Fever of Unknown Origin (FUO)

Introduction

Clinicians commonly refer to a febrile illness without an initially obvious etiology as fever of unknown origin (FUO). However, most febrile illnesses either resolve before a diagnosis can be made or develop distinguishing characteristics that lead to a diagnosis. FUO refers to a prolonged febrile illness without an established etiology despite intensive evaluation and diagnostic testing.

Cont. introduction

- Hundreds of conditions may cause FUO. Although infections remain a significant cause, most FUOs in the developed world are caused by non-infectious inflammatory disorders, with malignancy a much smaller percentage. Infection is likely to evolve with increased global travel and the use of immunomodulating drugs.
- The differential diagnoses of FUO depend on and continue to evolve based on regional factors, exposures, and available diagnostic tools.
- A significant percentage of FUO cases are caused by miscellaneous conditions, and there is no standard algorithm for evaluating FUO. The approach to diagnostic study is best guided by ongoing assessment for historical, physical, and basic laboratory clues. Following clues, beginning with the least invasive evaluation, avoids unnecessary harm and cost to the patient.

Definition

- Fever ≥38.3°C (≥101°F) on multiple occasions
- Duration ≥3 weeks
- No diagnosis after structured evaluation
- Diagnosis has not been made after ≥3 days of in hospital evaluation or ≥2 outpatient visits

General considerations:

- The intervals specified in the criteria for the diagnosis of FUO are ones intended to exclude patients with protracted but self-limited illnesses and to allow time for the usual radiographic, serologic, and cultural studies to be performed.

Cont. General considerations:

- Classifications of FUO:
  - Classic FUO
  - Hospital associated FUO (nosocomial):

    process is not present at admission, initial cultures are negative, diagnosis is still not known after one week
  - Neutropenic FUO:

    ANC <500/mL, initial cultures are negative, diagnosis is still not known after 3 days
  - HIV-associated FUO:

    patient is febrile for 4 or more weeks as outpatient, 3 days as inpatient, diagnosis is uncertain after 3 days of investigations with at least 2 days for cultures to incubate

Causes of FUO:

1. Infections – most common (~30–40%)
2. Neoplasms – ~10–20%
3. Autoimmune disorders:
4. Miscellaneous: drug fever, thromboembolism, thyroiditis
5. Undiagnosed FUO

Infective causes:

- Both systemic and localized infections can cause FUO.
- Tuberculosis and endocarditis are the most common systemic infective causes, but mycosis, viral diseases (EBV, CMV), toxoplasmosis, brucellosis, Q fever, cat scratch, salmonellosis are less common causes.
- The most common form of localized infections is occult abscesses. Cholangitis, osteomyelitis, UTI, dental abscesses, paranasal sinusitis can causes prolonged fever.

Neoplasms

- The most common are Lymphomas, Leukaemia.
- Post transplant lymphoproliferative disorders may also present with fever.
- Primary and metastatic tumours of the liver are frequently associated with fever, as are renal cell carcinomas.
- Atrial myxoma is an often forgotten neoplasm that may cause fever.
- CLL and multiple myeloma are rarely associated with fever, and should prompt a search for infection.

Autoimmune disorders

- Stills disease, SLE, cryoglobulinemia, polyarteritis nodosa are the most common causes of autoimmune associated FUO.

- Giant cell arteritis, polymyalgia rheumatica are exclusively seen in patients over 50 years, and are almost always associated with high ESR

Miscellaneous causes

- Many other conditions have been associated with FUO but are less common than the before mentioned diseases.

- Thyroiditis, sarcoidosis, Whipple disease, Familial Mediterranean Fever, recurrent pulmonary emboli, alcoholic hepatitis, drug fever, factitious fever are examples.

Undiagnosed fever

- Despite extensive evaluation, the diagnosis remains unclear in up to 50% or more of patients.
- Of these patients, the fever resolves spontaneously in about 75% with no diagnosis; in the remainder, more classic manifestations of the underlying disease appear over time.

Evaluation

- Because the evaluation of a patient with FUO is costly and time consuming, it is imperative to first document the presence of fever. This is done by observing the patient while the temperature is being taken. Associated findings that accompany fever include tachycardia, chills and piloerection.
- A thorough history including family, occupational, social (sexual practices, use of injection drugs), dietary (use of unpasteurized products, raw meat), exposure (animals, chemicals), travel may give clues to the diagnosis
- Repeated physical examination may reveal subtle clinical findings essential for diagnosis

Lab testing:

- CBC, ESR/CRP, LFTs
- Blood & urine cultures

  should always be obtained , preferably when the patient has not taken Abx for several days, and theses cultures should be held by the laboratory for 2 weeks to detect slow growing organisms
- HIV & TB testing
- Direct examination of blood smear

  may establish the diagnosis of malaria or relapsing fever

Imaging and Biopsy Strategy

- Chest Xray
- CT Chest/Abdomen/Pelvis → abscess, malignancy
- PET-CT

  For detecting cancers, vasculitis if CT scan is non diagnostic early in the investigation
- Echo:

  Should be done if one is considering endocarditis or atrial myxoma
- Biopsy → high diagnostic yield >50%

Management Principles

- Although an empiric course of antibiotics is sometimes considered for FUO, it is rarely helpful and may impact infectious diseases diagnosis (reducing the sensitivity of blood cultures)
  - Avoid empirical antibiotics unless unstable/neutropenic
  - Treatment directed at confirmed diagnoses only
  - Supportive care when needed (antipyretics)

When to refer:

- Hemodynamic instability
- Neutropenia/immunosuppression

  Any immune compromised patients (HIV, post transplant)
- New murmur (endocarditis)
- Weight loss

  Any patient with FUO and progressive weight loss, other constitutional signs.

When to admit

- Any patient who is rapidly declining with weight loss where hospital admission may expedite workup
- If FUO is present in immunocompromised patients,

  such as those who are neutropenic from recent chemotherapy or those who have undergone transplant

Thank you!