Chapter 29

AN APPROACH TO PYREXIA OF UNKNOWN ORIGIN

DEFINITIONS

PYREXIA OF UNKNOWN ORIGIN (PUO) IN ADULTS

Defined as a temperature higher than 38.3°C for more than three weeks, with no obvious source despite appropriate investigation. This strict definition prevents common and self-limiting medical conditions, especially acute viral illnesses, from being included as a cause of PUO.

Most febrile conditions are readily diagnosed on the basis of their presenting symptoms and a problem-focused physical examination. Occasionally, simple laboratory tests such as a full blood count or urine culture is required to make a definitive diagnosis. Viral illnesses (e.g. upper respiratory tract infections) account for most of these self-limiting cases and usually resolve within two weeks. The use of radiological investigations such as CT, MRI, SPECT, PET, ultrasound imaging, and newer microbiology tests such as PCR testing, have changed the diagnostic landscape of PUO.

Potential causes of PUO are divided into four categories which guide the appropriate investigation of a patient with PUO: classic, nosocomial, immune-deficient, and human immunodeficiency virus-related.

Failure to reach a definitive diagnosis in patients presenting with PUO is not uncommon and many cases remain undiagnosed. Even if an extensive investigation does not identify a cause for the PUO, these patients generally have a favourable outcome.

CATEGORY	CAUSES
Classic PUO: patients who meet the original criteria of PUO, with an emphasis on the ambulatory evaluation of these previously healthy patients. The revised criteria require an evaluation of at least three days in the hospital, three outpatient visits, or one week of intensive outpatient testing without clarification of the cause of the fever.	**Common** • Infection (abscesses; endocarditis; TB and complicated UTIs) • Malignancy • Connective tissue diseases (e.g. vasculitis, RA) **Rare** • Kikuchi's disease, an unusual form of necrotising lymphadenitis seen primarily in Japan • TRAPS (TNF-receptor associated periodic fever)

Nosocomial PUO: fever occurring on several occasions in a patient who has been hospitalised for at least 24 hours and has not manifested an obvious source of infection that could have been present before admission. A minimum of three days of evaluation without establishing the cause of fever is required to make this diagnosis	• Septic thrombophlebitis • Pulmonary embolism • *Clostridium difficile* enterocolitis • Catheter-associated infections • Drug-induced fever • Sinusitis (if nasogastric or nasotracheal tubes present)
Immune-deficient PUO (neutropaenic PUO): recurrent fever in a patient whose neutrophil count is 500 per mm^3 or less, and who has been assessed for three days without establishing the aetiology of the fever.	• Bacterial infection • Occult fungal infections e.g. hepatosplenic candidiasis and aspergillosis • Viral infections e.g. HSV or CMV (less common)
HIV-associated PUO is defined as recurrent fevers over a four-week period in an outpatient, or for three days in a hospitalised patient with HIV infection. Although acute HIV infection remains an important cause of classic PUO, the virus also makes patients with more advanced immune suppression susceptible to opportunistic infections.	• Infections e.g. *Mycobacterium tuberculosis, Mycobacterium avium-intracellulare* complex, *Pneumocystis jiroveci* pneumonia, toxoplasmosis, cryptosporidiosis and CMV infections • Non-infectious: lymphoma, Kaposi's sarcoma and immune reconstitution inflammatory syndrome
MISCELLANEOUS PUO	
Drug-induced fever: Most common. The diagnosis of drug fever is made by a therapeutic trial of stopping the suspected drug (with occasional rechallenge). Most patients will defervesce within 72 hours after stopping the offending drug, although some may not recover for weeks. **Complications from cirrhosis and hepatitis** (alcoholic, granulomatous, or lupoid) **Deep venous thrombosis** (rare cause) **Factitious fever:** patients who have some medical training or experience and a fever persisting longer than six months.	Hypersensitivity reaction to specific drugs such as diuretics, pain medications, antiarrhythmic agents, antiseizure drugs, sedatives, certain antimicrobials (sulfonamides, penicillins, nitrofurantoin, vancomycin, amphotericin B, antimalarials), antihistamines, barbiturates, and salicylates.

EVALUATING PUO: THREE-PHASE DIAGNOSTIC APPROACH

The main diagnostic approach with PUOs is a focused, efficient and effective diagnostic approach relevant to the history, physical findings and initial basic laboratory investigations, rather than a 'shotgun approach'. Ideally, the clinician should identify the predominant features of the clinical presentation to determine the general category of the PUO. A focused approach is more likely to lead to the correct diagnosis of the PUO, although the diagnostic evaluation may fail to identify a cause in as many as 30–50% of patients with PUO.

PHASE ONE: THE INITIAL PHASE

This phase consists of the detailed PUO history, physical examination, initial laboratory tests and a chest radiograph. This phase generally should provide the clinician with a general sense of what broad category the PUO may fall into and whether it is likely to be caused by an infection, by a rheumatic-inflammatory disorder or a neoplasm, and therefore limits the differential diagnostic possibilities of the subsequent focused phase two evaluation.

- History
  - Document the duration of fever and the fever pattern.
  - Recent travel, exposure to pets or other animals, work environment, exposure to other people with similar symptoms, drug and toxin history including antimalarial use, vaccination history, hobbies (e.g. spelunking), use of illicit drugs, a family history of fever and a sexual history.
  - Infectious PUOs are often accompanied by chills and night sweats, with or without weight loss (but not loss of appetite).
  - Rheumatic-inflammatory disorders is dominated by arthralgias, myalgias, or migratory chest or abdominal pain. These patients often have fatigue, but weight loss or night sweats are unusual findings.
  - Try to determine the presence of any localising symptoms with the history such as minor changes in cognition or behaviour (granulomatous meningitis) or jaw claudication (giant cell arteritis).
  - Neoplastic PUOs have symptoms of fatigue and weight loss with early and dramatic decrease in appetite.
  - Patients that do not fit in any of these categories could have a PUO due to a variety of miscellaneous disorders.
- Physical examination: A thorough and repeated physical examination and previous findings must be re-evaluated.

INITIAL LABORATORY INVESTIGATIONS INCLUDE

- Full blood count, differential and smear
- ESR or CRP
- Serum LDH
- Liver function tests
- 4th generation HIV ELISA
- Malaria screen (smears, quantitative buffy coat, PCR)
- Hepatitis serology (if transaminitis is present)
- Blood cultures
- Urine MC&S, other cultures such as TB as appropriate
- CXR

PHASE TWO: THE FOCUSED EVALUATION

This phase involves re-evaluating the patient using a focused PUO history and physical examination together with additional non-specific and specific laboratory and radiological tests. The effect is a narrowing of diagnostic possibilities and eliminating possibilities from further diagnostic consideration.

THE ADDITIONAL NON-SPECIFIC AND SPECIFIC LABORATORY TESTS INCLUDE

- Additional sets of blood cultures
- EBV serology
- CMV serology
- Syphilis serology
- Tuberculin skin test or TB interferon-gamma release assay
- Antinuclear antibodies (ANF/ANA)
- Rheumatoid factor
- DNA antibodies and ENA antibodies (if SLE is in the differential diagnosis)
- Serum protein electrophoresis
- Serum ferritin
- Cold agglutinins
- TSH, free T4 and thyroid antibodies (if subacute thyroiditis is suspected)
- Creatinine phosphokinase
- Radiological: CT chest and abdomen
- Transoesophageal echocardiogram

PHASE THREE

If no diagnosis is made after phase one and two investigations, then other diagnoses listed in the summary, should be considered and investigated if not already performed.

INFECTIONS	SPECIFIC LABORATORY TESTS
Bacterial endocarditis	Blood cultures – the yield increases with the number of cultures (three sets drawn from different sites over a period of at least several hours without administering antibiotics) Serology for organisms associated with culture-negative endocarditis: *Coxiella* (Q fever), *Bartonella, Brucella* Transoesophageal echocardiogram
Gastroenteritis *Clostridium difficile*	Stool microscopy and culture *C. difficile* PCR (especially in hospitalised patients)
Abscesses • Liver abscess • Subphrenic abscess • Dental abscess • Brain abscess • Pelvic abscess • Intra-abdominal abscess	Pus from any significant abscess should be cultured for aerobic and anaerobic bacteria, TB/fungi (if appropriate) If appropriate: *Entamoeba* antibodies (e.g. liver abscess) Panorex radiograph of jaws
Ascending cholangitis	Significant cholestasis may exist without jaundice being apparent ALP, AST, GGT, LDH, bilirubin (LFTs)

Urinary tract infection Chronic prostatitis Prostatic abscess	Mid-stream urine (MSU): microscopy and culture
Osteomyelitis Sinusitis	Microscopy and culture of pus Blood cultures Wound swab of contiguous skin lesions Bone biopsy for culture, if indicated FBC, differential WCC, CRP or ESR CT/MRI/bone scans
Typhoid fever	Blood culture Stool culture and stool *Salmonella* PCR Urine culture Bone marrow culture
Tuberculosis incl. • Renal TB • Miliary TB	Sputum, BAL, urine, FNA of lymph nodes – *Mycobacterium tuberculosis* culture, PCR TB blood cultures in patients with suspected disseminated TB. Bone marrow biopsy for PCR and culture in cases of suspected miliary TB or MAC
Brucellosis	Blood culture: ensure that the request alerts the laboratory to the possible diagnosis, as *Brucella* spp. may take up to two weeks to grow and laboratory handling of the organism is hazardous *Brucella* serology and *Brucella* PCR Bone marrow aspiration for culture, where there is a strong clinical suspicion and serological tests and blood cultures are negative
Fungal infection e.g. Cryptococcal infection, candidaemia Other deep fungal infections, e.g. emmonsiosis, histoplasmosis	Fungal blood cultures Cryptococcal antigen: blood, CSF, if appropriate Skin/liver biopsy for culture Bone marrow biopsy and fungal culture
Malaria and filariasis	Parasites: repeated thin and thick blood films, malaria QBC, malaria PCR
Leishmaniasis	Microscopy of bone marrow aspirate Liver or splenic biopsy Leishmania PCR
Tick bite fever Lyme disease Leptospirosis	*Rickettsia* serology, PCR *Borrelia* serology *Leptospira* serology

Toxoplasmosis *Pneumocystis jirovecii*	*Toxoplasma* serology, PCR *Pneumocystis jirovecii* PCR
Viral infectious mononucleosis	EBV serology and EBV viral load CMV serology and CMV viral load
HIV infection	HIV 4th generation ELISA: seroconversion usually occurs within 1 month but may be delayed up to 3 months. HIV viral load may be of use during this 'window period'
RHEUMATIC-INFLAMMATORY DISORDERS	**SPECIFIC LABORATORY TESTS**
Connective tissue diseases e.g. • Temporal arteritis (giant cell) • Still's disease (juvenile RA) • SLE • Polymyalgia rheumatica • Rheumatoid arthritis • Vasculitis • Sarcoidosis • Polyarteritis nodosa • Takayasu's arteritis • Wegener's granulomatosis	Antinuclear, DNA and extractable nuclear antigen antibodies Complement – C3 and C4 Rheumatoid factor Protein electrophoresis Antineutrophil cytoplasmic antibodies (ANCA) Angiotensin converting enzyme (ACE) Lymph node biopsy and histology
NEOPLASTIC DISORDERS	**SPECIFIC LABORATORY TESTS**
Malignancy	Fine needle aspirate, lymph node or lesion biopsy as appropriate Protein electrophoresis Folate, ferritin, uric acid, LDH FBC, ESR Bone marrow biopsy CT/MRI Tumour markers are unreliable as a screening test for occult malignancy
Renal cell adenocarcinoma	Urine cytology Urine microscopy: microscopic haematuria LFTs
Hepatocellular carcinoma	Alpha-foetoprotein Hepatitis B and C serology

MISCELLANEOUS DISORDERS	SPECIFIC LABORATORY TESTS
Granulomatous hepatitis and alcoholic cirrhosis	LFTs Protein electophoresis Liver biopsy
Atrial myxoma	Echocardiogram
Subacute thyroiditis (rarely) pheochromocytoma and adrenal insufficiency	TSH, free T4, thyroid antibodies
Inflammatory bowel disease	Lesion biopsy to establish diagnosis and to exclude other conditions Faecal calprotectin Imaging studies
Drug-induced fever e.g. with penicillins, isoniazid, methyldopa, phenytoin, allopurinol	
Hereditary periodic fever syndromes e.g. Familial Mediterranean fever, tumour necrosis factor receptor-1-associated periodic syndrome (also called TRAPS), hyper-IgD syndrome, Muckle-Wells syndrome, and familial cold auto-inflammatory syndrome	Clinical diagnosis CRP or ESR (intermittent elevation) Specialised genetic and immunological testing as appropriate
Occult haematoma, e.g. retroperitoneal haematoma	Imaging studies
Occult pulmonary embolus	D-dimer, CT chest, VQ scan
Factitious fever	

Therapeutic trials of antimicrobials or glucocorticoids rarely establish a diagnosis. In addition, the diagnostic yield of blood cultures and cultures of biopsy material will be reduced following the initiation of antibiotics. Antimicrobial agents could be expected to suppress but not cure an infectious process such as an occult abscess since adjunctive drainage would usually be required.