Fever of Unknown Origin: A Clinical Approach

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ABSTRACT

Fever of unknown origin (FUO) in the adult population remains a common challenge in clinical practice. Currently, a systematic approach to working up an admitted patient includes a thorough history and physical exam. The most likely cause can then be assigned to one of four broad categories: infection, inflammation, malignancy, or miscellaneous. These broader classes help guide initial diagnostic tests and avoid unnecessary, more invasive procedures. Nevertheless, despite a thorough workup, as many as 30% of all FUO cases are never solved. The current evidence points to a favourable prognosis for these cases and, thus, empiric treatment is generally not recommended. This review aims to help clinicians understand the broad differential diagnosis of FUO, and provides a summary of the current literature and evidence–based recommendations for working up FUO.

KEYWORDS: *fever, unknown origin, infection, diagnosis*

INTRODUCTION

Fevers of unknown origin (FUO) were first described in 1961 by Petersdorf and Beeson[1], when the pair outlined 100 patients that presented with FUO. Their research is best remembered for establishing the three criteria that define FUO. First, a minimum measured temperature of 38.3ºC was required. This eliminated the possibility of "habitual hyperthermia," a historical term used to describe a "chronic, moderate elevation of the body temperature" not caused by pathology.[2] Secondly, the febrile states should occur on several occasions over a period of at least three weeks. This eliminated self–limited entities such as viral illness. Finally, a minimum of one week of investigations was required to allow adequate time for test results to return.[1]

The modern definition of FUO is based on modifications around these criteria. These adaptations take into account four specific patient subtypes: classic, nosocomial, immune deficient (neutropenic), and HIV–associated. As listed in Table 1, in addition to having a documented fever of 38.3ºC (some clinicians may accept 38.0ºC), each category has a different set of criteria and list of likely causes. Given this extensive list, a systematic approach is crucial. This review aims to outline the broad differential diagnosis of FUO and to provide a summary of evidence–based recommendations for working up FUO. To do so, this article will describe the etiologies of FUO, and provide a clinical approach applicable to admitted patients that includes pertinent aspects of history–taking, physical examination, and diagnostic testing. Finally, it will discuss management when FUO remains unsolved.

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ETIOLOGIES

The differential diagnosis for FUO can be divided into four suggested classes: infection, malignancy, collagen vascular disease, and miscellaneous.[3] Table 2 outlines the proportion each class contributes, making use of the more general "inflammatory" class, and provides the most common etiologies within each.

While Table 2 serves as a useful starting point, the clinician must remember that FUO etiologies vary with demographics, geography, and time.[4] For example, with the advancement and increased accessibility of both serologic investigations and imaging modalities, the contributions of previously common diseases have decreased through time. Rheumatoid arthritis, systemic lupus erythematosus, and culture–positive infective endocarditis are examples of historically prevalent causes of FUO[3] which today, although still prevalent, are detected much earlier. It should be noted, however, that modern infective endocarditis causing FUO is usually secondary to culture-negative organisms or organisms that remain difficult to detect with currently available investigations.

CLINICAL APPROACH

History

The majority of FUOs are atypical presentations of common causes, such as those in Table 2.[3,5] Accordingly, a thorough history prevents ordering unneccessary tests in a shotgun approach, and may even reveal the diagnosis. Highest yield questions include asking about past medical history (e.g. recurrent TB, metastatic cancer, Crohn's disease), medications, family history (e.g. Mediterranean familial disease), animal contact (e.g. psittacosis from parakeet contact), sexual history (e.g. rectal abscesses from anal penetration), and travel history (e.g. amoebiasis).[3,7] Other

social practices including drug use, unusual diet (e.g. unpasteurised products), and environmental exposures may also be helpful.[7] Less helpful in history is the magnitude of the temperature readings, the patterns of fever, and response to antipyretics. These areas are not specific enough for diagnosis according to a study that looked at 346 FUO patients admitted to the National Institute of Health.[7]

A thorough history as described above helps the clinician decide whether the FUO etiology is due to infection, inflammation, malignancy, or sources that fall into the miscellaneous category.[8] Through the course of diagnostic work-up, repeat history should be taken to ensure no potential clues are missed.[5]

Physical Exam

An adequate physical exam is one that looks at every system for subtle clues, including full neurological, head and neck, musculoskeletal, dermatological, and fundoscopic exams. Changes in mental status, for example, may point to granulomatous meningitis. A thorough head and neck exam should assess the thyroid, oral cavity, temporal artery, and lymph nodes; this will help to rule out thyroiditis, dental abscesses, temporal arteritis, and lymphoma or tuberculosis, respectively.[3] New cardiac murmurs may point to infective endocarditis, and on dermatological exam, stigmata of infective endocarditis should be ruled out. Increased pigmentation should also be noted as it could indicate a late presentation of Whipple's disease, which is less commonly seen in modern practice due to earlier detection.[3]

As fever can result from virtually any pathology in any of the body's systems, a full physical exam is always warranted. Abnormalities should be noted as they may suggest a diagnosis that would otherwise be missed. Two studies have shown that up to 60% of abnormalities on physical exam have helped guide diagnosis.[3,8,13] Repeat exams should be conducted daily to ensure new findings are noted.

Investigations

If clues from the history and physical exam point to a likely diagnosis, initial investigations should be tailored around them. For example, if an infectious cause is high on the clinician's differential, tests such as AFB cultures, smears for malaria, or serology for VDRL, HIV, CMV, EBV, and ASO are useful starting points.[13] Investigations for malignancy may include peripheral smears, serum protein electrophoresis, endoscopies, and bone scans.[13] Autoimmune connective tissue diseases should trigger orders for antinuclear antibodies and rheumatoid factor.[13] By choosing the appropriate initial tests, a diagnosis can be reached in up to a quarter of FUO.[3]

When faced with a history and physical exam that are not helpful, the clinician should start with a basic set of tests to guide further workup. No uniform set of investigations has been established, but an appropriate group of tests should include complete blood count, electrolytes, liver enzymes and function tests, urinalysis, three blood cultures, rheumatologic markers (ANA, ANCA, RF), HIV antibody, tuberculin skin test and a chest x-ray.[3,7]

Further imaging with computer tomography (CT) of the abdomen should only be done if initial assessments are suggestive

Table 1. Categories of Fevers of Unknown Origin. All FUOs require a measured fever of at least 38.3ºC.[5,6]

Category	Criteria	Common Causes
Classic	• Duration of at least 3 weeks • Evaluation of at least 3 outpatient appointments or 3 days in hospital	Infection, malignancy, collagen vascular disease
Nosocomial	• Hospitalized at least 24 hours • Did not have a fever and was not incubating one on admission • Evaluation of at least 3 days	Clostridium difficile enterocolitis, drug-induced, pulmonary embolism, septic thrombophlebitis, sinusitis
Immune deficient (neutropenic)	• Neutropenia (ANC < 500/mm^3) • Evaluation of at least 3 days in	Opportunistic bacterial infections and fungal infections, herpes virus
HIV-associated	• Duration of at least 4 weeks as outpatient or 3 days as inpatient • Confirmed HIV	Cytomegalovirus, Mycobacterium avium-intracellulare complex, Pneumocystis carinii pneumonia, drug-induced, Kaposi's sarcoma, lymphoma

Table 2. Common causes of FUO[5,6,11,12]

Class	Contribution	Most Common Diseases
Infection	28%	Tuberculosis (especially extra-pulmonary) Abscesses (intra-abdominal, pelvic, dental, renal, perinephric) Endocarditis Osteomyelitis Epstein-Barr virus mononucleosis Cytomegalovirus Cat scratch disease Lyme disease Prostatitis
Inflammatory	21%	Adult Still's disease (adult juvenile rheumatoid arthritis) Polymyalgia rheumatica Temporal arteritis Rheumatoid arthritis (especially late onset) Systemic lupus erythematosus Inflammatory bowel disease
Malignancy	17%	Leukemia and lymphoma Metastatic cancers Renal cell carcinoma Colon carcinoma Hepatoma Myelodysplastic syndromes Pancreatic carcinoma Sarcomas
Miscellaneous	15%	Drug-induced fever Complications from cirrhosis Factitious fever Hepatitis (alcoholic, granulomatous, or lupoid) Deep venous thrombosis Sarcoidosis Mediterranean familial fever Hyperthyroidism
No diagnosis at time of discharge	19%	

of an abdominal cause or if the tests are not helpful in guiding further workup. This is because many CT abdomen scans do not lead to an actual diagnosis even when a lesion is noted.[3] In a prospective analysis, abnormalities on CT demonstrated more false positives than true positives – 28% and 20%, respectively.[6] Jumping to CT without just cause leads to unnecessary workup, needless radiation exposure, and opens doors to further invasive procedures such as laparatomies and biopsies.[3]

Further investigations, including imaging, biopsies, and serology, should be guided by reassessment of history, physical exam, and initial investigative results. As in the case of the CT abdomen, the clinician must consider the diagnostic yield of each test as well as its potential for false results.

When FUO remains unsolved

Despite a diligent workup of FUO, as many as 30% of cases remain unsolved at time of discharge.[13] Clinicians are then faced with the question of whether empiric treatment is necessary. In a study looking at 199 cases of FUO, 61 patients (30%) were discharged without a causal diagnosis. Thirty-one of these unsolved cases had defervesced by the time of discharge. At 5–year follow-up, only 2 of the 61 patients had died secondary to the FUO,[13] pointing to the generally favourable prognosis of untreated FUO.

For this reason, there is little role for empiric treatment of FUO. Current literature supports empiric treatment in only three specific situations: cases suggestive of culture–negative endocarditis, cryptic disseminated tuberculosis, and temporal arteritis that jeopardizes vision.[13]

SUMMARY

FUO remains a common challenge in clinical practice. A systematic approach to working up a patient includes a thorough history and physical exam. The most likely cause can then be assigned to one of four broad categories: infection, inflammation, malignancy, or miscellaneous. These broader classes help guide initial diagnostic tests and avoid unnecessary, more invasive procedures. Nevertheless, despite a thorough workup, as many as 30% of all FUO cases are never solved. The current evidence points to a favourable prognosis for these cases and, thus, empiric treatment is generally not recommended.

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