26 Fever of Unknown Origin

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DEFINITION

Clinicians commonly refer to any febrile illness without an initially obvious etiology as *fever of unknown origin* (FUO). Most febrile illnesses either resolve before a diagnosis can be made or develop distinguishing characteristics that lead to a diagnosis. The term *FUO* should be reserved for prolonged febrile illnesses without an established etiology despite intensive evaluation and diagnostic testing. This chapter focuses on classic FUO in the adult patient.

FUO was originally defined by Petersdorf and Beeson in 1961 as an illness of >3 weeks' duration with fever of ≥38.3°C (101°F) on two occasions and an uncertain diagnosis despite 1 week of inpatient evaluation. Nowadays, most patients with FUO are hospitalized if their clinical condition requires it, but not for diagnostic purposes only; thus the in-hospital evaluation requirement has been eliminated from the definition. The definition of FUO has been further modified by the exclusion of immunocompromised patients, whose workup requires an entirely different diagnostic and therapeutic approach. For the optimal comparison of patients with FUO in different geographic areas, it has been proposed that the quantitative criterion (diagnosis uncertain after 1 week of evaluation) be changed to a qualitative criterion that requires the performance of a specific list of investigations. Accordingly, FUO is now defined as:

1. Fever >38.3°C (101°F) on at least two occasions
2. Illness duration of ≥3 weeks
3. No known immunocompromised state
4. Diagnosis that remains uncertain after a thorough history-taking, physical examination, and the following obligatory investigations: determination of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level; platelet count; leukocyte count and differential; measurement of levels of hemoglobin, electrolytes, creatinine, total protein, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine kinase, ferritin, antinuclear antibodies, and rheumatoid factor; protein electrophoresis; urinalysis; blood cultures (n = 3); urine culture; chest x-ray; abdominal ultrasonography; and tuberculin skin test (TST).

ETIOLOGY AND EPIDEMIOLOGY

The range of FUO etiologies has evolved over time as a result of changes in the spectrum of diseases causing FUO, the widespread