ELSEVIER
SAUNDERS

INFECTIOUS
DISEASE CLINICS
OF NORTH AMERICA

Infect Dis Clin N Am 21 (2007) 1213–1220

Fever of Unknown Origin: Is There a Role for Empiric Therapy?

Charles S. Bryan, MD*, Divya Ahuja, MD

Department of Medicine, University of South Carolina School of Medicine, Two Medical Park, Suite 502, Columbia, SC 29203, USA

> *Fever in its varied forms is still with us … but it is of equal importance to know that the way has been opened, and that the united efforts of many workers in many lands are day by day disarming this great enemy of the race*. William Osler, 1896 [1].

To the question posed in the title to this article, the short answer is no. Set aside those cases in which findings strongly suggest a presumptive diagnosis, such as vegetations found on echocardiography; caseating granulomas in biopsy specimens; travel to an area where certain infections, such as malaria, are endemic; or clinical features that point to adult-onset Still's disease. Set aside those cases in which impaired host defenses predispose to infections by more-or-less predictable pathogens, such as advanced AIDS and chemotherapy-induced granulocytopenia. In the remaining cases of classic community-acquired fever of unknown origin (FUO), if by FUO one means prolonged FUO ($\geq$3 weeks) with no diagnosis established after at least 1 week of intensive investigation (ie, cases that fulfill the modified Petersdorf-Beeson criteria [2–4]), continued observation while searching for a cause nearly always constitutes the best strategy. In 1963 Sheon and Van Ommen [5] wrote: "One cannot overemphasize the value of expectant management…. The use of antibiotics on an empiric basis in a patient with obscure fever may create as well as resolve diagnostic problems … the best management consists of striving to make a correct diagnosis." In 1983, Hurley [6] similarly concluded: "The patient with classic protracted fever of unknown origin requires a methodical approach, and precision is of utmost importance. Fortunately, such a patient is rarely desperately ill, so the physician has time to perform the evaluation." More recently, Mackowiak and Durack [7] state that with rare exception, "A fundamental principle in the management of

* Corresponding author.
E-mail address: cbryan@gw.mp.sc.edu (C.S. Bryan).

doi:10.1016/j.idc.2007.08.007

classic FUO is that therapy should be withheld, whenever possible, until the cause of fever has been determined, so that it can be tailored to a specific diagnosis.'' We agree.

Most infectious disease specialists rank high among their contributions to society their advocacy for curtailing indiscriminate use of antimicrobial agents. Schooled in the subtleties of diagnosis and engaged by their colleagues mainly in a consultative capacity, infectious disease specialists typically strive to temper the use of potent drugs for marginal indications. Relieved of the pressure to ''do something now'' at the first point of clinical encounter and given the advantage of ''tincture of time,'' infectious disease specialists often recognize ''mistakes'' made by other physicians. One of the authors, while preparing a textbook of infectious diseases specifically for primary care physicians, asked 600 fellows of the Infectious Diseases Society of America to checkmark from a list of 23 diagnoses those in which they had determined that a mistake by a physician acting in a primary care capacity led to some combination of death, disability, or litigation [8]. Results are shown in Table 1. One should remember, however, Calvin Coolidge's admonition that ''any fool can criticize, and most fools do.'' The authors are aware of no similar survey of mistakes made by infectious disease specialists. Many and perhaps most experienced infectious disease consultants can recall occasional cases of ''true FUO'' that they would manage differently had they the opportunity to do it over again. Consider the following two cases seen by one of the authors (CSB).

Cases

An elderly retired dentist was seen in 1975 (before the availability of transesophageal echocardiography and imaging studies based on CT and nuclear MRI) for prolonged FUO. Physical examination was unremarkable except for a systolic murmur. He continued to be febrile after 2 months of observation and studies that included liver and bone marrow biopsies. His fever seemed to respond to empiric therapy for cryptic military tuberculosis, only to recur. His fever then seemed to respond to empiric therapy for culture-negative endocarditis only to recur again. Laparotomy revealed Hodgkin's disease.

A 56-year-old woman was seen in 2007 for suspected endocarditis with acute aortic regurgitation. She gave a history of intermittent fever, chills, and malaise of 4 months' duration. Blood cultures were sterile. Endocarditis was confirmed at surgery, during which she underwent replacement of the aortic valve and drainage of an adjacent myocardial abscess. Cultures of the excised valve and material from the abscess were sterile. She was treated with a regimen currently recommended for culture-negative endocarditis that, however, was probably inadequate for *Bartonella henselae*, subsequently identified by polymerase chain reaction of the excised heart valve and confirmed by silver stain and by serology (IgG titer $>1{:}512$). At the

Table 1
Frequency of diseases in which mistakes made by primary care physicians resulted in serious consequences

Condition	No. (%) of positive responses
Necrotizing soft tissue infection	112 (64)
Spinal epidural abscess	96 (55)
Sepsis syndrome	95 (54)
Endocarditis	94 (54)
Meningococcal disease	89 (51)
Tuberculosis	84 (48)
Herpes simplex encephalitis	82 (47)
Antibiotic toxicity	82 (47)
Pneumonia	80 (46)
Pneumococcal meningitis	80 (46)
Intra-abdominal sepsis	59 (34)
AIDS-related problem	58 (33)
Brain abscess	58 (33)
Toxic shock syndrome	58 (33)
Asplenia (failure to vaccinate)	57 (33)
Rocky Mountain spotted fever	54 (31)
Travel-related problems	54 (31)
Acute epiglottitis	35 (20)
Pelvic inflammatory disease	32 (18)
Clostridial syndrome	31 (18)
Haemophilus influenzae meningitis	29 (17)
Sphenoid sinusitis	22 (13)
Cavernous sinus thrombosis	21 (12)
Miscellaneous	32 (18)

From a survey sent to 600 fellows of the Infectious Diseases Society of America. The survey instrument listed 23 diagnoses (shown here) and asked the recipients to checkmark those diagnoses in which, in their experience, mistakes made by a physician acting in a primary care capacity had led to death, disability, or litigation. The rate of the response to the survey was 30%. These data do not indicate the actual incidence of mistakes made by primary care physicians, which some data suggest is relatively low. Rather, they indicate pitfalls in diagnosis and disease management as seen from the perspective of infectious disease specialists, who are usually consulted on especially difficult cases.

Data from Bryan CS. Infectious disease emergencies. In: Bryan CS, editor. Infectious diseases in primary care. Philadelphia: WB Saunders; 2002. p. 111–52.

time of this writing, she is asymptomatic and receiving appropriate therapy for *Bartonella* endocarditis.

In the first case, early laparotomy would have been preferable to empiric therapy because, in retrospect, the Pel-Ebstein fever of Hodgkin's disease toyed with the consultant. In the second case, which probably represents the first case of *B henselae* endocarditis reported from South Carolina, closer attention to the history would have facilitated earlier diagnosis because the patient had been scratched and bitten by a feral kitten before the onset of symptoms. These cases illustrate the truism that, as one internal medicine

resident put it, ''The three most important principles in medicine are diagnosis, diagnosis, and diagnosis.''

The generally favorable prognosis of prolonged fever of unknown origin that defies diagnosis

Studies to date suggest that cases of FUO that defy precise diagnosis after intensive investigation and prolonged observation generally carry a favorable prognosis. Larson and colleagues [9], in whose series 12% of 105 cases of FUO persisted without a diagnosis on follow-up, divided such fevers into two categories: those that resolved over time and those that did not. Most patients in the former group, they concluded, had ''an illness which best fits a self-limited prolonged viral infection,'' often with some combination of lymphadenopathy, splenomegaly, hepatomegaly, and abnormal liver function tests. Their five patients with prolonged or recurrent, undiagnosed FUO were all alive at the time of their publication. Knockaert and colleagues [10], in whose series 11% of 199 cases of FUO persisted without a diagnosis on follow-up for at least 5 years, determined the attributable mortality of undiagnosed FUO to be only 3.2%. These Belgian investigators also described 45 cases of ''recurrent or episodic'' FUO, defined as FUO meeting the Petersdorf-Beeson criteria but with fever-free intervals of at least 2 weeks' duration [11]. Only one death attributable to FUO occurred among the 23 patients for whom no final diagnosis was ever reached; the patient, who had refused readmission to the hospital, was suspected to have had temporal arteritis.

Situations that sometimes call for empiric therapy of fever of unknown origin, and the case for symptomatic therapy

Cunha [12] in 1996 recommended empiric therapy for FUO in only four situations: (1) antibiotics for culture-negative endocarditis; (2) low-dose corticosteroids for presumed temporal arteritis; (3) antituberculous drugs for suspected military tuberculosis in elderly patients; and (4) naproxen for suspected neoplastic fever. These four conditions are briefly reviewed next after first addressing the advisability of symptomatic therapy with corticosteroids or nonsteroidal anti-inflammatory agents (NSAIDs) for FUO.

A small, anecdotal, and amorphous body of published literature suggests a limited role for corticosteroids and NSAIDs for symptomatic therapy of FUO. Larson and colleagues [9] reported that anti-inflammatory drugs were only transiently successful, if at all, in those patients whose fevers resolved spontaneously and without a diagnosis. Two patients with febrile illnesses lasting 7 years or more, however, were concluded to have a steroid-responsive form of focal hepatitis. Larson and colleagues [9] referred to ''apparently similar patients'' with benign but chronic, steroid-responsive

FUO described in a personal communication by R.P. Aduan and D.C. Dale of the National Institutes of Health. Unfortunately, a MEDLINE search reveals no papers on FUO by either of these investigators. Larson and colleagues [9] also described cases resembling temporal arteritis, polymyalgia rheumatica, vasculitis, or adult-onset Still's disease that responded to steroids but for which no definitive diagnosis was reached. Knockaert and colleagues [10] reported that, among their 18 patients with prolonged undiagnosed FUO, four were treated with steroids and six with NSAIDs. They concluded that NSAIDs usually sufficed for symptomatic patients. Similarly, among their 21 surviving patients with "recurrent or episodic" FUO for whom no diagnosis was reached, seven received intermittent short-term therapy with NSAIDs or corticosteroids. There is probably a limited role for cautious use of NSAIDs or corticosteroids in symptomatic patients who are well-informed of the potential pitfalls of such therapy. As Larson and colleagues [9] put it, "There is no substitute for observing the patient, talking to him, and thinking about him," a process that involves "going over the patient again and again, repeating the history and physical examination, reviewing the chart, discussing the problem with colleagues to glean new ideas, and spending time in quiet contemplation of the clinical enigma."

Culture-negative endocarditis

Although data published through the years indicate that up to 31% of cases of infective endocarditis have sterile blood cultures, more recent studies suggest that only about 5% of cases are culture-negative when defined by strict criteria, sometimes backed by transesophageal echocardiography. Apart from cases in injecting drug users, optimum management remains controversial. Albrich and colleagues [13] have recently published a structured approach to diagnosis and management along with an extremely useful algorithm. Infectious disease consultants would do well to keep their paper and also the paper by Broqui and Raoult [14] on endocarditis caused by rare and fastidious microorganisms on file, because the distribution of recognized causes of culture-negative endocarditis seems to be changing. Application of polymerase chain reaction to excised heart valves can be of great value in cases that require surgical intervention [15,16]. There is general agreement that a regimen for empiric therapy should be appropriate for enterococci, nutrient-variant streptococci, and fastidious gram-negative bacilli of the HACEK group. To that end, an appropriate regimen consists of penicillin or ampicillin plus gentamicin or streptomycin plus ceftriaxone [17,18].

Cryptic disseminated tuberculosis

Current guidelines from the Centers for Disease Control and Prevention support the use of drugs for strongly suspected culture-negative pulmonary tuberculosis [19]. These guidelines are largely silent, however, on the issue of

when to treat suspected disseminated tuberculosis. This diagnosis should be suspected especially in elderly patients, who may present with an afebrile wasting illness [20]; in febrile patients with HIV-AIDS; in patients with rheumatoid arthritis treated with corticosteroids, methotrexate, or infliximab [21]; and in recipients of solid organ transplants [22]. There are no clear guidelines on what constitutes an adequate duration of a therapeutic trial in this situation. Because the bacillary populations of the individual lesions are substantially lower than those encountered in cavitary pulmonary tuberculosis, however, a response usually becomes apparent within 2 months unless the disease is caused by a multidrug-resistant strain. Patients should be informed of the potential for adverse reactions including hepatitis from isoniazid, optic neuritis from ethambutol, and drug interactions from rifamycin derivatives.

Temporal arteritis (giant cell arteritis)

Management of suspected temporal arteritis, an important cause of FUO in elderly persons sometimes complicated by blindness or cerebrovascular accident, is discussed elsewhere in this issue. Suspected visual impairment mandates immediate therapy with corticosteroids, because treatment after the onset of loss of visual acuity or central visual field defects rarely restores these deficits, and then only when corticosteroids are begun within 4 days of the onset of visual symptoms [23]. Temporal artery biopsy remains highly desirable and should be performed within 2 weeks from starting corticosteroids despite reports that characteristic changes are sometimes found when biopsies are delayed for longer periods [24]. Some data suggest that the addition of low-dose aspirin to a corticosteroid regimen lowers the incidence of intracranial ischemic events [25].

The naproxen test for differentiating between neoplastic and other causes of fever of unknown origin

Brief mention should be made of the naproxen test, because it was included among the indications for empiric therapy in Cunha's review [12] published in 1996. The naproxen test dates to a 1984 report by Chang and Gross to the effect that naproxen, a NSAID, induced a prompt, complete, and sustained lysis of fever in 14 of 15 cases of fever caused by neoplasm but in none of five cases of fever caused by infection [26]. More recently, Vandeerschuren and colleagues [27] concluded the naproxen test to be only 55% sensitive and 62% specific for neoplastic FUO. In retrospect, earlier investigators did not use tight criteria for FUO and may have had selection bias toward cases likely to be of neoplastic etiology. Moreover, there is no good theoretical explanation as to why NSAIDs should uniquely lyse fever caused by neoplasms and not fever from other causes [28].

Summary

The practice of medicine revolves around three questions: (1) What is wrong with the patient? (2) What can I do for the patient? (3) What will be the likely outcome? The advice of Celsus (25 BC–AD 50) that "better a doubtful remedy than none at all" generally rings true for acute life-threatening illnesses but seldom holds for cases of prolonged FUO ($\geq$3 weeks) that satisfy the modified Petersdorf-Beeson criteria. Patients with prolonged FUO and for whom no diagnosis is reached after months and years of intense observation generally have a favorable prognosis. Empiric therapy should be used only in carefully defined circumstances, with the patient's informed consent, and with the physician's commitment to keep searching for an etiology.

References

[1] Osler W. The study of the fevers of the South. JAMA 1896;26:999–1004.
[2] Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine (Baltimore) 1961;40:1–30.
[3] Durack DT, Street AC. Fever of unknown origin: reexamined and redefined. In: Remington JS, Swartz MN, editors. Current clinical topics in infectious diseases, vol. 3. Boston: Blackwell Science; 1991. p. 35–51.
[4] Bryan CS. Fever of unknown origin: the evolving definition. Arch Intern Med 2003;163: 1003–4.
[5] Sheon RP, Van Ommen RA. Fever of obscure origin. Am J Med 1963;34:486–99.
[6] Hurley DL. Fever in adults: what to do when the cause is not obvious. Postgrad Med 1983; 74:232–44.
[7] Mackowiak PA, Durack DT. Fever of unknown origin. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. 6th edition. Philadelphia: Elsevier Churchill Livingstone; 2005. p. 718–29.
[8] Bryan CS. Infectious disease emergencies. In: Bryan CS, editor. Infectious diseases in primary care. Philadelphia: W.B. Saunders Company; 2002. p. 111–52.
[9] Larson EB, Featherstone HJ, Petersdorf FG. Fever of undetermined origin: diagnosis and follow-up of 105 cases, 1970–1980. Medicine (Baltimore) 1982;61:269–92.
[10] Knockaert DC, Dujardin KS, Bobbaers HJ. Long-term follow-up of patients with undiagnosed fever of unknown origin. Arch Intern Med 1996;156:618–20.
[11] Knockaert DC, Vanneste LJ, Bobbaers HJ. Recurrent or episodic fever of unknown origin: review of 45 cases and survey of the literature. Medicine (Baltimore) 1993;72:184–96.
[12] Cunha BA. Fever of unknown origin. Infect Dis Clin North Am 1996;10:111–27.
[13] Albrich WC, Kraft C, Fisk T, et al. A mechanic with a bad valve: blood-culture-negative endocarditis. Lancet Infect Dis 2004;4:777–84.
[14] Broqui P, Raoult D. Endocarditis due to rare and fastidious bacteria. Clin Microbiol Rev 2001;14:177–207.
[15] Qin X, Urdahl KB. PCR and sequencing of independent genetic targets for the diagnosis of culture negative bacterial endocarditis. Diagn Microbiol Infect Dis 2001;40:145–9.
[16] Khulordava I, Miller G, Haas D, et al. Identification of the bacterial etiology of culture-negative endocarditis by amplification and sequencing of a small ribosomal RNA gene. Diagn Microbiol Infect Dis 2003;46:9–11.
[17] Fowler VG, Scheld WM, Bayer AS. Endocarditis and intravascular infections. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. 6th edition. Philadelphia: Churchill Livingstone; 2005. p. 975–1022.

[18] Moreillon P. Endocarditis and endarteritis. In: Cohen J, Powderly WG, editors. Cohen and Powderly: infectious diseases, vol. 1. 2nd edition. St. Louis: Mosby; 2004. p. 653–68.
[19] American Thoracic Society, CDC, and Infectious Diseases Society of America. Treatment of tuberculosis. MMWR Morb Mortal Wkly Rep 2003;52(No. RR-11):1–77.
[20] Ozbay B, Uzan K. Extrapulmonary tuberculosis in high prevalence of tuberculosis and low prevalence of HIV. Clin Chest Med 2002;23:351–4.
[21] Mayordomo L, Marenco JL, Gomez-Mateos J, et al. Pulmonary miliary tuberculosis in a patient with anti-TNF-alpha treatment. Scand J Rheumatol 2002;31:44–5.
[22] Korner MM, Hirata N, Tenderich G, et al. Tuberculosis in heart transplant recipients. Chest 1997;111:365–9.
[23] Hayreh SS, Zimmerman B, Kardon RH. Visual improvement with corticosteroid therapy in giant cell arteritis: report of a large study and review of literature. Acta Ophthalmol Scand 2002;80:353–67.
[24] Ah Kine D, Tijani SO, Parums DV, et al. Effects of prior steroid treatment on temporal artery biopsy findings in giant cell arteritis. Br J Ophthalmol 2002;86:530–2.
[25] Nesher G, Berkun Y, Mates M, et al. Low-dose aspirin and prevention of cranial ischemic complications in giant cell arteritis. Arthritis Rheum 2004;50:1332–7.
[26] Chang JC, Gross HM. Utility of naproxen in the differential diagnosis of fever of undetermined origin in patients with cancer. Am J Med 1984;76:597–603.
[27] Vanderschueren S, Knockaert DC, Peetermans WE, et al. Lack of value of the naproxen test in the differential diagnosis of prolonged fever. Am J Med 2003;115:572–5.
[28] Plaisance KI, Mackowiak PA. Antipyretic fever: physiologic rationale, diagnostic implications, and clinical consequences. Arch Intern Med 2000;160:449–56.