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Inquiry into the diagnostic workup of patients with fever of unknown origin

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Abstract

Background: The utility of algorithms in patients with fever of unknown origin (FUO) has not yet been determined. Before starting a prospective study on the utility of a staged diagnostic protocol in patients with FUO, we performed an inquiry among internists in each university hospital in the Netherlands to obtain insight into their diagnostic approaches to FUO.

Methods: Nineteen of 24 internists filled out a questionnaire. The first part consisted of a description of a patient with FUO having few potentially diagnostic clues and questions on the work-up of this patient with FUO. In the second part a multiple-choice form had to be filled out specifying the clinical situations in which one would order in general each of the 182 investigations mentioned.

Results: Regarding the first part, a median of 6 (2–16) possible diagnoses was mentioned. Many investigations would be ordered on the basis of this differential diagnosis. Regarding the second part, 38 investigations were ordered as a screening procedure by more than 50% of these internists. A median of 49 investigations was ordered as a screening procedure per internist and 103 investigations on suspicion of a possible diagnosis only.

Conclusions: Many investigations were used as screening procedures in the diagnostic process of patients with FUO. A two-staged diagnostic protocol was developed based on retrospective analysis of diagnostic management and data from this study. The diagnostic utility of this protocol will be tested in a large prospective multicentre study.

Keywords: Fever of unknown origin; Diagnostic procedures

1. Introduction

Fever of unknown origin (FUO) has been defined by Petersdorf and Beeson [1] as a febrile illness of more than 3 weeks duration, fever higher than 38.3°C on at least 3 occasions, and uncertain diagnosis after 1 week of diagnostic workup in a hospital. Despite many studies on this subject [1–6] and a variety of diagnostic methods currently available, the diagnostic workup in this group of patients remains a challenge.

Because of the diversity of causes of longstanding fever, it is difficult to construct algorithms that cover the complete spectrum of FUO. In the past some attempts were undertaken to outline diagnostic approaches [7–13]. None of these algorithms had a

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scientific basis but were merely proposed by an experienced physician. Although such guidance is of importance, it is difficult to extrapolate to the individual patient with FUO. Should all the examinations mentioned in staged protocols be done when no potentially diagnostic clues are present? What is the diagnostic yield of these investigations under various circumstances? Which patients have a greater risk of having a dangerous disease and is it possible to select the patients with benign fever?

Before starting a prospective study on FUO in which we wanted to test a staged diagnostic protocol, we performed a retrospective analysis of the diagnostic workup in 53 patients with FUO, presenting from 1988 to 1992 at our university hospital. Data on this study have been published [14]. Because of the abundant use of diagnostic techniques in this study, we performed an inquiry among internists to obtain insight into their approach to FUO.

2. Materials and methods

In each of the 8 university hospitals in the Netherlands, 3 internists were asked to fill out a questionnaire on diagnostic techniques potentially useful in patients with FUO. These diagnostic techniques had all been performed in the patients with FUO retrospectively studied by us [14]. Of these 24 internists, 19 filled out the questionnaire. Thirteen were working at general internal wards and had been registered for at least 5 years as internist. Six internists were licensed for the subspecialty of infectious diseases (ID-physicians).

The questionnaire consisted of two parts. In the first part, a case report was given, describing one of our patients with FUO. We asked the participants to propose a diagnostic workup after stating a differential diagnosis of the following case.

A 52-year-old man is hospitalized because of fever up to 39°C existing for more than 3 months. Occasionally, the fever is accompanied by chills. His medical history reveals fatigue for over 1 year; during the last year he lost 4 kg in weight. In addition, there are slight complaints of pollakisuria without strangury or urine abnormalities. He is a pigeon-fancier, but none of the pigeons has been ill. He has not travelled to tropical areas; there are neither arthralgia nor skin abnormalities and the rest of his medical history also is unremarkable. On examination he had an anaemic, grayish skin and a slightly enlarged spleen. Laboratory findings (leucocyte and platelet count, total serum protein, liver function tests, creatinine kinase, urinary analysis, faecal occult blood, creatinine, PPD, antinuclear antibody, rheumatoid factors) were normal, except for a sedimentation rate of 38 mm/h and a haemoglobin of 7.5 mmol/l. The X-ray of the chest was normal. Abdominal ultrasonography revealed a slightly enlarged spleen with a length of 14 cm and diffuse hepatomegaly.

Question 1: Which diagnoses would you consider at the time of presentation?

Question 2: In view of the diagnoses considered, which investigations would you perform?

Question 3: If you do not favour any diagnosis, which investigations would you perform as a screening procedure at presentation?

Question 4: If these investigations do not yield a diagnosis and the patient remains ill, which investigations would you perform at a later stage?

Table 1
Question asked on 182 investigations with a possible role in diagnostic process of patients with FUO

Question	Which of the investigations listed here would you order in a patient with FUO and at what stage of the diagnostic phase?
Answers	
1.	Always, in the first phase at presentation during the first week of admission or at first presentation in patients with fever lasting longer than 3 weeks.
2.	When routine studies after 1 week yield no diagnosis.
3.	When no diagnosis has been established after 1 month of negative studies.
4.	When no diagnosis has been made after several months.
5.	When minor clues to a specific disease are present, also with low suspicion.
6.	When major clues to a specific disease are present only, with high suspicion only.
7.	Never, not even when clues to a specific disease are present.

In the second part, we asked the participants to specify the clinical situations in which they would order each of 182 investigations. For each item there were 7 possible answers (Table 1). To facilitate interpretation, we summarized these answers and subdivided the answers into two groups. The first group of answers concerned investigations that were ordered as a screening procedure in patients without the presence of potentially diagnostic clues (PDCs) by the majority of internists; the threshold for these investigations can be considered low. The second group of investigations was ordered only when indicated by the presence of PDCs by the majority of internists; thus the threshold for the latter can be considered higher.

Data were statistically analyzed and compared with use of Mann-Whitney *U*-statistics. A *P*-value of < 0.05 (two-sided) was considered to be significant.

3. Results

With regard to the case presented, the number of **potential diagnoses** mentioned per internist was median 6 (range 2–16) (see Fig. 1). There was no significant difference between generalists and ID-physicians. The **potential diagnoses** most often mentioned as an answer to **question 1** were malignant lymphoma (18 ×), extra pulmonary tuberculosis (14 ×), solid tumor (8 ×), endocarditis (8 ×), *Cytomegalovirus* infection (7 ×), vasculitis (7 ×), bird fancier's lung (8 ×), psittacosis (6 ×), brucellosis (5 ×), infectious mononucleosis (5 ×), sarcoidosis (4 ×), toxoplasmosis (3 ×), persistent yersiniosis (3 ×) and malaria (3 ×). A variety of other diseases was mentioned only once or twice: parasitic infections, Q-fever, temporal arteritis, hyperthyroidism, polyarteritis nodosa, stomach cancer, colon cancer, prostatitis, Crohn's disease, colitis, leishmaniasis, syphilis, human immunodeficiency virus infection, adult-onset Still's disease, pulmonary embolism.

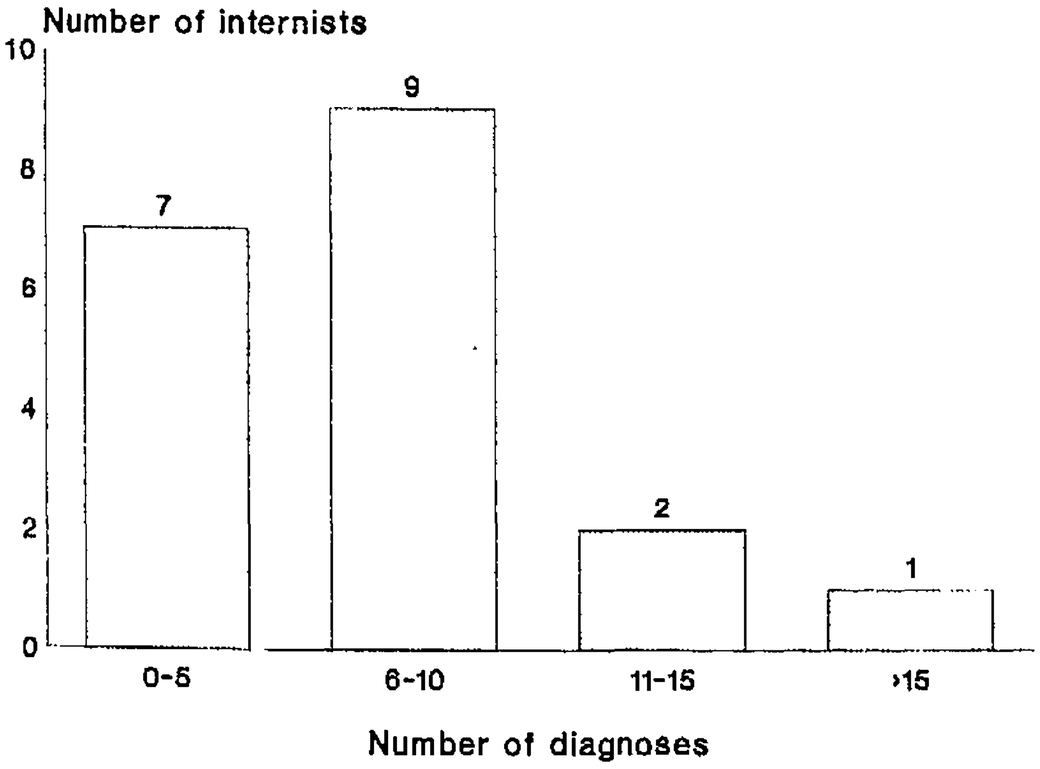

Fig. 1. Number of diagnoses per internist (median = 6).

With regard to the **second question**, based on the diagnoses considered, all internists would perform a series of investigations in the first stage of the diagnostic process. The investigations most commonly mentioned were: abdominal CT (11 ×), bone marrow aspiration for microscopic examination and culture (10 ×), serology for *Epstein-Barr virus*, *Cytomegalovirus* (7 ×), immunoglobulin E and serum precipitin against pigeon proteins (7 ×), serology for *Brucella* spp. (5 ×), for *Chlamydia psittaci* (4 ×), for *Yersinia enterocolitica* (4 ×), bone biopsy (4 ×), culture of expressed prostate secretion (3 ×), angiotensin-converting enzyme (3 ×), skin–muscle biopsy (3 ×), faecal cultures (3 ×). Other investigations would be performed only by 1 or 2 internists: C-reactive protein, serology for *Mycoplasma pneumoniae*, *Rickettsiae*, respiratory viruses, *Treponema pallidum*, *Toxoplasma gondii* and hepatitis B virus, serum immune electrophoresis, anaemia analysis, complement profile, circulating immune complexes, pulmonary function tests, serum calcium, CT of the chest, repeated blood cultures, mycobacterial cultures of urine and stomach contents, repeated urine analysis including microscopic evaluation of urine, cryoglobulin, lysis centrifugation blood cultures, triglycerides, transoesophageal echocardiography, scintigraphic techniques, serum T4, intravenous pyelography, gastroscopy, funduscopy, liver biopsy, arteriography.

With regard to the **third question**, 14 of the 19 internists would not perform any screening investigations in the first stage of the diagnostic process because of the presence of PDCs. The other 5 internists would perform a variety of investigations; each of these investigations was only mentioned once or twice.

With regard to the **fourth question**, investigations most often ordered in a later diagnostic phase as a screening procedure were: liver biopsy (10 ×), abdominal CT (8 ×), CT of the chest (4 ×), bone

biopsy (4 ×), bone marrow aspiration and culture (4 ×), repeated history and physical examination (3 ×) and X-ray of the colon (3 ×). Two internists (ID-physicians) would not perform any investigations at this stage of the diagnostic process. Other investigations were mentioned once or twice: specific precipitin against bird antigens, immunoelectrophoresis, serology for human immunodeficiency virus, stools for worms and cysts, blood cultures during high fever, anergy tests, complement state, serum immunoglobulin D, serology for *Borrelia burgdorfii*, *Coxiella burnetii*, hepatitis virus A and B, scintigraphic imaging techniques including bone scintigraphy, echocardiography, CT of the brain and pituitary gland, coloscopy, ventilation/perfusion scintigraphy, bronchoscopy, gastroscopy, temporal biopsy, X-ray of ileum, ear-nose-throat investigation, splenectomy.

The response to the second part of the questionnaire yielded a series of investigations to be performed by the majority of internists as screening procedures in patients without clues to possible diagnoses (Table 2). Investigations ordered because of clues pointing to possible diagnoses are listed in Table 3. A median of 49 (range, 13–102) investigations was ordered as a screening procedure and a median of 103 (range, 19–120) investigations only on suspicion of a possible diagnosis. Again there were no significant differences between generalists and ID-physicians.

Table 2
Investigations ordered as screening procedure in the absence of possible diagnostic clues by majority of internists (> 50%) within 1 month of diagnostic workup

Biochemical
Calcium; phosphate; amylase; thyroxine; thyroid-stimulating hormone;
immune electrophoresis of serum and urine; Bence Jones in urine; C-reactive protein;
angiotensin-converting enzyme; antinuclear antigen; anti-dsDNA;
anticytoplasmic antibodies; test for rheumatoid factor;
circulating immune complexes; complement; cryoglobulin

Microbiology
Blood cultures cultured for more than 1 week;
blood, urine and gastric contents for cultures for *Mycobacterium tuberculosis*;
bone marrow culture for *Mycobacterium*, *Brucella* spp.;
faecal examination for worms and eggs;
serology for *T. pallidum*, cytomegalovirus, Epstein-Barr virus, hepatitis B virus,
Mycoplasma pneumoniae, *Yersinia enterocolitica*, *Toxoplasma gondii*;
anti-streptolysin titre; repeated PPD; Paul Bunnel test

Histology
Bone marrow aspiration; bone biopsy

Imaging procedures
Abdominal CT; fundoscopy by ophthalmologist;
X-ray sinus, teeth, ultrasonography of pelvis and heart

Table 3
Investigations ordered because of presence of possible diagnostic clues by majority of internists (> 50%)

BiochemicalHaptoglobin; vitamin B_{12}; total iron concentration; iron-binding capacity; trace elements; cortisol;
catecholamine; specific IgE; extractable nuclear antigens;
antibodies against cardiolipin, thyroglobulin, parietal cells, intrinsic factor, mitochondria,
smooth muscle, heart muscle, tubular basal membrane, glomerular basal membrane, liver cell membrane

Microbiological
Blood smear for malaria; cerebrospinal fluid culture; liver biopsy culture;
serology for hepatitis A,B,C virus, respiratory viruses, human immunodeficiency virus, poliovirus, mumps virus, Dengue, *Mycoplasma pneumoniae*, *Salmonella* spp., *Borrelia burgdorfii*, *Coxiella burnetii*, *Rickettsia* spp., *Brucella* spp., *Chlamydia psittaci*, *Leptospira* spp., *Legionella* spp., *Schistosoma* spp., *Leishmania*, *Toxocara*, *Entamoeba* spp., *Aspergillus* spp., *Listeria monocytogenes*, cryptococcal antigen

Histology
Temporal artery biopsy; skin muscle and fascia biopsy; peripheral lung biopsy; lymph node biopsy;
ileal biopsy; rectal biopsy; lip biopsy; skin biopsy; cytology of cerebrospinal fluid;
pleural biopsy or puncture

Imaging procedures
Thoracic and brain CT; bone scintigraphy; thyroid scintigraphy;
ventilation and perfusion lung scintigraphy; gallium lung scintigraphy;
X-ray of stomach, spine, ilium, pelvis, colon, hands, feet, breasts, urinary tract;
lymphography; angiography of mesenteric vessels; ultrasonography of prostrate, heart;
endoscopy of lungs, colon, bladder, stomach, biliary tract

Additional investigations
Continuous temperature measurements, diagnostic laparotomy

4. Discussion

This study was undertaken to obtain more insight into the diagnostic approach of FUO used by internists in university hospitals in the Netherlands. In our retrospective study of the diagnostic process of FUO [14] we were unable to retrieve the reasons for ordering the large array of tests. It appeared that many investigations were done as screening procedures without justification by the presence of more specific clues and to exclude diseases which could possibly cause FUO. In the present study, we found that in a case like the one presented, internists on average mention 6 diagnostic possibilities. Despite some agreement, there is also a remarkable divergence of opinion regarding the differential diagnosis and the diagnostic approach. Apparently, most internists tend to give an overview of causes of FUO, and with help of this list, they order the investigations. Although according to some reports in the literature [15,16] patients with FUO without PDCs should probably have a different diagnostic approach from those with PDCs, it is our impression that this distinction is not made by these internists. Although the case we selected for the questionnaire had very few potentially diagnostic clues, many possible diagnoses were mentioned. If PDCs are not present, it is perhaps unlikely that investigations for some of these diseases are useful. This is for instance true for *Cytomegalovirus* infection, all patients with *Cytomegalovirus* infection described in some series on FUO had lymphocytosis and atypical lymphocytes in the peripheral blood smear [1,3]. Also, patients without a heart murmur are not likely to have endocarditis [1,5]. Finally, without any blood disorders it is very unlikely that a bone marrow aspiration will lead to a diagnosis. In patients with FUO finally diagnosed as having leukaemia, all patients had anaemia or leukopenia [2,3].

When looking at Tables 2 and 3 it is obvious that many investigations are ordered in patients with FUO as screening procedures, without knowledge of the diagnostic yield of these investigations in that particular setting. This method of approach in daily practice is a reflection of many papers on FUO in which also the presence of PDCs is not taken into account when final diagnosis and outcome are discussed. This is remarkable since many authors of review papers on FUO and of chapters in textbooks suggest Sutton's law in the approach to the patient [7,8,17–19]. The problem with algorithms as proposed in the literature is that they cannot be extrapolated to highly heterogeneous groups of patients with FUO [7–13].

Table 4
Diagnostic protocol for FUO of which validity has to be examined

A. Obligatory investigations minimally performed in all patients after inclusion

Sedimentation rate; haemoglobin; mean cellular volume; platelet count; leukocyte count and differential

count; serum urea nitrogen; creatinine; sodium; potassium; protein; protein fractions; alkaline phosphatase;

aminotransferase; lactate dehydrogenase; creatine phosphokinase; antinuclear antibodies; rheumatoid factors;

urinary analysis; faeces for occult blood; blood cultures aerobic and anaerobic (3×); tuberculin test;

urine, faeces and sputum culture when indicated; chest X-ray; ultrasonography of upper abdomen

B. Phase 1 of diagnostic protocol in patients without PDCs

Pulse/rectal temperature measurement by observer; fundoscopy by an ophthalmologist;

calcium, phosphate, urate, amylase and TSH/T4; immunoelectrophoresis of serum and urine; CRP, ACE,

ANCA, anti-dsDNA, ASO, cryoglobulin, C3, C4, CH50; cytomegalovirus, Epstein-Barr virus,

Mycoplasma, *Brucella*, *Toxoplasma*, *Borrelia*, *Coxiella*, *Treponema*, *Yersinia* serology;

blood cultures incubating > 1 week, blood cultures, gastric fluid, urine cultures for tuberculosis;

stools for worms, eggs, cysts; bone marrow aspiration and culture for *Mycobacterium*, *Brucella*, *Yersinia*;

^{111}In-IgG scintigraphy, X-ray of sinus and teeth, ultrasonography of pelvis

C. Phase 2 of diagnostic protocol in patients without PDCs.

(performed when phase 1 does not reveal PDCs or diagnosis)

Hepatitis B serology; anergy tests; liver biopsy/culture for *Mycobacterium* and other bacteria and fungi;

repeated chest X-ray; IgD in serum; crista biopsy/culture for *Mycobacterium*, *Brucella* and common bacteria;

echocardiography; CT of abdomen and chest; X-ray colon; temporal artery biopsy in patients over 55 years

Abbreviations: ACE = angiotensin-converting enzyme; ANCA = antineutrophil cytoplasmic autoantibodies; ASO = antistreptolysin O test; C = complement; CH50 = total haemolytic complement; CRP = C-reactive peptide; CT = computed tomography; dsDNA = double-stranded deoxyribonucleic acid; IF = immunofluorescence; ^{111}*In-IgG* = *indium-111-labeled polyclonal human immunoglobulin G*; PDCs = *potentially diagnostic clues*; PPD = *purified protein derivative*; T4 = *thyroxine*; TSH = *thyroid-stimulating hormone*.

In this study we found that many investigations are used as screening procedures in the diagnostic process of patients with FUO whereas the diagnostic yield from these techniques in this setting has not been established. The use of diagnostic protocols and algorithms has neither been validated. We developed a standardized diagnostic protocol based on a retrospective analysis of diagnostic management [14] and data from this study. This staged protocol (Table 4) consists of an obligatory part used in the first week of admission and a two-staged diagnostic part only to be used in patients without potentially diagnostic clues (PDCs). A prospective study on the diagnostic yield of this staged screening diagnostic protocol is in progress.

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