Approach to Fever of Unknown Origin

INFECTIOUS DISEASE

58% — KEY DECISION RULE
FDG-PET/CT in classic FUO[6]
pooled diagnostic yield (sensitivity 86%, specificity 52%)

Fever ≥38.3 °C on several occasions for ≥3 wk, still undiagnosed

→ Confirm fever; repeat full history (travel, animals, drugs) and exam; stop non-essential drugs[1,2]

→ CBC, smear, CMP, LDH, ESR, CRP, ferritin, 3 BCx, UA, HIV, IGRA, CXR; CT C/A/P, then PET/CT[2,6,12]

→ **Unstable, high-risk host, GCA or HLH?**

Yes →

High risk: culture, treat, admit, consult[2,12]

- Hypotension or sepsis
- Neutropenia: ANC <0.5 ×10⁹/L
- Transplant, biologics, AIDS
- Vision loss, jaw claudication: GCA
- Ferritin >3000 µg/L, cytopenias, spleen: HLH

→ **Cultures first; GCA: prednisone 40–60 mg now; rheum ≤24 h[8,12]**

If stable: which category?

	Infection ~38%	Inflammatory ~21%	Neoplasm ~12%	Other
CAUSES	• **Endocarditis (incl. culture-negative)** • **TB (extrapulmonary), occult abscess** • Malaria; EBV, CMV, HIV; brucella, Q fever	• **Giant cell arteritis, PMR** • Adult-onset Still disease • SLE, vasculitis, sarcoid, IBD	• **Lymphoma** • Leukemia, myeloproliferative, myeloma • Renal cell, liver, colon cancer	• Drug fever; VTE, hematoma • **HLH** • Thyroiditis, periodic fever, factitious
CLUES	• Murmur, emboli; valve, device, IDU[7] • Travel, animals, raw milk, TB birthplace • Night sweats; dental or surgical history	• Age >50: headache, jaw claudication • Daily spikes, salmon rash, arthritis[1] • High ESR/CRP; very high ferritin (Still)	• Drenching sweats, weight loss, nodes • High LDH, cytopenias, splenomegaly	• β-lactam, ASM; rash, eosinophilia uncommon[12] • Ferritin >3000 µg/L, cytopenias, ↑TG[12] • Episodic fever, well between[4]
WORKUP	• 3 culture sets before antibiotics; echo[7] • IGRA; malaria smears; serology[1,12] • Tissue biopsy: histology, AFB culture[12]	• ANA, RF, ANCA, CK, ferritin, SPEP[12] • Temporal + axillary ultrasound first[9] • Temporal biopsy if ≥55 y, no lead[4]	• SPEP, free light chains; smear review[12] • PET/CT unhelpful if ESR, CRP normal[5] • Excisional node, liver or marrow biopsy	• Stop drug: fever settles in ≤1 wk[12] • HScore; sIL-2R, marrow biopsy[10,11] • Leg Doppler; TSH; fever diary
MANAGE	• Treat organism; drain abscess • No empiric antibiotics if stable[1,12]	• GCA: prednisone 40–60 mg now; rheum ≤24 h[8] • Otherwise no empiric steroids[1]	• Tissue before any steroids[1] • Hematology or oncology referral	• HLH: dexamethasone ± etoposide[11] • No diagnosis in 23–51% of FUO[3,4] • Then observe: most resolve[12]

Stethopedia
stethopedia.ca/approach/fever-of-unknown-origin

Evidence [1] Haidar 2022, N Engl J Med [2] Wright 2024, Open Forum Infect Dis [3] Fusco 2019, BMC Infect Dis [4] Bleeker-Rovers 2007, Medicine [5] Bleeker-Rovers 2007, Eur J Nucl Med [6] Takeuchi 2016, J Nucl Med [7] Fowler 2023, Clin Infect Dis [8] Mukhtyar 2026, Ann Rheum Dis [9] Dejaco 2024, Ann Rheum Dis [10] Fardet 2014, Arthritis Rheumatol [11] La Rosée 2019, Blood [12] Manual 2024–25, pp. 129, 134