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Diagnostic Advances in Fever of Unknown Origin: A Clinical Perspective

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Introduction

Fever of Unknown Origin (FUO) remains one of the most challenging diagnostic entities in clinical medicine, despite the evolution of modern diagnostic tools and methodologies. First defined by Petersdorf and Beeson in 1961, FUO was originally characterized by a fever higher than 38.3°C (101°F) on several occasions, lasting more than three weeks and without a diagnosis after one week of hospital investigation. Over the years, modifications to this definition have been proposed to accommodate outpatient evaluation and technological progress. The causes of FUO encompass a broad spectrum of diseases including infections, malignancies, Non-Infectious Inflammatory Diseases (NIIDs) and miscellaneous conditions, with a significant percentage remaining undiagnosed despite extensive work-up. The diagnostic landscape for FUO has significantly evolved over the past two decades, driven by advances in imaging, serological testing, molecular diagnostics and multidisciplinary approaches. This article provides a detailed overview of recent diagnostic innovations in the evaluation of FUO from a clinical standpoint [1].

Description

One of the most profound impacts on FUO diagnosis has been the expansion of advanced imaging modalities. Traditional radiographic investigations have given way to more sophisticated tools such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET), Particularly Fluorodeoxyglucose-Pet (FDG-PET). These technologies allow for whole-body imaging, the identification of occult abscesses, malignancies, or vasculitis and play a crucial role in cases where physical examination and basic lab work fail to yield a diagnosis. FDG-PET/CT, for example, has proven valuable in identifying metabolically active sites that may not be apparent through conventional imaging or clinical presentation. It is particularly useful in detecting large vessel vasculitis or infected prostheses. Additionally, contrast-enhanced ultrasound and diffusion-weighted MRI are being increasingly utilized to identify infectious and inflammatory foci without the need for invasive procedures [2]. Parallel to imaging advances, the development of targeted serological and immunological markers has enhanced diagnostic accuracy in FUO. For infectious causes, next-generation serologies can detect antibodies against rare or atypical pathogens such as Bartonella henselae , Coxiella burnetii , or Brucella species. In inflammatory and autoimmune disorders, biomarkers like antineutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA) and serum ferritin levels are vital. Elevated serum ferritin, for instance, is an important clue toward adult-onset Still's disease or hemophagocytic lymphohistiocytosis (HLH). Cytokine profiling, while still largely in the research domain, has shown promise in differentiating between infectious and autoimmune causes of prolonged fever. Additionally, the use of procalcitonin and C-reactive protein (CRP) continues to guide clinicians in distinguishing bacterial infections from other inflammatory states, although these markers are not diagnostic on their own.

Another major advance is the use of molecular diagnostic tools, particularly polymerase chain reaction (PCR) and next-generation sequencing (NGS). These methods allow for the rapid identification of pathogens from blood or tissue samples without the need for culture, which is particularly useful for fastidious or slow-growing organisms. Multiplex PCR panels can simultaneously test for a wide array of viral, bacterial and fungal pathogens. NGS offers unbiased pathogen detection and has already been used to diagnose rare causes of FUO such as Leptospira , Mycobacterium tuberculosis , or Histoplasma capsulatum in atypical presentations. These technologies are especially helpful in immunocompromised patients, where the clinical presentation of infection may be subtle and conventional testing unreliable. In selected cases, tissue biopsy guided by imaging, followed by molecular analysis, can provide the definitive diagnosis.

Conclusion

The diagnosis of fever of unknown origin remains a formidable clinical challenge, requiring a careful, methodical and often multidisciplinary approach. However, the recent decades have witnessed significant progress in diagnostic capabilities through innovations in imaging, serology, molecular biology and clinical informatics. These tools have improved the diagnostic yield in FUO and reduced the number of undiagnosed cases, although a substantial fraction still remains unexplained. Incorporating advanced imaging like FDG-PET/CT, molecular diagnostics including PCR and NGS and serological markers into the diagnostic algorithm allows for a more targeted and effective investigation. Furthermore, the evolving role of artificial intelligence and decision-support tools promises to refine diagnostic pathways further. Despite technological progress, the clinician's judgment, detailed history-taking and physical examination remain irreplaceable components of the FUO workup. As research continues and access to advanced diagnostics improves globally, it is expected that both the time to diagnosis and patient outcomes in FUO cases will improve significantly.

Acknowledgement

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Conflict of Interest

None.

References

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