

Fever of Unknown Origin (FUO): Diagnostic Challenges and Emerging Insights

Introduction

Fever of unknown origin (FUO) is defined as a prolonged fever exceeding 38.3°C (101°F) for more than three weeks, without an established diagnosis despite appropriate investigation. FUO remains a complex clinical challenge due to its diverse etiologies, ranging from infections and autoimmune disorders to malignancies and rare genetic syndromes. Accurate and timely diagnosis is critical to guide management, reduce morbidity, and prevent complications.

Etiology and Diagnostic Approach

The causes of FUO are broadly categorized into four groups: infections, non-infectious inflammatory diseases (NIIDs), malignancies, and miscellaneous conditions. Infections, such as tuberculosis or endocarditis, remain a common cause worldwide, while autoimmune and autoinflammatory syndromes, including vasculitis and adult-onset Still's disease, are increasingly recognized. Malignancies, particularly lymphomas, also contribute to FUO cases.

A structured diagnostic approach is essential. This typically includes detailed patient history, physical examination, laboratory tests (complete blood counts, inflammatory markers, serology), imaging studies (CT, PET-CT), and tissue biopsies when indicated. Advanced molecular techniques, such as next-generation sequencing for pathogen detection,

are expanding the diagnostic toolkit and improving the identification of elusive causes.

Clinical Implications and Management

Management of FUO is guided by the underlying cause, which often requires multidisciplinary collaboration. Empirical therapy may be considered in critically ill patients, but indiscriminate use of antibiotics or immunosuppressants can obscure the diagnosis. Monitoring inflammatory markers and repeated assessments are essential for guiding further investigation.

In some cases, FUO remains unexplained despite exhaustive workup, representing a subset of idiopathic FUO. These patients often have a favorable prognosis but require careful long-term follow-up to detect late-onset disease manifestations.

Conclusion

Fever of unknown origin continues to challenge clinicians due to its broad and evolving spectrum of causes. Advances in diagnostic imaging, molecular techniques, and a systematic approach have improved identification of underlying etiologies. Continued research, combined with careful clinical assessment, is crucial to enhance diagnosis, tailor treatment, and improve outcomes for patients presenting with FUO. Multidisciplinary collaboration remains key in navigating this complex and heterogeneous clinical entity.

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