Innersense
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SRL Global Knowledge Forum
Expanding Horizons

Pyrexia of Unknown Origin: Laboratory Workup

Pyrexia/ fever of undetermined or unknown origin (PUO/ FUO), of obscure origin, or fever without an apparent cause can occur due to many clinical conditions and remains a diagnostic challenge in clinical practice. The etiology of FUO varies markedly among different age groups, geographic areas, and seasons.

There is no gold "standard" process to investigate the etiology of FUO. Patients who present with FUO are often subjected to unnecessary over-the-counter laboratory tests and antimicrobial therapies.

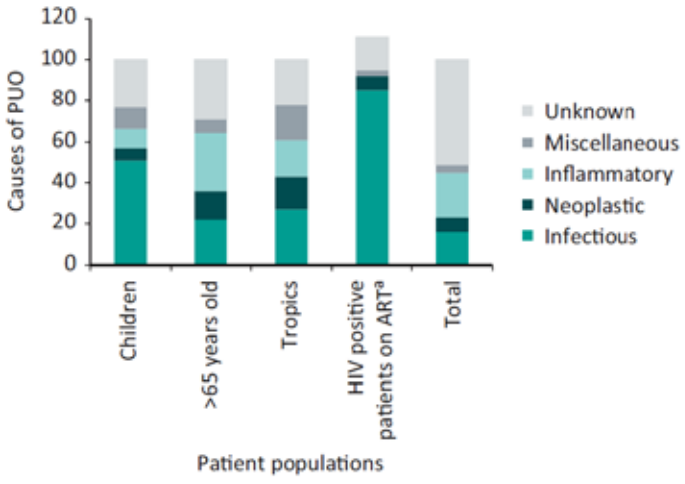
Definition and Causes

FUO was first defined by Petersdorf and Beeson in 1961, who defined FUO as body temperature above 38.3°C (101°F) on three or more occasions and duration of illness of at least three weeks, in which no diagnosis was made after one week of hospital admission. In the following years this definition was modified. Immunocompromised patients are now excluded, as these patients have other etiologies of FUO and need a different therapeutic approach. To reflect the increasing outpatient-based healthcare it was suggested to shorten the duration of investigation to three inpatient days or three outpatient visits. However, as investigations in three outpatient visits and three inpatient days cannot be compared, different causes of FUO will be found in admitted patients. Instead of using arbitrary quantitative time criteria, a quantitative criterion of obligatory investigations was implemented in the definition. The current definition of FUO is:

- Temperature ≥38.3°C (101°F) on at least two occasions
- Duration of illness ≥3 weeks or multiple febrile episodes in ≥3 weeks
- Not immunocompromised (neutropenia for ≥1 week in the 3 months prior to the start of fever; known HIV infection; known hypogammaglobulinemia or use of 10 mg prednisone or equivalent for ≥2 weeks in the 3 months prior to the start of the fever)
- Diagnosis uncertain despite thorough history-taking, physical examination and the following investigations: erythrocyte sedimentation rate or C-reactive protein, haemoglobin, platelet count, leukocyte count and differentiation, electrolytes, creatinine, total protein, protein electrophoresis, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, antinuclear antibodies, rheumatoid factor, microscopic urinalysis, ferritin, three blood cultures, urine culture, HIV serology, chest X-ray, abdominal ultrasonography and tuberculin skin test

Etiology

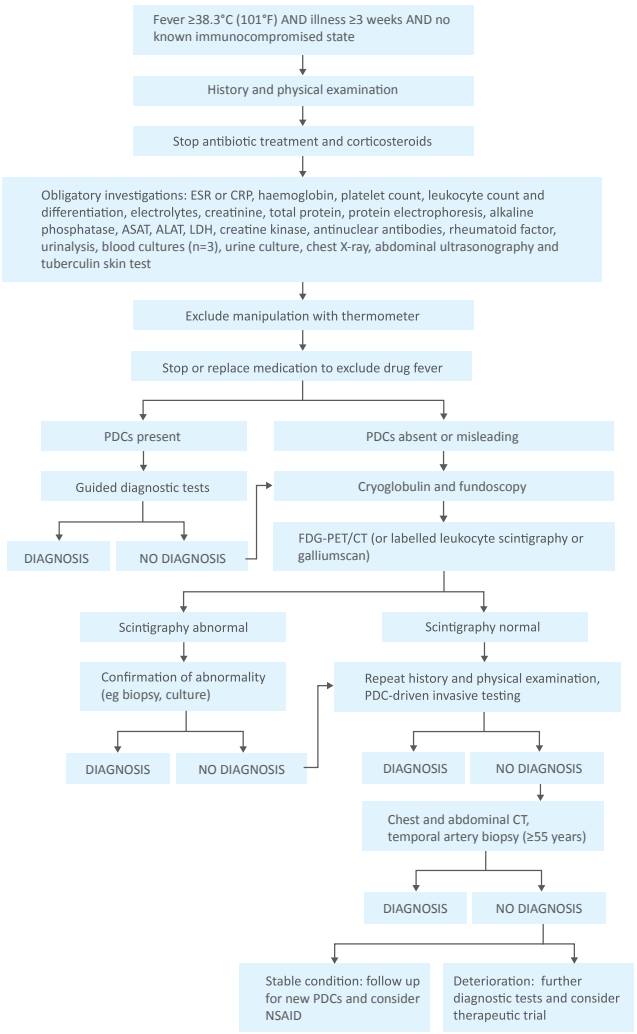
Over 200 causes of FUO have been described in the literature. These causes can be subdivided in four categories: infections (30-40%), neoplasms (20-30%), non-infectious inflammatory diseases (NIID, this group includes autoimmune and rheumatic diseases, vasculitis syndromes and granulomatous disorders; 10-15%) and miscellaneous causes (15-20%). A fifth category is considered by some authors as the idiopathic presentation of FUO, or true FUO. Tuberculosis was found to be the commonest cause of FUO in Indians.



Relative causes of PUO in different patient populations expressed as % (2)

Investigation

More than 50 years after the first definition of FUO, it still remains a diagnostic challenge. Evaluation starts with the identification of potential diagnostic clues (PDCs). PDCs are defined as all signs, symptoms and abnormalities pointing towards a possible diagnosis. PDCs are identified by complete and repeated history taking. The history should include information on previous medical history, drug use, family history, travel history, sexual history, unusual exposure due to occupation or hobbies, and animal contacts. The search for PDCs is further carried out by a careful physical examination. Drug fever and factitious fever have to be excluded. When PDCs are absent or misleading, FUO should be further evaluated following a standard diagnostic protocol with a major role for FDG-PET/CT which has a high diagnostic yield of 84% sensitivity and 86% specificity.



Flow chart of diagnosis of PUO (5)

Prognosis

The overall prognosis of FUO is determined by the underlying disease. Despite all the current diagnostic and therapeutic tools, the mortality rate for FUO remains around 12-35%. However, the group that remains without a definite diagnosis (idiopathic FUO) presents a good prognosis, usually with the cessation of the fever after four weeks or more, with mortality of 3.2% in five years. Treatment with NSAIDs or corticosteroids increases this proportion even further. Records show that 51-100% of these patients can recover spontaneously. The greater mortality in patients with FUO is represented by neoplastic etiologies.

References

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Tests Offered at SRL

Test	Method	Test Code
Advanced Fever Panel with COVID-19 RT-PCR (CBC, ESR, Malaria, Dengue NS Ag, Rapid Typhi IgM, COVID-19 RT-PCR)	Automated Cell Counter/ Automated (Photometrical Capillary Stopped Flow Kinetic Analysis)/ Manual (Modified Westergren) Bactecculture/ Rapid Immunoassay/ Nephelometry/ Dipstick & Microscopy/ RT-PCR	2003
Comprehensive Fever Panel with COVID-19 Antigen Test (CBC, ESR, Malaria, Dengue NS Ag, Rapid Typhi IgM, COVID-19 Ag)		2004
Comprehensive Fever Panel with COVID-19 IgG Test (CBC, ESR, Malaria, Dengue Virus Ab, WIDAL, COVID-19 IgG)		2005
Fever Screening Panel (CBC, ESR, CRP, Blood Culture/ Sensitivity, Rapid Typhi IgM, Malaria Ag Detection & Urinalysis)		5012
Fever Panel-1 (CBC, ESR, WIDAL, Blood Smear For Malaria Parasite, Urinanalysis)		1338
Fever Panel-2 (CBC, ESR, SGPT, Blood Smear For Malaria Parasite, Urinanalysis)		1338ALT
Rheumatic Fever Panel (ASO, CRP, ESR, Throat Swab Culture/ Sensitivity)	Immunoturbidometry, Culture/ Nephelometry/ LPA	5001

Contact the nearest SRL laboratory for details on related diagnostic tests and panels.