Fever of Unknown Origin in the Hospitalized Patient

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KEYWORDS

• Pyrexia • Differential diagnosis • Vasculitis • Malignancy • Infection

HOSPITAL MEDICINE CLINICS CHECKLIST

1. Fever of unknown origin (FUO) is defined as pyrexia of greater than 38.3°C for at least 3 weeks with no identified cause after 3 days of hospital evaluation or at least 3 outpatient visits.
2. Infections remain a leading cause of FUO, including FUO caused by uncommon presentations of typical infectious syndromes and by more rare infectious pathogens. Investigation of infectious causes should be guided by a patient's medical history and exposure history.
3. Adult Still disease and giant-cell arteritis are the most common rheumatologic causes for FUO in young adults and the elderly, respectively.
4. A wait-and-watch approach may be a reasonable strategy in patients with FUO who are clinically stable after an extensive investigation is completed. Empiric antibiotic therapy is generally necessary only in patients who are clinically unstable or neutropenic, or in those with a history of immunosuppression.

INTRODUCTION

Fever of unknown origin (FUO) is defined as pyrexia of greater than 38.3°C for at least 3 weeks with no identified cause after 3 days of hospital evaluation or at least 3 outpatient visits.[1] It remains a challenging and sometimes frustrating experience for both the patient and the health care provider to determine the exact cause of FUO. There are no large randomized prospective trials or protocols designed for workup or management of this condition. Consequently, evidence-based guidelines do not exist. There is vast

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disagreement among experts as to what constitutes an adequate workup. The incidence of FUO in the 1980s was approximately 5%, and it has steadily declined since then because of advances in imaging techniques and improved culture techniques.[2] This article highlights the most important causes of FUO in hospitalized patients, describes a rational approach to investigating the underlying cause, and provides a general framework on how to manage FUO.

DEFINITION

1. What is FUO? How is it classified?

FUO was first defined by Petersdorf and Beeson[1] in 1961 as: (1) fever higher than 38.3°C on multiple occasions; (2) duration of fever greater than 3 weeks; and (3) failure to reach a diagnosis after a thorough evaluation in the hospital for at least 1 week. This period of fever lasting 3 weeks was chosen to allow for self-limited viral infections to improve spontaneously, and also to allow appropriate and thorough investigation in the outpatient setting.[1] Over the ensuing 4 decades, as technology has made great strides, our ability to identify and treat FUO has vastly improved, and this led Durack and Street[3] to propose a revised definition that essentially identifies 4 different categories of FUO:

1. Classic FUO: Essentially the same classic definition of FUO, except that at least 3 outpatient visits are required or an "intelligent and invasive" ambulatory investigation has been performed.
2. Nosocomial FUO: Fever on several occasions in a hospitalized patient in whom acute infection was not manifest or incubating on admission. This definition requires at least 3 days of investigation, including at least 2 days of incubation of cultures without a revealing diagnosis.
3. Neutropenic FUO: Fever in a patient with an absolute neutrophil count of less than 0.5×10^9/L or that is expected to fall to this level in 1 to 2 days, and for which no specific cause is identified after 3 days of investigation.
4. Human immunodeficiency virus (HIV)-associated FUO: Fever on several occasions in patients with HIV infection over a period of 4 weeks as outpatients or more than 3 days for hospitalized patients.

2. What are the various causes of FUO?

This article focuses on a diagnostic approach to the classic definition of FUO in a hospital setting. Determining the cause of FUO in hospitalized patients remains an elusive task. There are more than 200 reported causes of FUO reported in the literature.[4,5] Based on 11 series including more than 1000 patients between 1995 and 1994,[6] the etiology of FUO is:

- Infection 28%
- Inflammatory or autoimmune diseases 21%
- Undiagnosed 19%
- Malignancy 17%

It is generally accepted that the proportion of FUO caused by infections and malignancy has decreased while autoimmune/inflammatory diseases and undiagnosed causes have increased.[2,7] In a recent study of FUO in the Netherlands, inflammatory and autoimmune disease represented the most common cause (22%) in patients who were eventually diagnosed.[8] An aging population, access to diagnostic imaging,