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From Unknown to Understood: Revisiting Pyrexia of Unknown Origin

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Abstract

Background: Fever of Unknown Origin, now termed Pyrexia of Unknown Origin, is defined as temperature $>38.3^{\circ}\text{C}$ for >3 weeks with no diagnosis after 1 week of inpatient investigation. PUO remains a diagnostic challenge due to its diverse and often atypical etiologies. Contrary to perception, it is more commonly caused by atypical manifestations of common diseases rather than rare conditions. Tuberculosis is the single most common cause of FUO globally, especially in endemic regions. Other major contributors include infections, malignancies, and non-infectious inflammatory disorders. A systematic and stepwise approach is essential to reduce unnecessary investigations and avoid diagnostic delays.

Case Summary: The clinical approach begins with detailed history and examination focusing on fever pattern, associated systemic symptoms, and risk factors. Key history points include onset and character of fever, night sweats, weight loss, cough, headache, joint pain, burning micturition, abdominal pain, recent travel, TB contact, animal exposure, sexual history, IV drug use, recent hospitalization, dental procedures, and medication history. Physical examination should target signs of occult infection, malignancy, or vasculitis. Special attention is given to FUO with headache, where CSF analysis for HSV, Cryptococcus, and *M. tuberculosis* is warranted.

Results: Diagnostic evaluation should prioritize common causes before pursuing rare etiologies. In suspected miliary TB, CT chest plus bone marrow/lymph node/liver biopsy improves yield. TST/IGRA may be falsely negative in miliary TB, malnutrition, or immunosuppression and does not exclude TB. For suspected vasculitis, fundoscopy for retinal vasculitis and temporal artery biopsy in elderly patients are useful. 18F-FDG PET-CT serves as an adjunct to localize lesions in malignancy or large-vessel vasculitis like Giant Cell Arteritis, though it cannot establish diagnosis alone.

Conclusion: Management of PUO depends on establishing a definitive diagnosis. Once diagnosed, start targeted therapy. Most undiagnosed cases resolve spontaneously. Empirical antibiotics are reserved for hemodynamic instability or neutropenia. In TB-endemic regions with positive TST/IGRA and risk factors, empirical anti-TB therapy may be considered, but alternative diagnoses must be reconsidered if fever persists beyond 6 weeks. NSAIDs may be trialed in undiagnosed cases, while glucocorticoids should be avoided as they can mask symptoms and delay diagnosis.