Although scintigraphic techniques do not directly provide a definitive diagnosis, they often identify the anatomic location of a particular ongoing metabolic process and, with the help of other techniques such as biopsy and culture, facilitate timely diagnosis and treatment. Pathologic FDG uptake is quickly eradicated by treatment with glucocorticoids in many diseases, including vasculitis and lymphoma; therefore, glucocorticoid use should be stopped or postponed until after FDG-PET is performed. Results reported in the literature and the advantages offered by FDG-PET indicate that conventional scintigraphic techniques should be replaced by FDG-PET/CT in the investigation of patients with FUO at institutions where this technique is available. FDG-PET/CT is a relatively expensive procedure whose availability is still limited compared with that of CT and conventional scintigraphy. Nevertheless, FDG-PET/CT can be cost-effective in the FUO diagnostic workup if used at an early stage, helping to establish an early diagnosis, reducing days of hospitalization for diagnostic purposes, and obviating unnecessary and unhelpful tests.

LATER-STAGE DIAGNOSTIC TESTS

In some cases, more invasive tests are appropriate. Abnormalities found with scintigraphic techniques often need to be confirmed by pathology and/or culture of biopsy specimens. If lymphadenopathy is found, lymph node biopsy is necessary, even when the affected lymph nodes are hard to reach. In the case of skin lesions, skin biopsy should be undertaken. In one study, pulmonary wedge excision, histologic examination of an excised tonsil, and biopsy of the peritoneum were performed in light of PDCs or abnormal FDG-PET results and yielded a diagnosis.

If no diagnosis is reached despite scintigraphic and PDC-driven histologic investigations or culture, second-stage screening diagnostic tests should be considered (Fig. 26-1). In three studies, the diagnostic yield of screening chest and abdominal CT in patients with FUO was ~20%. The specificity of chest CT was ~80%, but that of abdominal CT varied between 63% and 80%. Despite the relatively limited specificity of abdominal CT and the probably limited additional value of chest CT after normal FDG-PET, chest and abdominal CT may be used as screening procedures at a later stage of the diagnostic protocol because of their noninvasive nature and high sensitivity. Bone marrow aspiration is seldom useful in the absence of PDCs for bone marrow disorders. With addition of FDG-PET, which is very sensitive in detecting lymphoma, carcinoma, and osteomyelitis, the value of bone marrow biopsy as a screening procedure is probably further reduced. Several studies have shown a high prevalence of giant cell arteritis among patients with FUO, with rates up to 17% among elderly patients. Giant cell arteritis often involves large arteries and in most cases can be diagnosed by FDG-PET. However, temporal artery biopsy is still recommended for patients ≥55 years of age in a later stage of the diagnostic protocol: FDG-PET will not be useful in vasculitis limited to the temporal arteries because of the small diameter of these vessels and the high levels of FDG uptake in the brain that overlies them. In the past, liver biopsies have often been performed as a screening procedure in patients with FUO. In each of two recent studies, liver biopsy as part of the later stage of a screening diagnostic protocol was helpful in only one patient. Moreover, abnormal liver tests are not predictive of a diagnostic liver biopsy in FUO. Liver biopsy is an invasive procedure that carries the possibility of complications and even death. Therefore, it should not be used for screening purposes in patients with FUO except in those with PDCs for liver disease.

In patients with unexplained fever after all of the above procedures, the last step in the diagnostic workup—with only a marginal diagnostic yield—comes at an extraordinarily high cost in terms of both expense and discomfort for the patient. Repetition of a thorough history-taking and physical examination and review of laboratory results and imaging studies (including those from other hospitals) are recommended. Diagnostic delay often results from a failure to recognize PDCs in the available information. In these patients with persisting FUO, waiting for new PDCs to appear probably is better than ordering more screening investigations. Only when a patient's condition deteriorates without providing new PDCs should a further diagnostic workup be performed.

TREATMENT FEVER OF UNKNOWN ORIGIN

Empirical therapeutic trials with antibiotics, glucocorticoids, or antituberculous agents should be avoided in FUO except when a patient's condition is rapidly deteriorating after the aforementioned diagnostic tests have failed to provide a definite diagnosis.

ANTIBIOTICS AND ANTITUBERCULOUS THERAPY

Antibiotic or antituberculous therapy may irrevocably diminish the ability to culture fastidious bacteria or mycobacteria. However, hemodynamic instability or neutropenia is a good indication for empirical antibiotic therapy. If the TST is positive or if granulomatous disease is present with anergy and sarcoidosis seems unlikely, a therapeutic trial for tuberculosis should be started. Especially in miliary tuberculosis, it may be very difficult to obtain a rapid diagnosis. If the fever does not respond after 6 weeks of empirical antituberculous treatment, another diagnosis should be considered.

COLCHICINE, NONSTEROIDAL ANTI-INFLAMMATORY DRUGS, AND GLUCOCORTICOIDS

Colchicine is highly effective in preventing attacks of familial Mediterranean fever but is not always effective once an attack is well under way. When familial Mediterranean fever is suspected, the response to colchicine is not a completely reliable diagnostic tool in the acute phase, but with colchicine treatment most patients show remarkable improvements in the frequency and severity of subsequent febrile episodes within weeks to months. If the fever persists and the source remains elusive after completion of the later-stage investigations, supportive treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) can be helpful. The response of adult-onset Still's disease to NSAIDs is dramatic in some cases. The effects of glucocorticoids on giant cell arteritis and polymyalgia rheumatica are equally impressive. Early empirical trials with glucocorticoids, however, decrease the chances of reaching a diagnosis for which more specific and sometimes life-saving treatment might be more appropriate, such as malignant lymphoma. The ability of NSAIDs and glucocorticoids to mask fever while permitting the spread of infection or lymphoma dictates that their use should be avoided unless infectious diseases and malignant lymphoma have been largely ruled out and inflammatory disease is probable and is likely to be debilitating or threatening.

ANAKINRA

Interleukin (IL) 1 is a key cytokine in local and systemic inflammation and the febrile response. The availability of specific IL-1-targeting agents has revealed a pathologic role of IL-1-mediated inflammation in a growing list of diseases. Anakinra, a recombinant form of the naturally occurring IL-1 receptor antagonist (IL-1Ra), blocks the activity of both IL-1α and IL-1β. Anakinra is extremely effective in the treatment of many autoinflammatory syndromes, such as familial Mediterranean fever, cryopyrin-associated periodic syndrome, tumor necrosis factor receptor–associated periodic syndrome, hyper-IgD syndrome, and Schnitzler's syndrome. There is a growing list of other chronic inflammatory disorders in which the reduction of IL-1 activity can be highly effective. A therapeutic trial with anakinra can be considered in patients whose FUO has not been diagnosed after later-stage diagnostic tests. Although most chronic inflammatory conditions without a known basis can be controlled with glucocorticoids, monotherapy with IL-1 blockade can provide improved control without the metabolic, immunologic, and gastrointestinal side effects of glucocorticoid administration.