TABLE 26-3 ALL REPORTED CAUSES OF RECURRENT FEVER[a]

Infections	
Bacterial, nonspecific	Apical granuloma, diverticulitis, prostatitis, recurrent bacteremia caused by colonic neoplasia or persistent focal infection, recurrent cellulitis, recurrent cholangitis or cholecystitis, recurrent pneumonia, recurrent sinusitis, recurrent urinary tract infection
Bacterial, specific	Bartonellosis, brucellosis, chronic gonococcemia, chronic meningococcemia, louse-borne relapsing fever (*Borrelia recurrentis*), melioidosis (*Pseudomonas pseudomallei*), Q fever (*Coxiella burnetii),* salmonellosis, *Spirillum minor* infection, *Streptobacillus moniliformis* infection, syphilis, tick-borne relapsing fever (*Borrelia duttonii*), tularemia, Whipple's disease (*Tropheryma whipplei*), yersiniosis
Fungal	Coccidioidomycosis, paracoccidioidomycosis
Parasitic	Babesiosis, malaria, toxoplasmosis, trypanosomiasis, visceral leishmaniasis
Viral	Cytomegalovirus infection, Epstein-Barr virus infection, herpes simplex
Noninfectious Inflammatory Diseases	
Systemic rheumatic and autoimmune diseases	Ankylosing spondylitis, antiphospholipid syndrome, autoimmune hemolytic anemia, autoimmune hepatitis, Behçet's disease, cryoglobulinemia, gout, polymyositis, pseudogout, reactive arthritis, relapsing polychondritis, systemic lupus erythematosus
Vasculitis	Churg-Strauss syndrome, giant cell vasculitis/polymyalgia rheumatica, hypersensitivity vasculitis, polyarteritis nodosa, urticarial vasculitis
Granulomatous diseases	Idiopathic granulomatous hepatitis, sarcoidosis
Autoinflammatory syndromes	Adult-onset Still's disease, Blau syndrome, CAPS[b] (cryopyrin-associated periodic syndrome), Crohn's disease, DIRA (deficiency of the IL-1 receptor antagonist), familial Mediterranean fever, hemophagocytic syndrome, hyper-IgD syndrome (HIDS, also known as mevalonate kinase deficiency), juvenile idiopathic arthritis, PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne), PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, adenitis), recurrent idiopathic pericarditis, SAPHO (synovitis, acne, pustulosis, hyperostosis, osteomyelitis), Schnitzler's syndrome, TRAPS (tumor necrosis factor receptor–associated periodic syndrome)
Neoplasms	
	Angioimmunoblastic lymphoma, Castleman's disease, colon carcinoma, craniopharyngioma, Hodgkin's disease, non-Hodgkin lymphoma, malignant histiocytosis, mesothelioma
Miscellaneous	
	Adrenal insufficiency, aortic-enteral fistula, aseptic meningitis (Mollaret's syndrome), atrial myxoma, brewer's yeast ingestion, cholesterol emboli, cyclic neutropenia, drug fever, extrinsic allergic alveolitis, Fabry's disease, factitious disease, fraudulent fever, Gaucher's disease, hypersensitivity pneumonitis, hypertriglyceridemia, hypothalamic hypopituitarism, inflammatory pseudotumor, metal fume fever, milk protein allergy, polymer fume fever, pulmonary embolism, sclerosing mesenteritis
Thermoregulatory Disorders	
Central	Hypothalamic dysfunction
Peripheral	Anhidrotic ectodermal dysplasia, exercise-induced hyperthermia, pheochromocytoma

[a]This table includes all causes of recurrent fever that have been described in the literature. [b]CAPS includes chronic infantile neurologic cutaneous and articular syndrome (CINCA, also known as neonatal-onset multisystem inflammatory disease, or NOMID), familial cold autoinflammatory syndrome (FCAS), and Muckle-Wells syndrome.

should be asked to return during a febrile episode so that the history, physical examination, and laboratory tests can be repeated during a symptomatic phase. Further diagnostic tests, such as scintigraphic imaging (see below), should be performed only during a febrile episode because abnormalities may be absent between episodes. In patients with recurrent fever lasting >2 years, it is very unlikely that the fever is caused by infection or malignancy. Further diagnostic tests in that direction should be considered only when PDCs for infections, vasculitis syndromes, or malignancy are present or when the patient's clinical condition is deteriorating.

Scintigraphy Scintigraphic imaging is a noninvasive method allowing delineation of foci in all parts of the body on the basis of functional changes in tissues. This procedure plays an important role in the diagnosis of patients with FUO in clinical practice. Conventional scintigraphic methods used in clinical practice are ^{67}Ga-citrate scintigraphy and ^{111}In- or ^{99m}Tc-labeled leukocyte scintigraphy. Focal infectious and inflammatory processes can also be detected by several radiologic techniques, such as CT, MRI, and ultrasound. However, because of the lack of substantial pathologic changes in the early phase, infectious and inflammatory foci cannot be detected at this time. Furthermore, distinguishing active infectious or inflammatory lesions from residual changes due to cured processes or surgery remains critical. Finally, CT and MRI routinely provide information only on part of the body, while scintigraphy readily allows whole-body imaging.

Fluorodeoxyglucose Positron Emission Tomography ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has become an established imaging procedure in FUO. FDG accumulates in tissues with a high rate of glycolysis, which occurs not only in malignant cells but also in activated leukocytes, and thus permits the imaging of acute and chronic inflammatory processes. Normal uptake may obscure pathologic foci in the brain, heart, bowel, kidneys, and bladder. In patients with fever, bone marrow uptake is frequently increased in a nonspecific way due to cytokine activation, which upregulates glucose transporters in bone marrow cells. Compared with conventional scintigraphy, FDG-PET offers the advantages of higher resolution, greater sensitivity in chronic low-grade infections, and a high degree of accuracy in the central skeleton. Furthermore, vascular uptake of FDG is increased in patients with vasculitis. The mechanisms responsible for FDG uptake do not allow differentiation among infection, sterile inflammation, and malignancy. However, in patients with FUO, since all of these disorders are causes of FUO, FDG-PET can be used to guide additional diagnostic tests (e.g., targeted biopsies) that may yield the final diagnosis. Improved anatomic resolution by direct integration with CT (FDG-PET/CT) has further improved the accuracy of this modality.

Overall rates of helpfulness in final diagnosis of FUO are 40% for FDG-PET and 54% for FDG-PET/CT. In one study, FDG-PET was never helpful in diagnosing FUO in patients with a normal CRP level and a normal ESR. In two prospective studies in patients with FUO, FDG-PET was superior to ^{67}Ga-citrate scintigraphy, with a similar or better diagnostic yield and results that were available within hours instead of days. In one study, the sensitivity of FDG-PET was greater than that of ^{111}In-granulocyte scintigraphy (86% vs 20%) in patients with FUO.