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ANTIBIOTICS AND ANTITUBERCULOUS THERAPY Antibiotic or antituberculous therapy may irrevocably diminish the ability to culture bacteria. However, hemodynamic instability or neutropenia is a good indication for empirical antibiotic therapy. If the TST or IGRA is positive, or if granulomatous disease is pres ent with anergy and sarcoidosis seems unlikely, or in any patient coming from an endemic region with a clinical picture fitting extrapulmonary tuberculosis, a trial of antituberculous therapy may be started, but not before mycobacterial cultures and, if avail able, mycobacterial PCR testing have been performed on material collected from the suspected location of inflammation. 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 If the fever persists and the source remains elusive after comple tion of investigations, supportive treatment with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) can be helpful. The response of Still’s disease to NSAIDs is dramatic in some cases. Colchicine is highly effective in preventing attacks of familial Medi terranean fever (FMF) but is not always effective once an attack is underway. When FMF is suspected, the response to colchicine is not a completely reliable diagnostic tool in the acute phase, but within weeks to months of continuous colchicine treatment, most patients show remarkable improvements in the frequency and severity of subsequent febrile episodes. Therefore, colchicine may be tried in patients with features compatible with FMF, especially when these patients originate from a high-prevalence region. In patients suffer ing from pericarditis as one of the main associated symptoms, col chicine may also be effective to prevent recurrent attacks. If Behçet’s disease is considered likely, colchicine may also have favorable effect. The effects of glucocorticoids on giant cell arteritis and polymy algia rheumatica are impressive. Early empirical trials with gluco corticoids, however, decrease the chances of reaching a diagnosis for which more specific, less morbid, and sometimes life-saving treatment might be more appropriate, such as malignant lym phoma. The ability of 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 sufficiently ruled out and inflammatory disease is prob able and is likely to be debilitating or threatening. INTERLEUKIN-1 INHIBITION 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 inflamma tion 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 effec tive in the treatment of many autoinflammatory syndromes, such as FMF, cryopyrin-associated periodic syndrome, tumor necrosis factor receptor–associated periodic syndrome, mevalonate kinase deficiency (hyper-IgD syndrome), Schnitzler's syndrome, and Still's disease. There are many other chronic inflammatory disorders in which anti-IL-1 therapy is highly effective. A therapeutic trial with anakinra can be considered in patients whose FUO has not been diagnosed after later-stage diagnostic tests and show signs of IL1-driven inflammation, such as serositis, elevated CRP, and elevated ferritin. When autoinflammation is considered in the differential diagnosis, IL-1 inhibition is preferred over corticosteroids to pre vent the metabolic, immunologic, and gastrointestinal side effects of glucocorticoid administration, and because IL-1 inhibition has superior efficacy. ■ ■PROGNOSIS The prognosis of patients with FUO mostly depends on the underly ing disease. In patients in whom FUO remains unexplained despite

extensive evaluation, the prognosis is favorable. The risk of FUO-related mortality is probably highest during the early phases of the diagnostic process: in a cohort study including 168 patients without a final diag nosis, all four patients who died did so during the index admission; in two of them, diagnoses were made upon autopsy (intravascular lym phoma and bilateral pneumonia).

Large cohort studies in patients remaining without a diagnosis report high percentages of spontaneous resolution of fever and a mor tality of 8% or less during several years of follow-up. 18F-FDG-PET/CT may be helpful to predict which patients will resolve because normal 18F-FDG-PET/CT scans are associated with higher rates of spontane ous resolution. Syncope CHAPTER 23 ■ ■FURTHER READING Betrains A et al: update on imaging in fever and inflammation of unknown origin: Focus on infectious disorders. Clin Microbiol Infect 18:S1198, 2023. Erdem H et al: Classical fever of unknown origin in 21 countries with different economic development: An international ID-IRI study. Eur J Clin Microbiol Infect Dis 42:387, 2023. Mulders-Manders C et al: Fever of unknown origin. Clin Med 15:280, 2015. van Rijsewijk N et al: Molecular imaging of fever of unknown origin: An update. Semin Nucl Med 53:4, 2023. Wright WF et al: Fever of unknown origin (FUO): A call for new research standards and updated clinical management. Am J Med 135:173, 2022. Section 3 Nervous System Dysfunction Roy Freeman, Satish R. Raj

Syncope Syncope is a transient, self-limited loss of consciousness due to acute global impairment of cerebral blood flow. The onset is rapid, dura tion brief, and recovery spontaneous and complete. Other causes of transient loss of consciousness need to be distinguished from syncope; these include seizures, vertebrobasilar ischemia, hypoxemia, and hypo glycemia. A syncopal prodrome (presyncope) is common, although loss of consciousness may occur without any warning symptoms. Typical presyncopal symptoms include lightheadedness or faintness, dizziness, weakness, fatigue, and visual and auditory disturbances. The causes of syncope can be divided into three general categories: (1) neurally medi ated syncope (also called reflex or vasovagal syncope), (2) orthostatic hypotension, and (3) cardiac syncope. Neurally mediated syncope comprises a heterogeneous group of disorders that are characterized by a transient change in the reflexes responsible for maintaining cardiovascular homeostasis. Episodic vasodilation (or loss of vasoconstrictor tone), decreased cardiac output, and bradycardia occur in varying combinations, resulting in tempo rary failure of blood pressure control. In contrast, in patients with orthostatic

hypotension due to autonomic failure, these cardiovascular homeostatic reflexes are chronically impaired. Cardiac syncope may be due to arrhythmias or structural cardiac diseases that cause a decrease in cardiac output. The clinical features, underlying pathophysiologic mechanisms, therapeutic interventions, and prognoses differ markedly among these three causes. ■ ■EPIDEMIOLOGY AND NATURAL HISTORY Syncope is a common presenting problem, accounting for ~3% of all emergency department (ED) visits and 1% of all hospital admissions. The annual cost for syncope-related hospitalization in the United States

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