General Internal Medicine for the Physician

Fever of unknown origin

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The recognition that fever was a symptom rather than a disease in itself is often attributed to the father of clinical thermometry, Carl Reinhold August Wunderlich[1]. The clinical and laboratory diagnosis of the various then unknown causative infectious agents became a central concern of nineteenth and early twentieth century medicine. However, the term 'fever (or pyrexia) of unknown origin' (FUO) was coined only in 1961 when Petersdorf and Beeson published their seminal series of 100 cases[2] at a time when the problem moved from the fever hospitals to the modern general hospital.

An imperfect definition

Petersdorf and Beeson defined FUO on the basis of a documented fever of above 38.3°C, persisting for more than three weeks and undiagnosed after one week of investigations in hospital. The criteria have remained largely unchanged, but the original definition has since been criticised on several grounds. First, the temperature criterion is inconsistent with what is now known about the normal range of body temperature, namely, that the 99% confidence intervals in normal subjects are 37.1°C in the morning and 37.7°C in the evening[3]. Secondly, their concern to exclude 'habitual hyperthermia'[4] – a condition for which little or no evidence exists – is now outdated. The threshold of three weeks for 'acute self-limiting infectious diseases' might also be thought over-cautious. More importantly, the panel of investigations carried out in the 'one week' in hospital has never been specified, making comparisons between studies dubious. Following proposed revisions by Durack and Street[5], Petersdorf suggested that 'one week of intelligent and intensive investigation, which in most cases could be conducted as an outpatient', would suffice. The evolution of modern medicine has led not only to a change in the speed and available means of investigation but also to the existence of groups in whom undiagnosed fever is a much more urgent problem, namely, neutropenic, HIV-positive and critically ill patients. The approach to these patients is different in detail, if not conceptually, from that of 'classical' FUO and is not dealt with specifically in this article.

A diagnostic challenge

In published case reports and series, the number of conditions presenting as an FUO has now grown to more than 200, almost none of which exceeds a prevalence of 5% in any series. The theory of diagnostic testing underscores why FUO remains such a challenge for the clinician – even a diagnostic test with a sensitivity and specificity of 95% cannot raise the post-test probability of a disease to over 50% if the pre-test probability is 5% or less. Many of the diagnostic tests available for such uncommon diseases perform considerably less well than this, and the clinician is faced with a bewildering number of unattractive bets at much less than even odds. FUO is a serious clinical situation with mortality estimated at up to 30% at one year[4], yet a diagnosis is reached in a mean of 80% of cases, in a median of three weeks[6,7]. So how can prompt and efficient diagnosis be achieved?

A clinical compass

Clinicians should be forearmed with a knowledge of the local epidemiology of the syndrome in order to be able to make a sensible estimate of the pre-test probabilities. Despite the wealth of literature on FUO, only six prospective studies[2,6–10] of more than 50 patients using an explicit definition have appeared from Europe

Table 1. Prospective studies of fever of unknown origin (FUO) in Europe and USA 1952–94.

Study	Infection	Neoplasia	Rheumatological	Miscellaneous	No diagnosis
Petersdorf[2] (1952–57)	36	19	15	23	7
Sheon[8] (1959–60)	13	10	8	6	23
Howard[9] (1969–76)	37	31	19	8	5
Larson[10] (1979–80)	32	33	18	9	13
Knockaert[6] (1980–89)	45	14	38	51	51
De Kleijn[7] (1992–94)	43	21	33	20	50
Total	*206*	*128*	*131*	*117*	*149*
% of cases	*28.2*	*17.5*	*17.9*	*16.0*	*20.4*

and the USA (Table 1). It is worth pointing out that, overall, even in recent studies from Europe the most common diagnosis, after the infectious diseases, is 'no diagnosis', followed by neoplasia, rheumatological and miscellaneous conditions. Paired retrospective studies from Spain suggest that this ranking may be undergoing change (Fig 1)[11].

In Europe, patients with FUO are usually about 50 years old. Their commonest infections are intra-abdominal abscesses, disseminated cytomegalovirus and tuberculosis (TB). The commonest rheumatological diagnosis is temporal arteritis, while haematological malignancies outnumber solid tumours by 2:1. It is useful to compare this with two recent prospective studies from Chandigarh[12] and Delhi[13] in which the commonest infections were TB, visceral leishmaniasis, typhoid and amoebic liver abscess, and the commonest rheumatological diagnosis was systemic lupus erythematosus (Fig 2). The diagnostic outcome depends not only on the local epidemiology but also on the available diagnostic facilities. Unsurprisingly, conditions which remain common to both situations are usually those for which no universally satisfactory diagnostic tests exist.

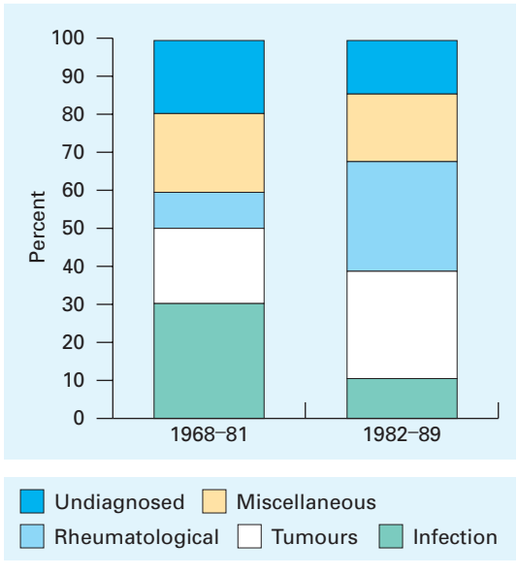

Fig 1. Changing pattern of disease in Spain 1968–81 (n=133) and 1982–89 (n=85)[11].

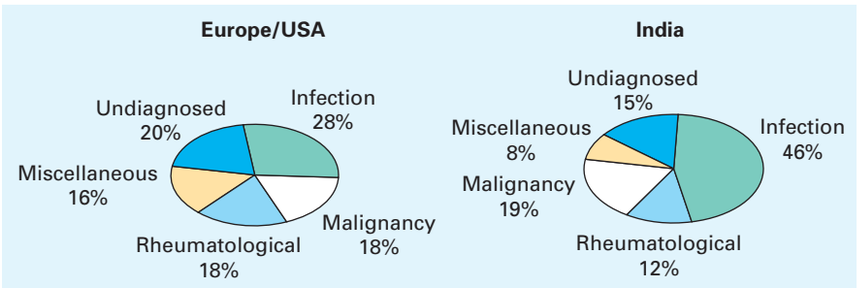

Fig 2. Spectrum of diagnoses (a) Europe/USA[2,6–10], (b) India[12,13].

The diagnostic approach

Physical examination

In the single study which prospectively examined the process of diagnosis[7], repeated clinical assessment revealed 'potentially diagnostic clues' (PDCs) in up to 90% of patients. One or more of these findings was considered to have led to the correct diagnosis in approximately two-thirds of the patients, though in retrospect only half of these had PDCs which were considered helpful. The most common PDCs were relevant past medical or social history, weight loss, headache, myalgia, arthralgia, diarrhoea, vertigo or pulmonary abnormalities.

Laboratory investigations

The application of a battery of laboratory tests (the habitual response of some clinicians to an FUO) proved inefficient if PDCs were not present – such tests were helpful in retrospect in only 1–3%, and engendered a similar rate of false-positive results[7]. For instance, abnormal liver function tests are a common finding in FUO (ca 50%), with a positive predictive value for diagnostic liver biopsy of only 8–14%[14]. However, the combination of anaemia and abnormal serum electrophoresis with a sustained pattern of fever is associated with an ultimate probability of 88% for reaching a diagnosis, whereas with a recurrent pattern in which both these tests are normal a diagnosis can be reached in only 7%[7].

Imaging

To date, advances in imaging seem to have resulted in only modest improvements in the diagnosis of FUO. Though approximately three ultrasound or computed tomography (CT) scans are carried out per patient, only about 10% are diagnostically useful[15,16]. CT may be overinterpreted, with a specificity as low as 67%[15], and it has neither increased the proportion of diagnostic biopsies[16] nor reduced the total number of invasive procedures[11]. Total body gallium-67 scanning appeared to hold great promise but has suffered from similar poor specificity[10,17]. Where specific PDCs are present, indium-111-immunoglobulin G imaging may be as useful for detecting localised inflammation[18].

Biopsy

Tissue biopsy is the commonest mode of ultimate diagnosis, but only one in four procedures is unequivocally diagnostic. Exploratory laparotomy[2,10,11,15] still has a place despite the introduction of improved non-invasive diagnostic tests and laparoscopy. Sutton's apocryphal law, to 'go where the money is', is not

generally helpful when the potential site of the fever remains inapparent[19] and can lead to unnecessary invasive investigations. Biopsy of generalised lymphadenopathy, for instance, is associated with a high diagnostic yield (≤70%), whereas biopsy of isolated cervical lymphadenopathy is almost never helpful[15]. Where PDCs are absent, the only 'blind' biopsies with a reasonable yield are bone marrow trephine[15] and temporal artery biopsy in the over-55s[20].

Prognosis

For the patient with an FUO, the maxim 'no news is good news' is generally valid. If no diagnosis can be reached after a thorough investigation, fever will resolve in over two-thirds of cases by two years, with 3% mortality in this group at five years[21]. The prognosis otherwise depends on the underlying disorder, with the highest mortality associated with malignancy.

A *deus ex machina* for modern medicine

It is likely that the diagnostic problem of the patient with FUO will never be 'solved' simply by advances in medical technology since it is irreducibly related to the nature of diagnostic reasoning and disease classification as much as to the definition itself. The management of FUO can teach physicians much about both the provisional and imprecise nature of nosology and the balancing of diagnostic zeal against maintaining the dignity and best interests of the patient.

Key Points

- **Infectious diseases remain the commonest causes of fever of unknown origin**
- **The syndrome has more than 200 causes, each with a prevalence of 5% or less**
- **Diagnosis is possible in 80% of patients in a median time of three weeks**
- **Clinical reassessment can be a useful guide to further investigations**
- **Blind diagnostic testing is not an efficient strategy and may subject the patient to multiple and unnecessary invasive procedures**
- **Mortality at one year is high, but the prognosis is good if a diagnosis is not possible after thorough work-up**

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