
de Kleijn EM, Vandenbroucke JP, van der Meer JW.

Source

Department of Medicine, University Hospital St. Radboud, Nijmegen, The Netherlands.

Abstract

Internal medicine wards in all 8 university hospitals in the Netherlands participated in this prospective study of fever of unknown origin (FUO) from January 1992 until January 1994 in order to update information on the spectrum of diseases causing FUO. We used fixed epidemiologic entry criteria to achieve completeness of enrollment and to avoid unintended selection bias. After entry, immunocompetent patients were included using criteria for FUO according to Petersdorf and Beeson (30). A standardized diagnostic protocol was used, and potentially diagnostic clues (PDCs) and their use in the diagnostic process were prospectively registered. Thus, the criteria of classic FUO have been adjusted to modern times: immunocompromised patients are excluded, and the time-criterion "1 week in hospital without a diagnosis" has been replaced by a quality-criterion stating that certain investigations must be performed as a minimum, and PDCs must be followed adequately for at least 1 week, without a diagnosis being reached. A total of 167 immunocompetent patients with FUO were thus retrieved, of whom 43 (25.7%) had infections, 21 (12.6%) had neoplasms, and 40 (24.0%) had noninfectious inflammatory diseases. No diagnosis was made in 50 patients (29.9%), 37 of whom recovered spontaneously. This study confirms the changing spectrum of diseases causing FUO. Indeed, as shown by another recent study, the group of patients with FUO in whom no diagnosis can be made is expanding, and mostly it concerns self-limiting or benign fevers. Others have suggested that this trend is not really occurring (29). We did not place patients with diseases of unknown origin in the "nondiagnosis" group, and indeed made presumptive diagnoses when necessary. Nevertheless, this category of undiagnosed fevers is increasing. We believe that the higher percentage of undiagnosed cases can be attributed to the greater use of advanced diagnostic techniques attendant on an increased number of self-limited illnesses in patients meeting criteria for FUO. Because of ongoing development in diagnostic techniques and the prospective influence on the spectrum of diseases causing FUO, studies should be
performed regularly to update information on this subject. Because the number of outpatient evaluations for FUO is expected to increase, patients seen on an outpatient basis should be included in future studies. To avoid unwanted selection bias, fixed epidemiologic entry criteria should be used to ensure completeness of enrollment. To shorten the period of collecting data, multicentric studies can be done using standardized diagnostic protocols. In patients with recurrent fever or fever lasting longer than 6 months, the chance of reaching a diagnosis is significantly lower, and especially in this group one should exercise the greatest caution to avoid abundant and extensive diagnostic procedures. The diagnostic process in patients with FUO remains an intriguing problem in medicine. Recent microbiologic techniques may be useful as an approach to the relatively large proportion of patients in whom we now fail to make a diagnosis.


de Kleijn EM, van Lier HJ, van der Meer JW.

Source

Department of Medicine, University Hospital St. Radboud, Nijmegen, The Netherlands.

Abstract

From January 1992 until January 1994, we used a standardized diagnostic protocol for the 167 immunocompetent patients with fever of unknown origin (FUO) admitted on the internal medicine wards in all 8 university hospitals in the Netherlands. This protocol consisted of a standardized coded history and standardized physical examination for all 167 patients. A number of additional obligatory investigations had to be performed in the first week of admission for all patients, and all potentially diagnostic clues (PDCs) thus retrieved had to be registered. In the presence of PDCs, specific investigations had to be performed based on the differential diagnosis. In the absence of PDCs or in the presence of only misleading PDCs, patients underwent a screening 2-staged diagnostic protocol. In 162 (97%) patients, PDCs were present after 1 week of admission. In 61 patients these PDCs were all misleading. The likelihood of reaching a diagnosis in patients with PDCs was not significantly higher than that in patients without PDCs, probably because of the high proportion of misleading PDCs. The likelihood of establishing a diagnosis was significantly lower (< 10%) only for patients with recurrent fever, normal erythrocyte sedimentation rate (ESR), and normal hemoglobin. All other PDCs were not significantly different in patients
with a diagnosis compared with patients without a diagnosis. The screening 2-staged diagnostic protocol proved useful in 10 of 43 patients in whom it was used. The screening value of immunologic and microbiologic serology and endocrine investigations was nil; these investigations probably should be performed only when PDCs for the disease searched for are present. Scintigraphic techniques, echocardiography, and other imaging procedures were never helpful in our population in the absence of PDCs. Many patients with FUO had nonspecific anemia and disturbed liver chemistry. In the presence of these findings alone, without other more specific PDCs, the likelihood of reaching a diagnosis with help of bone marrow aspiration was nil, and with help of liver biopsy, it was low. Enteric biopsy was never helpful. If lymphadenopathy was confined to the cervical or inguinal region (with negative chest X-ray and abdominal ultrasound), lymph node biopsy was not helpful, in contrast to patients having generalized lymphadenopathy, in whom the technique had a yield of 79%. As shown in this study, the search for PDCs remains an important tool for establishing the diagnosis in patients with FUO, although in many cases these PDCs appear to be misleading. Directed diagnostic workup--using the PDCs retrieved by repeated, meticulous history taking and physical examination--remains the most efficient and intellectually satisfactory way to solve the problem of FUO in the individual patient. A standard protocol in patients with FUO in whom the obligatory investigations, as used by us, do not lead to the diagnosis can be limited to the tests that proved to be of some use as screening procedure: temporal biopsy in patients older than 55 years; fundoscopy; serology (Western blot) for Yersinia enterocolitica; serum for cryoglobulin at an early stage of the diagnostic process; and bone biopsy, liver biopsy, abdominal computed tomography (CT), and chest CT at a later stage. Repeating a thorough history-taking, physical examination, and obligatory investigations and waiting for PDCs to appear probably is better than ordering more screening investigations in the hope that something abnormal will come up. Supportive treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) can be helpful at this stage. Only rarely do patients deteriorate while using NSAIDs without presenting new PDCs. In these rare patients, further diagnostic workup should be performed or a therapeutic trial with, for example, antibiotics, steroids, or antituberculous agents started.


**A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic protocol.**

Bleeker-Rovers CP, Vos FJ, de Kleijn EM, Mudde AH, Dofferhoff TS, Richter C, Smilde TJ, Krabbe PF, Oven WJ, van der Meer JW.

**Source**
Abstract

We conducted a prospective study to update our knowledge of fever of unknown origin (FUO) and to explore the utility of a structured diagnostic protocol. From December 2003 to July 2005, 73 patients with FUO were recruited from 1 university hospital (n = 40) and 5 community hospitals (n = 33) in the same region in The Netherlands. FUO was defined as a febrile illness of >3 weeks' duration, a temperature of >38.3 degrees C on several occasions, without a diagnosis after standardized history-taking, physical examination, and certain obligatory investigations. Immunocompromised patients were excluded. A structured diagnostic protocol was used. Patients from the university hospital were characterized by more secondary referrals and a higher percentage of periodic fever than those referred to community hospitals. Infection was the cause in 16%, a neoplasm in 7%, noninfectious inflammatory diseases in 22%, miscellaneous causes in 4%, and in 51%, the cause of fever was not found (no differences between university and community hospitals). There were no differences regarding the number and type of investigations between university and community hospitals. Significant predictors for reaching a diagnosis included continuous fever; fever present for <180 days; elevated erythrocyte sedimentation rate, C-reactive protein, or lactate dehydrogenase; leukopenia; thrombocytosis; abnormal chest computed tomography (CT); and abnormal F-fluorodeoxyglucose positron emission tomography (FDG-PET). For future FUO studies, inclusion of outpatients and the use of a set of obligated investigations instead of a time-related criterion are recommended. Except for tests from the obligatory part of our protocol and cryoglobulins in an early stage, followed by FDG-PET, and in a later stage by abdominal and chest CT, temporal artery biopsy in patients aged 55 years or older, and possibly bone marrow biopsy, other tests should not be used as screening investigations.


A comprehensive evidence-based approach to fever of unknown origin.

Mourad O, Palda V, Detsky AS.

Source

Department of Medicine, University of Toronto, Ontario, Canada. MouradO@smh.toronto.on.ca

Abstract
**BACKGROUND:**

Fever of unknown origin (FUO) is defined as a temperature higher than 38.3 degrees C on several occasions and lasting longer than 3 weeks, with a diagnosis that remains uncertain after 1 week of investigation.

**METHODS:**

A systematic review was performed to develop evidence-based recommendations for the diagnostic workup of FUO. MEDLINE database was searched (January 1966 to December 2000) to identify articles related to FUO. Articles were included if the patient population met the criteria for FUO and they addressed the natural history, prognosis, or spectrum of disease or evaluated a diagnostic test in FUO. The quality of retrieved articles was rated as "good," "fair," or "poor," and sensitivity, specificity, and diagnostic yield of tests were calculated. Recommendations were made in accordance with the strength of evidence.

**RESULTS:**

The prevalence of FUO in hospitalized patients is reported to be 2.9%. Eleven studies indicate that the spectrum of disease includes "no diagnosis" (19%), infections (28%), inflammatory diseases (21%), and malignancies (17%). Deep vein thrombosis (3%) and temporal arteritis in the elderly (16%-17%) were important considerations. Four good natural history studies indicate that most patients with undiagnosed FUO recover spontaneously (51%-100%). One fair-quality study suggested a high specificity (99%) for the diagnosis of endocarditis in FUO by applying the Duke criteria. One fair-quality study showed that computed tomographic scanning of the abdomen had a diagnostic yield of 19%. Ten studies of nuclear imaging revealed that technetium was the most promising isotope, showing a high specificity (94%), albeit low sensitivity (40%-75%) (2 fair-quality studies). Two fair-quality studies showed liver biopsy to have a high diagnostic yield (14%-17%), but with risk of harm (0.009%-0.12% death). Empiric bone marrow cultures showed a low diagnostic yield of 0% to 2% (2 fair-quality articles).

**CONCLUSIONS:**

Diagnosis of FUO may be assisted by the Duke criteria for endocarditis, computed tomographic scan of the abdomen, nuclear scanning with a technetium-based isotope, and liver biopsy (fair to good evidence). Routine bone marrow cultures are not recommended.

**Comment in**

- The following popper user interface control may not be accessible. Tab to the next button to revert the control to an accessible version.

  Destroy user interface control
  An evidence-based approach to fever of unknown origin.
  [Arch Intern Med. 2003]
Fever of unknown origin: historical and physical clues to making the diagnosis.

Tolia J, Smith LG.

Source

Department of Infectious Diseases, St. Michael's Medical Center, 111 Central Avenue, Newark, NJ 07104, USA. sachitatolia@hotmail.com

Abstract

Fever of unknown origin (FUO) has fascinated and perplexed clinicians for over a century. No published guidelines exist on the approach to FUO, and studies have demonstrated that a diagnosis is never established in up to 30% of cases. A comprehensive history and physical examination are the keys to establishing a diagnosis in patient with FUO. This article provides a systematic approach to the diagnosis of FUO by delineating the most important elements of a comprehensive history and physical examination.

[How to explore a fever of unknown origin in adult patients?].

[Article in French]
Vertenoel G, Servais S, Beguin Y.

Source
Abstract

Fever of unknown origin (FUO), with more than 200 potential causes, can represent a real diagnostic challenge. For the work-up of FUO, the first step is to pay attention to each element revealed by a detailed history, a complete physical examination and by some basic diagnostic tests. These elements may constitute some clues that can guide the physician for the prescription of further appropriate diagnostic examinations and procedures. If there is no real specific clues, a pet-scan seems to be useful for the work-up of FUO.


[Chest pain and fever].

[Article in German]
Bassetti S, Kober L, Martina B, Zimmerli W.

Source

Medizinische Universitäts-Poliklinik, Departement Innere Medizin, Kantonsspital, Basel.

Abstract

A 26 year old women was seen at our outpatient clinic because of fever, dyspnea, chest pain and night sweats. An echocardiography revealed a moderate pericardial effusion. Therapy with a nonsteroidal anti-inflammatory drug was started, but the patient did not improve clinically. A new left pleural effusion became manifest. Usual laboratory tests, serological tests and examination of pleural effusion were not conclusive. However, a tuberculin skin test was positive. The etiologic diagnosis of this pericarditis and pleuritis was obtained by thorascoscopic pleural biopsy, which yielded Mycobacterium tuberculosis.