatment of
patients with
FUO

Definitions of FUO

Original (1961)

- Temperature $\geq 101^{\circ}\text{F}$ (38.3°C) on several separate occasions
- Fever lasting longer than **3 weeks**
- Evaluation of at least **1 week** in the hospital

Revised (1991)

- Temperature $\geq 101^{\circ}\text{F}$ on several separate occasions
- Fever lasting longer than **3 weeks**
- Evaluation of at least **3 outpatient visits** or **3 days in inpatient care**

Qualitative

- Temperature $\geq 101^{\circ}\text{F}$ documented clinically on several separate occasions
- **Appropriate initial diagnostic workup** (inpatient or outpatient) does not reveal etiology of fever

Individuals at Greater Risk of Developing FUO

Children

HIV

Organ
transplant
recipients

Elderly

Febrile
Neutropenia

Hospitalized
patients

Returning
travelers

FUO Categories

1. Classic FUO

- Infection
- Malignancy
- Collagen vascular disease

2. Nosocomial FUO

- *Clostridioides difficile*
- Drug-induced
- Post-operative complications
- Transfusion related reactions
- Venous thromboembolism

FUO Categories

3. Immune deficient (neutropenic) FUO

- Opportunistic bacterial infections
- Aspergillus
- Candidiasis
- Herpes virus

4. HIV-related FUO

- Cytomegalovirus
- *Mycobacterium avium-intracellulare* complex
- *Pneumocystis carinii* pneumonia
- Drug-induced
- Kaposi's sarcoma
- Lymphoma

Differential Diagnosis

Infection (20-40%)

- Endocarditis
- Complicated urinary tract infection
- Sinusitis
- Dental abscesses
- Abdominal or pelvic abscesses
- Tuberculosis
- Epstein-Barr virus
- Osteomyelitis
- Lyme disease

Malignancy (20-30%)

- Colorectal cancer
- Leukemia
- Lymphoma
- Metastatic cancers
- Renal cell carcinoma
- Pancreatic carcinoma

Differential Diagnosis

Non-infectious inflammatory diseases (10-30%)

- Systemic lupus erythematosus
- Rheumatoid arthritis
- Gout
- Sarcoidosis
- Crohn's disease
- Adult still's disease

Miscellaneous (10-20%)

- Drug-induced
- Deep venous thrombosis
- Complications from cirrhosis

Undiagnosed (50%)

Drug-Induced Fever

- Fever disappears after the discontinuation of the offending agent
 - Rechallenge drug? Controversial.
- Patients are frequently unaware of their fevers and appear “inappropriately well”
- Relative bradycardia may occur
- Multiple mechanisms; overall poorly or incompletely understood
 - Hypersensitivity = most common cause
- **Antimicrobial** agents are the most common cause of drug fever
 - Especially beta-lactams, sulfonamides, and Macrobid

Agents
Commonly
Associated
with Drug-
Induced Fever

Anticonvulsants

- Barbiturates
- Carbamazepine
- Phenytoin

Antihistamines

- Cimetidine
- Ranitidine

Antimicrobials

- Carbapenems
- Cephalosporins
- Erythromycin
- Isoniazid
- Minocycline
- Nitrofurantoin
- Penicillins
- Rifampin
- Sulfonamides

Agents
Commonly
Associated
with Drug-
Induced Fever

Cardiovascular Medications

- Captopril
- Hydralazine
- Hydrochlorothiazide
- Methyldopa
- Nifedipine
- Procainamide
- Quinidine

Nonsteroidal Anti-Inflammatory

- Ibuprofen
- Salicylates
- Sulindac

Others

- Allopurinol
- Heparin
- Meperidine
- Phenothiazines

Drugs or drug classes	Estimated time to onset
Antimicrobial agents <ul style="list-style-type: none"> • Isoniazid • Minocycline • Sulfasalazine 	1 to 5 weeks <ul style="list-style-type: none"> • Hours to 3 weeks • 3 weeks to 2 years • 3 weeks
Allopurinol	3 to 9 weeks
Azathioprine	1 day to 2 weeks
Antiseizure medications <ul style="list-style-type: none"> • Phenytoin • Carbamazepine 	<ul style="list-style-type: none"> • 1 to 8 weeks • 2 days to 3 weeks
Cardiovascular agents <ul style="list-style-type: none"> • Quinidine • Methyldopa 	<ul style="list-style-type: none"> • 2 weeks to 6 months • 11 days to 3 weeks
Chemotherapeutic agents (eg, gemcitabine)	3 days
Hydroxyurea	1 day to 6 weeks

Common Fever Patterns



Continuous Fever

Body temperature is consistently elevated

Remittent Fever

Elevated body temperature is interrupted by daily normal fevers

Hectic Fever

Continuous but fluctuating fever that is characterized by wide swings that do not return to baseline temperature

TREATMENT



Initial Diagnostic Workup

History & Physical Examination:

- Past medical history
- Review of Systems
 - Weight loss, fatigue, myalgias, abdominal discomfort, etc.
- Drug and toxin history
 - OTC
 - Antipyretic use
- Recent Travel
- Occupation
- Animal exposures
- Family history
- Sexual history
- Jaundice, focal erythema, rash, etc.

Phase I: Non-specific Labs

CBC, including differential and platelet count

C-reactive protein

Erythrocyte sedimentation rate

CMP (including hepatitis serologies if liver function tests are abnormal)

Blood cultures

Chest radiograph

CT/MRI of abdomen/pelvis

Antinuclear antibodies

Rheumatoid factor

Ferritin

Epstein-Barr serology

Cytomegalovirus serology

Bartonella serology

Hepatitis serology

HIV serology

Phase II: Additional Non-specific Labs

Phase III: Invasive Diagnostic Testing

Tissue biopsy

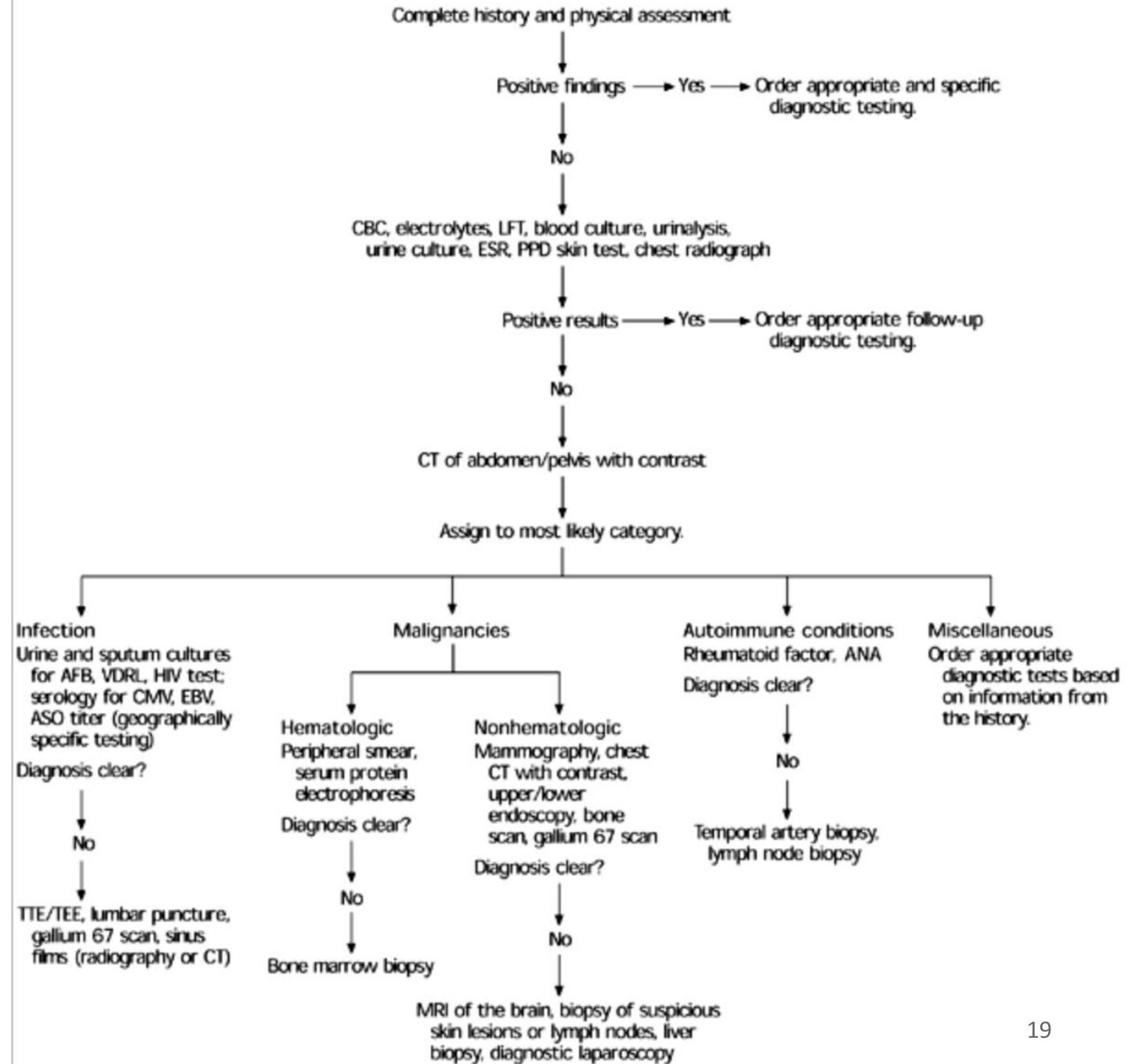
Lymph node biopsy

Bone marrow biopsy

Liver biopsy

Exploratory laparotomy

Diagnosis of Fever of Unknown Origin



Example Flowchart

Empiric Antibiotics

- Antibiotics may delay diagnosis of some occult infections
- Use if:
 - Suspecting infectious source
 - No cause for fever is found despite extensive investigation and patient deteriorates
- Always get blood cultures prior to starting antibiotics
- Recommend discontinuing antibiotics if negative work-up after ~72 hours even if patient continues spiking fevers

Prognosis

The overall prognosis is determined by the underlying disease(s).

Elderly patients and those with malignant neoplasms have the poorest prognosis.

When the cause of FUO cannot be established, prognosis is usually good, and mortality is low.

Role of the Pharmacist

Be familiar with the agents commonly associated with drug-induced fevers

Monitor the duration of empiric antibiotics and recommend discontinuation when appropriate

Let's practice!

DJ: 32-year-old female

- Presents to ED with...
 - Abdominal pain x 3 days
 - Severity: 8/10
 - Vomiting
 - Fever
 - Temp: 103.1 F
 - WBC: 34
- PMH: Diabetes, hypertension, CKD 4, recent COVID-19 infection

1.) MD consults pharmacy to dose vancomycin and zosyn for FUO. What is our next step? Select the correct answer(s).

- A. Order a MRSA nasal swab
- B. Ensure blood cultures are drawn prior to starting antibiotics
- C. Vancomycin loading dose not necessary; start a maintenance dose.

2.) 5 days later, DJ's condition worsens and she continues to spike fevers. The diagnosis remains unknown despite numerous investigations and thorough diagnostic workup. Blood cultures finalized and revealed no growth. What is our next step?

- A. Continue current treatment
- B. Broaden coverage; add antifungal agent
- C. Recommend discontinuation of antibiotics

References

Brown I, Finnigan NA. Fever of Unknown Origin. 2021 Aug 25. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. PMID: 30335298.

Hersch EC, Oh RC. Prolonged febrile illness and fever of unknown origin in adults. *Am Fam Physician*. 2014 Jul 15;90(2):91-6. PMID: 25077578.

Mulders-Manders C, Simon A, Bleeker-Rovers C. Fever of unknown origin. *Clin Med (Lond)*. 2015;15(3):280-284. doi:10.7861/clinmedicine.15-3-280

Patel RA, Gallagher JC. Drug fever. *Pharmacotherapy*. 2010 Jan;30(1):57-69. doi: 10.1592/phco.30.1.57. PMID: 20030474.

Roth AR, Basello GM. Approach to the adult patient with fever of unknown origin. *Am Fam Physician*. 2003 Dec 1;68(11):2223-8. PMID: 14677667.

Spelman D, Mangalore RP. Drug fever. UpToDate. https://www.uptodate.com/contents/drug-fever?search=drug+induced+fever&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Published June 23, 2021.



Questions?