Review: Fair evidence supports several tests in investigating fever of unknown origin

Mourad O, Palda V, Detsky AS. **A comprehensive evidence-based approach to fever of unknown origin.** Arch Intern Med. 2003;163:545-51.

QUESTION

What are the best approaches for a diagnostic workup of fever of unknown origin (FUO)?

DATA SOURCES

Studies were identified by searching MEDLINE (1966 to 2000) and by reviewing the references of relevant studies.

STUDY SELECTION

Studies were selected if they were published in English; they examined the natural history, prognosis, or spectrum of disease associated with FUO, or evaluated a diagnostic test for FUO; the patients had a temperature > 38.3 °C on several occasions lasting > 3 weeks; and the diagnosis remained uncertain after 1 week of investigation in hospital. Exclusion criteria were immunosuppression; age < 18 years; HIV; cancer; or patient groups outside of North America, western Europe, or Scandinavia.

DATA EXTRACTION

Data were extracted on the performance and yield of the diagnostic tests. Study quality was assessed according to research design and internal validity (good, fair, or poor).

MAIN RESULTS

Diagnostic tests, beyond clinical evaluation and basic investigations, for which supporting evidence existed were abdominal computed tomography (CT), nuclear imaging, the Duke criteria for endocarditis, liver biopsy, temporal artery biopsy, and leg Doppler imaging. Test performance, quality rating of the studies, and recommendations for the tests' use are in the Table. Bone marrow culture had a low yield (0% to 2%) in 2 fair-quality studies. Uncertainty existed for surgical exploration of the abdomen because of the poor quality of the 8 identified studies. No evidence existed for evaluating echocardiography alone, magnetic resonance imaging, bone scan, or D-dimer assay.

CONCLUSION

Fair evidence supports the use of computed tomography, some nuclear imaging tests, the Duke criteria, liver biopsy, temporal artery biopsy, and leg Doppler imaging in the evaluation of fever of unknown origin.

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Tests for investigating fever of unknown origin (FUO)*

Tests	Effectiveness	Level of evidence	Number and quality of studies	Recommendation
Abdominal computed tomography	Sens 71%; spec 71%	Fair	1 fair	Recommended
Nuclear imaging	Sens 40% to 82%; spec 69% to 94%	Fair	6 fair; 4 poor	Technetium and indium 111-labeled white blood cell scans recommended; indium 111 IgG and gallium 67 scans not recommended
Duke criteria	Spec 99%	Fair	1 fair	Recommended
Liver biopsy	Diagnostic yield 14% to 17%	Fair	2 fair	Recommended
Temporal artery biopsy	—	—	—	Recommended for diagnosing temporal arteritis in older patients with FUO
Leg Doppler imaging	—	—	—	Recommended for diagnosing deep venous thrombosis, a cause in 2% to 6% of patients with FUO

*Sens = sensitivity; spec = specificity.

COMMENTARY

Fever is a cardinal manifestation of disease. When fever is prolonged and its cause is elusive, it becomes a perplexing and frustrating problem for all involved. FUO represents a classic internal medicine problem, considered by many to be the ultimate diagnostic challenge for an astute clinician (1).

For evidence-based enthusiasts, the "U" in FUO means that no single gold standard exists against which to judge diagnostic tests. So what can we make of an "evidence-based approach"? Given > 200 possible causes of FUO, an evidence-based algorithm will probably help only in a general sense. Useful information in approaching FUO answers the following questions: What causes are possible (population-specific knowledge of the contemporary diseases causing prolonged fever [2])? What diseases are easily diagnosed or missed with available diagnostic tests? And where do clinicians typically fall short?

The review by Mourad and colleagues properly indicates that occult disease in the abdomen is still common enough to justify using abdominal CT early, and their review supports the value of considering objective endocarditis criteria for another occult cause of fever. However, as Vanderschueren and colleagues (3) observed, with improvements in imaging, bacteriology, and serology over the past 25 years, the real change in distribution of the so-called "big three" (infection, cancer, and rheumatologic disease) has been a marked increase in the proportion of noninfectious inflammatory diseases causing FUO. Thus, there has been a change from 15% to 19% in earlier series to nearly 40% of diagnosed cases in a more contemporary series (3).

The methods most likely to be decisive are history and evolution of the condition and a biopsy. A careful history with attention to the evolution of the illness and a willingness to carefully reexamine diagnostic material are good, common sense strategies, reinforced by the realization that many patients are labeled as FUO because previous clinicians have overinterpreted or misinterpreted nonspecific findings. This often leads to a biopsy based on objective evidence or a syndromic diagnosis.

Less well-known is the fact that because we are better at diagnosing not only cancer, infections, and now noninfectious inflammatory diseases, the prognosis for persons with undiagnosed FUO is better, too: 50% to 100% recover spontaneously according to Mourad and colleagues, and > 90% were well in Vanderschueren's recent series (3). In Alt and Barker's 1930 series (4), > 30% of those discharged without a diagnosis died, probably from undiagnosed cancer or infectious causes.

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References

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