Fever Of Unknown Origin: Differentials and Workup

Fever of unknown origin is defined by **(a) temperature greater than 38.3°C (101°F) on several occasions, (b) more than 3 weeks' duration of illness, and (c) failure to reach a diagnosis after a one week of intensive inpatient investigation.**

Assessment should include observation of the fever pattern, detailed history and physical examination, laboratory tests, and non-invasive and invasive procedures.

This definition excludes common short self-limiting infections and those that have been investigated and diagnosed within 3 weeks.

Causes and Differential diagnoses

Identified causes can be categorized as infectious, connective tissue, neoplastic, or miscellaneous.

For common diseases to be considered it is worth noting that:

- Most cases of prolonged obscure fever are instances of well-known diseases presenting
- Actual pattern of graphic record, despite the emphasis in traditional books, is so variable as not to be practically
- An aggressive diagnostic effort is justified as the cure is possible in some infections (accounts for 50% being due to viral infection):
- Tuberculosis: This is the commonest cause of pyrexia of unknown origin. The lesions of miliary TB may not be visible easily on x-rays until the disease is well advanced. Sites like kidneys and tubo-ovarian region raise diagnostic

Specific bacterial infections without distinctive localizing signs. The commonest here are salmonellosis and

- Deep-seated bacterial abscesses, g., subphrenic or periphrenic abscess, purulent infections of the large bowel or female pelvic organs. Reactivated old osteomyelitis should be considered as well.
- Infective endocarditis is especially due to atypical organisms, g., Q-fever, aspergillus.

Viral infections:

- Anicteric hepatitis virus infection
- Neoplasms (10–20% in children).

Lymphomas: These are the commonest among the neoplastic causes of Diagnosis may be difficult if lesions are deep-seated retroperitoneal nodes.

Leukemia: Contrary to common belief, it is extremely rare for leukemia to present with fever

Solid tumors: The commonest among solid tumors is hypernephroma with pancreatic carcinoma,

and sarcomas coming next although presentation with fever alone is

Immunogenic diseases: These diseases may present with fever only for several The common ones are rheumatoid arthritis, systemic lupus erythematosus, polyarthritis nodosa, rheumatic fever, and cranial arteritis polymyalgia in the old.

Other causes:

- Chronic granulomatous hepatitis
- Recurrent small pulmonary
- Drug
- Liver
- Habitual hyperthermia: Usually young adult female with imperfect thermoregulation
- The cause may remain unknown in 10–20% of the cases.

Temperature: Rarely exceeds 6oC. It is mentioned because no action needs to be taken.

Workup in the fever of unknown origin

In this case do not assume that all information was gathered or was gathered accurately by the previous clinicians and should not simply copy details of previously recorded history (eg, family history, social history). Even when the initial evaluation was thorough, patients often remember new details when questioning is repeated.

You should not ignore previous test results and should not repeat tests without considering how likely results are to be different (eg, because the patient's condition has changed, because a disorder develops slowly).

History

History aims to uncover focal symptoms and facts (eg, travel, occupation, family history, exposure to animal vectors, dietary history) that suggest a cause.

History of present illness should cover duration and pattern (eg, intermittent, constant) of fever. Focal pain often indicates the location (although not the cause) of the underlying disorder.

Review of systems should include nonspecific symptoms, such as weight loss, anorexia, fatigue, night sweats, and headaches. Also, symptoms of connective tissue disorders (eg, myalgias, arthralgias, rashes) and GI disorders (eg, diarrhea, steatorrhea, abdominal discomfort) should be sought.

A past medical history should include disorders known to cause fever, such as cancer, TB, connective tissue disorders, alcoholic cirrhosis, inflammatory bowel disease, rheumatic fever, and hyperthyroidism.

You should note disorders or factors that predispose to infection, such as immunocompromised state (eg, due to disorders such as HIV infection, cancer, diabetes, or use of immunosuppressants), structural heart disorders, urinary tract abnormalities, operations, and insertion of devices (eg, IV lines, pacemakers, joint prostheses).

Drug history should include questions about specific drugs known to cause fever.

Social history should include questions about risk factors for infection such as injection drug use, high-risk sexual practices (eg, unprotected sex, multiple partners), infected contacts (eg, with TB), travel, and possible exposure to animal or insect vectors.

Risk factors for cancer, including smoking, alcohol use, and occupational exposure to chemicals, should also be identified.

Family history should include questions about inherited causes of fever (eg, familial Mediterranean fever).

Medical records are checked for previous test results, particularly those that effectively rule out certain disorders.

Physical examination

The general appearance, especially for cachexia, jaundice, and pallor, is noted.

The skin is thoroughly inspected for focal erythema and rash inspection should include the perineum and feet, particularly in diabetics, who are prone to infections in these areas.

Check for cutaneous findings of endocarditis, including painful erythematous subcutaneous nodules on the tips of digits (Osler nodes), nontender hemorrhagic macules on the palms or soles (Janeway lesions), petechiae, and splinter hemorrhages under the nails.

The entire body (particularly over the spine, bones, joints, abdomen, and thyroid) is palpated for areas of tenderness, swelling, or organomegaly; digital rectal examination and pelvic examination are included.

The teeth are percussed for tenderness (suggesting apical abscess).

During palpation, any regional or systemic adenopathy is noted; eg, regional adenopathy is characteristic of cat-scratch disease in contrast to the diffuse adenopathy of lymphoma.

The heart is auscultated for murmurs (suggesting bacterial endocarditis) and rubs (suggesting pericarditis due to a rheumatologic or infectious disorder).

Sometimes key physical abnormalities in patients with fever of unknown origin are or seem so subtle that repeated physical examinations may be necessary to suggest causes (eg, by detecting new adenopathy, heart murmurs, rash, or nodularity and weak pulsations in the temporal artery).

Diagnostic Investigations in Fever of unknown origin

The routine investigations listed below should be done before a diagnosis of PUO is made:

- Complete Blood count
- Blood culture and sensitivity
- Urinalysis

- Chest X-Ray
- Urea and electrolytes
- Liver function tests
- Erythrocyte sedimentation rate

Additional investigations that need to be done include the following:

- Repeated history taking and examination may detect:
    - New clinical features that give a
    - Old clinical signs previously missed or
- New tests:
    - Immunological: rheumatoid factor (Rh factor), antinuclear antibody (ANA), anti-streptolysin O titer (ASOT).
    - Most PUOs have abdominal involvement hence, do: barium studies of GIT; intravenous urography; scan liver, spleen, kidneys either computerized axial tomography or
    - Withhold drugs for a few Fever disappears in drug fevers.
- ECG may detect right heart strain in embolism
- Invasive procedures
- Liver biopsy
- Finally, diagnostic laparotomy may be done by a very experienced surgeon required.

Prognosis:

10–20% causes remain unknown; 5–10% mortality rate.