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 the ribs overlying the posterior surface of the liver which may elicit tenderness in patients with posterior liver abscesses. Tenderness in the right iliac fossa might indicate bowel-related sepsis, such as an appendix mass, while bimanual examination may reveal an enlarged or tender kidney. The patient's posture should be noted; flexion of the hip points to a possible psoas abscess. Examination of the peri- neum is mandatory in febrile neutropenic patients; it may reveal septic necrosis spreading from the rectum. Enlarged lymph nodes should be carefully sought in the neck and in the axilla, where they are easily overlooked. The entire skin should be inspected for rash or for areas of inflammation. The spine should be palpated and percussed looking for angulation or tenderness. The nervous system should be examined if there is evidence of menin- gitis, encephalitis, or focal neurological symptoms. Investigations These should be phased in the interests of both time and money and to avoid misleading false-positives. Initial blood tests must include a specific test for malaria if the patient has travelled to an endemic area. Blood samples for culture should be taken before antibiotics are started. Patients who have been started on antibiotics before in- vestigation should have them stopped, provided it is judged safe to do so, and blood taken for culture 24 h later. The chest radiograph should be inspected on admission. A chest radiograph may reveal areas of consolidation in patients without any respiratory symptoms and hilar lymphadenopathy in patients without palpably enlarged nodes elsewhere. Conversely, a normal chest radiograph does not exclude early pneumonia. All patients should have a properly taken midstream or clean-catch urine sample sent for analysis. Liaison with the microbiology laboratory is essential, and prompt delivery of specimens is a priority. Investigations involving cell counts (i.e. cerebrospinal fluid and urine microscopy), must be car- ried out on the day they were obtained. Initial investigations are therefore: • Background—full blood count, urea and electrolytes, liver func- tion tests, C-reactive protein • Specific—blood culture, malaria test if indicated, urine analysis, chest radiograph In assessing the results of these tests, the clinician must be aware of the significance of collateral effects, such as thrombocytopenia in dissem- inated intravascular coagulation and malaria, and moderate elevations of transaminases in bacteraemia from any focus. The nature of bacteria isolated from blood culture often indicates the need for attention to a likely source (e.g. Streptococcus viridans to endocarditis, Streptococcus milleri to

endocarditis or liver abscess, Streptococcus bovis to both endo- carditis and neoplasm of the colon), while a mixture of Gram-negative rods and anaerobes points to liver abscess or gut-related sepsis. Second phase investigations If the initial investigations do not point to a particular focus, imaging of the abdomen should be performed. Ultrasound examination is good for detecting fully liquefied liver abscesses and hydronephrosis and may point to focal sepsis or enlarged nodes. If ultrasound is negative, a CT scan should be considered. Increasingly PET/CT scanning is used in the investigation of unexplained fever. Therapeutic trials A therapeutic trial of an antibacterial may be indicated when, for example, the patient reports temporary improvement following a previous course and the investigations outlined above have proved unhelpful. The spectrum covered by the previous antibiotic should be taken into consideration when selecting the trial agent. For example, a response to flucloxacillin might suggest the need for a more protracted course of antistaphylococcal therapy. It is essential to compare the re- sponse to treatment with the response expected in the condition that has been provisionally diagnosed. In most bacterial infections pyrexia will settle within 48 h of starting appropriate antibacterial therapy, but there are notable exceptions, including typhoid fever, any abscess with a volume of more than about 10 ml, and conditions in which there is a significant host response to the infection, such as the development of pleural effusion in patients with pneumococcal pneumonia. A trial of antituberculosis chemotherapy is routine in patients in whom this infection is likely on clinical grounds, while awaiting cul- ture results. It should also be considered when a tissue biopsy reveals granulomata. Finally, when the history suggests the possibility of systemic Still's disease with criteria either fulfilled or approximated, or when a pa- tient over the age of 50 has intermittent fever and symptoms con- sistent with giant cell arteritis, a trial of corticosteroids should be considered. This should not be delayed, but if the patient does not show clear improvement within 5 days of starting prednisolone 60 mg daily, the trial should be stopped. Such a course carries only a small risk of significant adverse effects, and the likelihood of infec- tion 'lighting up' is, in practice, very small. 8.2.2 Fever of unknown origin Steven Vanderschueren ESSENTIALS Fever of unknown origin refers to a prolonged febrile illness that per- sists without diagnosis after careful initial assessment. Although over 200 causes have been described, including rare diseases, most cases are due to familiar entities presenting in an atypical fashion. Causes of fever of unknown origin—the 'big three' are (1) infections— including tuberculosis, endocarditis, abdominal and hepatobiliary infections and abscesses, complicated genitourinary tract infections, pleuropulmonary infections, bone and joint infections, salmonellosis, cytomegalovirus, Epstein–Barr virus, and HIV; (2) tumours—including lymphoma; and (3) multisystem inflammatory conditions—including connective tissue diseases, vasculitic syndromes, and granulomatous disorders. A miscellaneous category including factitious fever, ha- bitual hyperthermia, and drug fever deserves consideration early in

 a patient's workup, since timely recognition may avert invasive and expensive procedures. Clinical approach to the patient with fever of unknown origin— the clinician must rely on a very careful and thorough clinical his- tory and examination that does not neglect any part of the body, followed by appropriately targeted investigations directed by knowledge of the broad spectrum of diseases and local epidemi- ology. As advocated by Sutton's law—'go where the money is'— the approach should follow any possible diagnostic clues, which may sometimes be subtle. If clues are absent or prove misleading, then screening imaging techniques can focus further investigation, but a rigid algorithm and a blind pursuit of increasingly complex tests are ill-advised. Likewise, therapeutic trials without firm founda- tion are rarely

diagnostically rewarding. If the diagnosis in a stable patient remains elusive despite vigorous effort, a watchful waiting approach is warranted as most patients with fever of persistently unknown origin do well. Definition Original definition Most fevers are readily explained or resolve rapidly. Fever with un- clear cause or source at first sight should not be labelled fever (or pyrexia) of unknown (or undetermined) origin (FUO). Defined properly, true FUO is uncommon and is encountered once or twice a month at most teaching hospitals. A strict definition, which should not be changed too rapidly, is necessary for comparison of litera- ture data and to guide clinicians faced with this rather rare clinical problem. The three criteria initially proposed by Petersdorf and Beeson in 1961 are: (1) an illness of at least 3 weeks' duration, (2) a fever (temperature more than 38.3°C on at least three occasions), and (3) no established diagnosis after 1 week of hospital investiga- tion. The first criterion eliminates acute, self-limiting, frequently viral diseases and the second eliminates habitual hyperthermia, an entity commonly diagnosed at that time. Update of the initial definition In 1991, Durack and Street suggested modification of the third criterion to an uncertain diagnosis after at least three outpatient visits or at least 3 days in hospital. This revision reflected trends in medical practice, including a shift towards outpatient manage- ment, advances in diagnostic techniques, and an accelerated pace of investigation. They also divided FUO into four groups: classic FUO, nosocomial FUO, neutropenic FUO, and HIV-associated FUO. In the last three groups the case mixture differs from that of classic FUO, and the predominance of nosocomial and op- portunistic infections in these often frail patients frequently justifies early empirical antimicrobial therapy. The present chapter focuses on classic, community-acquired FUO in immunocompe- tent adults. Contemporary definition of classic fever of unknown origin Recently, it has been suggested that the third criterion should be changed from a quantitative to a qualitative one, specifying which particular examinations are necessary before an unsolved prolonged febrile illness classifies as FUO, rather than an arbitrary number of hospital days or outpatient visits. These minimum re- quirements (Box 8.2.2.1) should be adapted to regional, mainly infectious, epidemiological factors. Finally, a protracted unex- plained febrile illness with fever below 38.3°C but with persist- ently raised inflammatory markers should probably be approached similarly. These proposed changes culminated in a modern defin- ition of classic FUO (Box 8.2.2.2), which can be used for the next few decades. Causes Diagnostic spectrum The list of differential diagnoses is among the longest and most challenging in internal medicine, encompassing more than 200 entities. Common and uncommon causes of FUO in adults are listed in Boxes 8.2.2.3 and 8.2.2.4. These causes are conveniently classified into five categories: (1) infections, (2) malignancies, Box 8.2.2.1 Minimum diagnostic evaluation to qualify as fever of unknown origin • Comprehensive history (including accompanying symptoms, travel history, sexual risk behaviour, profession, hobbies, contact with ani- mals (pets, birds, insects) and ill persons, family history, use of medi- cations and illicit drugs, past medical and surgical history, transfusion, presence of foreign material) • Meticulous physical examination (eyes, mucosal surfaces, temporal arteries, skin, hands and nails, lymph nodes, thyroid, heart, lungs, ab- domen, genitalia, rectal examination, musculoskeletal system, neuro- logical examination, vascular examination) • Erythrocyte sedimentation rate, C-reactive protein, serum protein electrophoresis • Complete blood count, including differential and platelet count • Routine blood chemistry, including creatinine, sodium, potassium, lac- tate dehydrogenase, bilirubin, liver enzymes, creatine kinase • Antinuclear and antineutrophil cytoplasmic antibodies • Urinalysis, including microscopic examination • Routine blood and urine cultures taken while not receiving antibiotics, cultures of other normally sterile fluids (e.g. from joints, pleura, or cere- brospinal space) whenever appropriate • Tuberculin skin test or interferon-γ release assay (IGRA) • Chest radiograph •

Abdominal ultrasonography (including pelvis) • Further evaluation of any abnormalities detected by above tests (e.g. HIV serology, hepatitis serology, echocardiography in case of cardiac murmur, blood smear for malaria in the traveller, Epstein–Barr virus, and cytomegalovirus serology in case of reactive lymphocytosis) Box 8.2.2.2 Modern definition of classic fever of unknown origin • Illness of more than 3 weeks duration • Temperature of at least 38.3°C, or lower temperature with laboratory signs of inflammation, on at least three occasions • No diagnosis or reasonable (eventually confirmed) diagnostic hypoth- esis after an initial diagnostic investigationa • Exclusion of nosocomial fevers and severe immunocompromise aSee Box 8.2.2.1.

 (3) noninfectious inflammatory diseases, (4) miscellaneous causes, and (5) undiagnosed cases. Infections predominated in earlier case series, in paediatric series, and in series from developing countries and from secondary care hospitals. In recent series from western European and Japanese referral centres, non- infectious inflammatory disease (comprising connective tissue disorders, vasculitides, and granulomatous disorders) surpassed infections as the most prevalent category. Despite innovative rapid microbiological techniques, old and emerging infectious dis- eases will remain an important source of FUO, due to increasing global travel, migration, implantation of devices, and resistance of microorganisms. Somewhat counterintuitively, the proportion of undiagnosed cases is highest in referral centres and has risen over recent decades, amounting to 25–50% of cases. This apparent loss of diagnostic yield is partially attributable to the improved diagnostic armamentarium that reveals the aetiology or source well before a febrile illness turns into FUO. Yet the cause of some prolonged fevers remains unknown despite vigorous clinical Box 8.2.2.3 Common causes of classic fever of unknown origin in adults Infections • Tuberculosis • Endocarditis • Abdominal and hepatobiliary infections and abscesses • Complicated genitourinary tract infections • Pleuropulmonary infections • Bone and joint infections • Salmonellosis (including typhoid fever) • Cytomegalovirus, Epstein–Barr virus, HIV Neoplasms • Haematological - Non-Hodgkin’s lymphoma - Hodgkin’s disease - Leukaemia • Solid - Adenocarcinoma (e.g. colon, kidney) Metastatic Noninfectious inflammatory diseases • Connective tissue diseases - Adult-onset Still’s disease - Polymyalgia rheumatica - Rheumatoid arthritis - Sjögren’s syndrome - Systemic lupus erythematosus • Vasculitis syndromes - Giant cell arteritis - Polyarteritis nodosa - Granulomatosis with polyangiitis • Granulomatous disorders - Inflammatory bowel disease - Sarcoidosis Miscellaneous • Drug fever • Habitual hyperthermia • Factitious fever • Subacute thyroiditis • Venous thromboembolism • Haematoma Box 8.2.2.4 Rare causes of fever of unknown origin in adults Infections • Bartonellosis (including Bartonella henselae, B. quintana), brucellosis, campylobacteriosis, gonococcaemia, melioidosis, meningococcemia, listeriosis, tularaemia, yersiniosis • Chlamydial infections (including psittacosis), ehrlichioses, rickettsioses, Coxiella burnetii (Q fever) • Nontuberculous mycobacteria, leprosy • Febris recurrens, leptospirosis, Lyme disease, rat-bite fever, syphilis • Actinomycosis, nocardiosis, Whipple’s disease • Human herpesvirus type 8, parvovirus B19 • Aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococ cosis, histoplasmosis, mucormycosis, pneumocystosis, sporotrichosis • Amoebiasis, babesiosis, echinococcosis, fascioliasis, malaria, leish- maniasis, schistosomiasis, toxocariasis, toxoplasmosis, trichinosis, trypanosomiasis • Malakoplakia, xanthogranulomatous pyelonephritis • Central nervous system infection, dental infection, upper respiratory tract infection, wound infection • Intravenous catheter infection, infected vascular graft, mycotic aneurysm Neoplasms and related conditions • Haematological malignancies - Angioimmunoblastic T-cell lymphoma - Intravascular lymphoma - Amyloidosis - Hypereosinophilic syndrome - Multiple myeloma - Myelodysplastic syndromes - Myelofibrosis • Solid tumours - Atrial myxoma - Hepatoma - Renal cell

carcinoma - Other (more than 30 reported), with or without necrosis, with or without metastases Noninfectious inflammatory diseases • Connective tissue diseases - Acute rheumatic fever - Crystal-induced arthropathy - Eosinophilic fasciitis - Felty's syndrome - Mixed connective tissue disease - Inflammatory myositis - Relapsing polychondritis - Seronegative spondylarthropathy • Vasculitis syndromes - Behçet's disease - Henoch–Schönlein purpura - Mixed cryoglobulinaemia - Takayasu's arteritis - Urticarial vasculitis Miscellaneous • Addison's disease, hyperparathyroidism, hyperthyroidism, hypothal- amic hypopituitarism, phaeochromocytoma • Erythema multiforme, erythema nodosum, linear IgA dermatosis, Sweet's disease • Castleman's disease, inflammatory pseudotumour of lymph nodes, Kikuchi's disease • Vogt–Koyanagi–Harada syndrome (continued)

8.2.2 Fever of unknown origin 667 efforts. In larger series, even autopsy failed to unravel the cause of the FUO in a substantial minority. Subpopulations The cause of FUO differs among subpopulations. The importance of geographical origin and the immune status of the host have already been alluded to, and age matters as well. In older people, giant cell arteritis, tuberculosis, malignancies, and drug fever are important considerations, while in younger adults, viral infections, particularly cytomegalovirus infection, adult-onset Still's disease, habitual hyper- thermia, factitious fever, and undiagnosed cases are more prevalent. In recurrent or episodic FUO, defined as at least two episodes of fever with fever-free intervals of at least 2 weeks and seeming remis- sion of the underlying illness, traditional causes such as infections and malignancies are less frequently implicated. Recurrent FUO is especially challenging, as a final diagnosis is established in no more than one-half of the patients. As the duration of the fever increases, the likelihood of an infectious cause decreases. Common diseases prevail Although the possible aetiologies of FUO are myriad, a limited list of disorders (Box 8.2.2.3) accounted for the great majority of diag- noses in published series. Most patients do not have esoteric dis- eases, unfamiliar to the clinician, but rather are exhibiting atypical manifestations of common illnesses. A few examples may illustrate this point. The forms of tuberculosis that give rise to FUO are often disseminated disease, yet without the characteristic miliary pattern on chest radiograph, or extrapulmonary disease without clear lo- calizing features; tuberculin skin tests and sputum smears are often negative. The forms of endocarditis that enter the FUO spectrum are frequently culture-negative or are caused by fastidious organ- isms; a new regurgitant murmur or signs of peripheral emboli are frequently absent. Leukaemia presents as an FUO characteristically in the aleukaemic phase. Giant cell arteritis may manifest with con- stitutional symptoms only (anorexia, weight loss, fever), without polymyalgia or arteritic signs and symptoms, and without a strik- ingly elevated erythrocyte sedimentation rate. Likewise, in sub- acute thyroiditis, localizing symptoms and signs may be subtle or nonexistent. Approach to the adult with classic fever of unknown origin Ruling out the 'little three' For didactic and practical purposes, it is convenient to split the aeti- ologies into the 'big three' and the 'little three'. The 'big three' are infections, neoplasms, and noninfectious inflammatory diseases, which together represent the bulk of diagnoses. The 'little three' comprise factitious fever, habitual hyperthermia, and drug fever. While these three causes are numerically less important, consid- ering them from the start may prevent painstaking and invasive investigations. For this reason, at an early stage, fever should be verified, temperature charts recorded, and an effort made to stop all nonessential medications and switch essential ones to unrelated alternatives. Factitious fever Due to either manipulation of the thermometer or self-induced disease (e.g. by self-injection of contaminated materials), this characteristically occurs in young women, often health profes- sionals. Discrepancy between symptoms and clinical and labora- tory findings raises the suspicion of fraudulent fever. Unexplained polymicrobial

bacteraemia, serial episodes of bacteraemia by dif- ferent pathogens, or recurrent soft tissue infections suggest self- induced infection. Habitual hyperthermia This is also seen mainly in young women who complain of ‘flu-like’ and functional symptoms. In this syndrome, which overlaps with chronic fatigue syndrome and fibromyalgia, the diurnal variation in body temperature is maintained. Evening temperatures are on average 0.5°C higher than morning temperatures, body temperature rises especially following physical and intellectual activity, the re- sponse to antipyretics is poor, and temperatures only occasionally exceed 38.3°C. Laboratory evaluation, including acute-phase react- ants, is entirely unremarkable. Drug fever Virtually any drug can cause fever, with the possible exceptions of digitalis and aminoglycosides. The mechanisms are multiple and often poorly understood, with hypersensitivity being most common. Examples of drugs causing FUO include anticonvul- sants, antimicrobials (such as minocycline, β-lactams, vanco- mycin, sulphonamides, and nitrofurantoin), antihistamines, nonsteroidal anti-inflammatory drugs (including salicylates), antihypertensives (hydralazine, methyldopa), antiarrhythmics (quinidine, procainamide), and allopurinol. Patients may have been on the offending drug for prolonged periods. Fever is rarely the sole Box 8.2.2.4 Continued • Giant haemangioma • Dissecting aneurysm • IgG4-related disorders • Thrombophlebitis • Cholesterol embolism, polytetrafluoroethylene (Teflon) embolism, silicone embolism • Antiphospholipid syndrome • Cyclic neutropenia, haemolytic anaemia, haemoglobinopathies, macrophage activation (haemophagocytic) syndrome, vitamin B12 deficiency • Schnitzler’s syndrome • Dressler’s syndrome (postmyocardial infarction syndrome) • Cerebrovascular accident, epilepsy • Alcoholic hepatitis, autoimmune hepatitis, cirrhosis (with active ne- crosis), primary sclerosing cholangitis • Extrinsic allergic alveolitis, hypersensitivity pneumonitis, interstitial pneumonia • Hereditary periodic fever syndromes (familial Mediterranean fever, tumour necrosis factor receptor-1-associated periodic syndrome, hyper-IgD syndrome, Muckle–Wells syndrome, familial cold autoin flammatory syndrome) • Gaucher’s disease, Fabry’s disease • Hypertriglyceridaemia • Erdheim–Chester disease

 manifestation but may be accompanied by rash, urticaria, mucosal ulceration, eosinophilia, and other haematological abnormalities, hepatic or renal dysfunction, or pulmonary involvement. Phenytoin and carbamazepine are notorious for inducing a pseudolymphoma syndrome. Some patients with drug fever look severely ill and toxic, while others look and feel surprisingly well. Withdrawal of the offending drug usually results in defervescence within 72–96 hours. Rechallenge is generally safe unless organ damage (e.g. hepatitis or interstitial nephritis) has occurred, but is rarely performed in clin- ical practice. Formal allergy testing is sometimes used to confirm the diagnosis of drug allergy, particularly if the patient appears to have multiple drug allergies or is likely to require treatment with a particular drug or related drugs in the future. Fever characteristics While recording and monitoring of body temperature are imperative, fever height and pattern do not contribute much to diagnosis. The few entities that have a distinctive fever pattern (e.g. non-falciparum malaria or cyclic neutropenia) are rare, as are fever patterns thought to be characteristic of other diseases, such as Pel–Ebstein fever (a relapsing fever that disappears and reappears at intervals of several days) in Hodgkin’s disease. Other features that lack diagnostic dis- crimination among the numerous sources of FUO are the presence of night sweats, weight loss, chills, and relative bradycardia (a heart rate lower than expected for the degree of fever). The naproxen test was proposed on the assumption of a selective antipyretic activity against neoplastic fever, but in clinical practice the accuracy of this test too is too low to be discriminatory. Go where the money is The diagnostician confronted with FUO should keep in mind Sutton’s law: ‘go where the money is’. Possible diagnostic clues elicited from the history, physical

examination, and the prelim- inary diagnostic evaluation (Box 8.2.2.1) should, of course, guide further investigation, but many cases become a FUO because these clues are misleading. Whenever possible, the clinician should strive to achieve microbiological or pathological confirmation. Any sus- pected focal abnormality that is accessible should be aspirated or biopsied. Close communication with the microbiologist and the pathologist will increase the diagnostic yield. Molecular methods, such as polymerase chain reaction studies, are increasingly an asset in selected cases. When diagnostic clues are either absent or misleading, an indi- vidualized approach is preferable. Indeed, there are no useful or evidence-based rigid algorithms. Screening imaging techniques Imaging is used primarily to localize abnormalities for further evalu- ation. Due to the higher spatial resolution compared with chest radio- graphs and ultrasound of the abdomen, CT scanning of thorax or abdomen is useful when looking for focal disease, mainly infectious or neoplastic. In the near future, the role of MRI in the work-up of FUO is anticipated to grow as its benefits relative to CT are demar- cated. Nuclear imaging studies are potential tools for FUO workup. The choice between a whole variety of radiopharmaceuticals depends on local availability, cost, and skill. We do not advocate tracers that are more specific for infections, such as labelled leucocytes, because a var- iety of inflammatory and neoplastic conditions enter the differential diagnosis, not just infections. In particular, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) is an established inflam- mation tracer technique in FUO, yielding the diagnosis in 25–40% of patients and performing at least as well as gallium scintigraphy. However, unlike gallium, fluorodeoxyglucose is taken up in vasculitic lesions in large blood vessels (giant cell arteritis and Takayasu's arter- itis), which are classic causes of FUO. The combined and integrated use of FDG-PET and CT improves diagnostic accuracy. Selective testing The imaging studies may unmask hidden infectious, neoplastic, and inflammatory foci, but endoscopic techniques (e.g. gastrointes- tinal endoscopy, bronchoscopy), selective radiographs (e.g. of teeth, sinuses, sacroiliac joints), or contrast studies (e.g. gastrointestinal series, arteriography) should be ordered only when there is a well- founded and specific clinical suspicion. They should not be used as routine tests for FUO. This is even more the case for invasive pro- cedures such as mediastinoscopy, thoracoscopy, or laparoscopy, techniques that are being replaced increasingly by less invasive ultra- sound echoendoscopy, or CT-guided biopsy. Nowadays, explora- tory laparoscopy is restricted to exceptional situations (e.g. when peritoneal carcinomatosis or tuberculosis are suspected and other tests have failed). Likewise, biopsies of lymph nodes, bone marrow, or liver, and lumbar puncture can be diagnostic, but should not be performed blindly, in the absence of firm suspicion of pathological involvement. The only biopsy that may be routinely performed is temporal artery biopsy in a patient over the age of 50 with a pro- longed unexplained fever and vigorous acute-phase response, even in the absence of arteritic symptoms. Giant cell arteritis is one of the most frequent diagnoses in this age group and carries a serious risk of visual loss and other ischaemic complications. Watchful waiting An undirected pursuit of often increasingly costly and invasive tests is discouraged. Instead, when the diagnosis remains in doubt, all data (including those from other hospitals) should be critically re- viewed, and history taking, physical examination, and some basic tests (e.g. white blood cell count with differential, creatine kinase, urinalysis, chest radiograph) repeated in an effort to find clues that were previously overlooked or inapparent. There is no substitute for observing, talking to, and thinking about the patient. If the diagnosis cannot be established after intelligent thorough investigation, an ex- pectant approach is justified if the patient's condition is stable. In published series, most patients with FUO who left hospital without a diagnosis did remarkably well. Therapeutic trials Therapeutic trials are seldom diagnostically rewarding and tend to obscure, rather than illuminate. In contrast to the approach to fever in immunocompromised patients (Chapter 8.2.4), the gen- eral goal when dealing with classic FUO is

to ascertain the diag- nosis before starting therapy. Antipyretics, mainly nonsteroidal anti-inflammatory drugs, may be symptomatically useful but rarely aid diagnosis. Blind administration of corticosteroids is discour- aged. Infections such as tuberculosis may seemingly respond initially, only to deteriorate thereafter. Most patients have already had a failed trial of antibiotics before referral to secondary or tertiary care. Defervescence following administration of an antimicrobial

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