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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

is ~$2.4 billion. Syncope has a lifetime cumulative incidence of up to 40% in the general population. A bimodal age distribution exists; the peak incidence in the young occurs between ages 10 and 30 years, with a median peak around 15 years. Neurally mediated syncope is the etiol ogy in the vast majority of these cases. In older adults, there is a sharp rise in the incidence of syncope after 70 years of age.

In population-based studies, neurally mediated syncope is the most common cause of syncope. The incidence is higher in women than men. In young subjects, there is often a family history in first-degree relatives. Cardiovascular disease due to structural disease or arrhythmias is the next most common cause in most series, particularly in ED settings and in older patients. Orthostatic hypotension also increases in prevalence with age because of the reduced baroreflex responsiveness, decreased cardiac compliance, and attenuation of the vestibulosympathetic reflex associated with aging. Other contributors are reduced fluid intake and vasoactive medications, also more likely in this age group. In the elderly, orthostatic hypotension is more common in institutionalized than community-dwelling individuals, most likely explained by a greater prevalence of predisposing neurologic disorders, physiologic impair ment, and vasoactive medication use among institutionalized patients. PART 2 Cardinal Manifestations and Presentation of Diseases Syncope of noncardiac and unexplained origin in younger indi viduals has an excellent prognosis; life expectancy is unaffected. By contrast, syncope due to a cardiac cause, either structural heart disease or a primary arrhythmic disorder, is associated with an increased risk of sudden cardiac death and mortality from other causes. Similarly, the mortality rate is increased in individuals with syncope due to ortho static hypotension related to age and the associated comorbid condi tions (Table 23-1). The likelihood of hospitalization and mortality risk are higher in older adults. ■ ■PATHOPHYSIOLOGY The upright posture imposes a unique physiologic stress upon humans; most, although not all, syncopal episodes occur from a standing posi tion. Standing results in pooling of 500–1000 mL of blood in the lower extremities, buttocks, and splanchnic circulation. The dependent pooling leads to a decrease in venous return to the heart and reduced ventricular filling that result in diminished cardiac output and blood pressure. These hemodynamic changes provoke a compensatory reflex response, initiated by the baroreceptors in the carotid sinus and aortic arch, resulting in increased sympathetic outflow and decreased vagal nerve activity (Fig. 23-1). The reflex increases peripheral resistance, venous return to the heart, and cardiac output and thus limits the fall in blood pressure. If this response fails, as is the case chronically in orthostatic hypotension and transiently in neurally mediated syncope, hypotension and cerebral hypoperfusion occur. TABLE 23-1 High-Risk Features Indicating Hospitalization or Intensive Evaluation of Syncope Chest pain suggesting coronary ischemia Features of congestive heart failure Moderate or severe valvular disease Moderate or severe structural cardiac disease Electrocardiographic features of ischemia History of ventricular arrhythmias Prolonged QT interval (>500 ms) Repetitive sinoatrial block or sinus pauses Persistent sinus bradycardia Bi- or trifascicular block or intraventricular conduction delay with QRS duration ≥120 ms Atrial fibrillation Nonsustained ventricular tachycardia Family history of sudden death Preexcitation syndromes Brugada pattern on electrocardiogram Palpitations at time of syncope Syncope at rest or during exercise

Syncope is a form of transient loss of consciousness (TLOC) that is a consequence of global cerebral hypoperfusion. It represents a failure of cerebral blood flow autoregulatory mechanisms.

Myogenic factors, local metabolites, and to a lesser extent autonomic neurovascular control are responsible for the autoregulation of cerebral blood flow (Chap. 318). The latency of the autoregulatory response is 5–10 s. Typically, cerebral blood flow ranges from 50–60 mL/min per 100 g brain tissue and remains relatively constant over perfusion pressures ranging from 50–150 mmHg. Cessation of blood flow for 6–8 s will result in loss of consciousness, while impairment of consciousness ensues when blood flow decreases to 25 mL/min per 100 g brain tissue. From the clinical standpoint, a fall in systemic systolic blood pres sure to ~50 mmHg or lower will usually result in syncope. A decrease in cardiac output and/or systemic vascular resistance—the determinants of blood pressure—thus underlies the pathophysiology of syncope. Common causes of impaired cardiac output include decreased effec tive circulating blood volume, increased thoracic pressure, massive pulmonary embolus, cardiac brady- and tachyarrhythmias, valvular heart disease, and myocardial dysfunction. Systemic vascular resis tance may be decreased by central and peripheral autonomic nervous system diseases, sympatholytic medications, and transiently during neurally mediated syncope. Increased cerebral vascular resistance, most frequently due to hypocarbia induced by hyperventilation, may also contribute to the pathophysiology of syncope. Two patterns of electroencephalographic (EEG) changes occur in syncopal subjects. The first is a “slow-flat-slow” pattern in which nor mal background activity is replaced with high-amplitude slow delta waves. This is followed by sudden flattening of the EEG—a cessation or attenuation of cortical activity—followed by the return of slow waves, and then normal activity. A second pattern, the “slow pattern,” is char acterized by increasing and decreasing slow wave activity only. The EEG flattening that occurs in the slow-flat-slow pattern is a marker of more severe cerebral hypoperfusion. Despite the presence of myoclonic movements and other motor activity during some syncopal events, EEG seizure discharges are not detected. CLASSIFICATION ■ ■NEURALLY MEDIATED SYNCOPE Neurally mediated (reflex; vasovagal) syncope is the final pathway of a complex central and peripheral nervous system reflex arc. There is a transient change in autonomic efferent activity with increased parasympathetic outflow, plus sympathoinhibition, resulting in brady cardia, vasodilation, and/or reduced vasoconstrictor tone (the vasode pressor response) and reduced cardiac output. The resulting fall in systemic blood pressure can then reduce cerebral blood flow to below the compensatory limits of autoregulation (Fig. 23-2). In order to develop neurally mediated syncope, a functioning autonomic nervous system is necessary, in contrast to syncope resulting from autonomic failure (discussed below). Multiple triggers of the afferent limb of the reflex arc can result in neurally mediated syncope. In some situations, these can be clearly defined, e.g., orthostatic stress, and stimulation of the carotid sinus, the gastrointestinal tract, or the bladder. Often, however, the trigger is less easily recognized and the cause is multifactorial. Under these circumstances, it is likely that different afferent pathways converge on the central autonomic network within the medulla that integrates the neural impulses and mediates the vasodepressor-bradycardic response. Classification of Neurally Mediated Syncope Neurally mediated syncope may be subdivided based on the afferent pathway and pro vocative trigger. Vasovagal syncope (the common faint) is provoked by intense emotion, pain, and/or orthostatic stress, whereas the situational reflex syncopes have specific localized stimuli that provoke the reflex vasodilation and bradycardia that leads to syncope. The underlying mechanisms have been identified and pathophysiology delineated for most of these situational reflex syncopes. The afferent trigger may originate in the pulmonary system, gastrointestinal system, urogenital system, heart, and carotid sinus in the carotid artery (Table 23-2).

FIGURE 23-1 The baroreflex. A decrease in arterial pressure unloads the baroreceptors—the terminals of afferent fibers of the glossopharyngeal and vagus nerves—that are situated in the carotid sinus and aortic arch. This leads to a reduction in the afferent impulses that are relayed from these mechanoreceptors through the glossopharyngeal and vagus nerves to the nucleus of the tractus solitarius (NTS) in the dorsomedial medulla. The reduced baroreceptor afferent activity produces a decrease in vagal nerve input to the sinus node that is mediated via connections of the NTS to the nucleus ambiguus (NA). There is an increase in sympathetic efferent activity that is mediated by the NTS projections to the caudal ventrolateral medulla (CVLM) (an excitatory pathway) and from there to the rostral ventrolateral medulla (RVLM) (an inhibitory pathway). The activation of RVLM presympathetic neurons in response to hypotension is thus predominantly due to disinhibition. In response to a sustained fall in blood pressure, vasopressin release is mediated by projections from the A1 noradrenergic cell group in the ventrolateral medulla. This projection activates vasopressin-synthesizing neurons in the magnocellular portion of the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus. Blue denotes sympathetic neurons, and green denotes parasympathetic neurons. (From R Freeman: Neurogenic orthostatic hypotension. N Engl J Med 358:615, 2008. Copyright © 2008 Massachusetts Medical Society. Reprinted with permission.)

HR (bpm)

BP (mm Hg)

A B Time (s) FIGURE 23-2 A. The paroxysmal hypotensive-bradycardic response that is characteristic of neurally mediated syncope. Noninvasive beat-to-beat blood pressure and heart rate are shown >5 min (from 60 to 360 s) of an upright tilt on a tilt table. B. The same tracing expanded to show 80 s of the episode (from 80 to 200 s). BP, blood pressure; bpm, beats per minute; HR, heart rate.

HR (bpm)

BP (mm Hg)

Time (s)

TABLE 23-2 Causes of Syncope A. Neurally Mediated Syncope Vasovagal syncope Provoked fear, pain, anxiety, intense emotion, sight of blood, unpleasant sights and odors, orthostatic stress Situational reflex syncope Pulmonary Cough syncope, wind instrument player's syncope, weightlifter's syncope, "mess trick"a and "fainting lark,"b sneeze syncope, airway instrumentation Urogenital Postmicturition syncope, urogenital tract instrumentation, prostatic massage Gastrointestinal Swallow syncope, glossopharyngeal neuralgia, esophageal stimulation, gastrointestinal tract instrumentation, rectal examination, defecation syncope Cardiac Bezold-Jarisch reflex, cardiac outflow obstruction Carotid sinus Carotid sinus sensitivity, carotid sinus massage Ocular Ocular pressure, ocular examination, ocular surgery B. Orthostatic Hypotension Primary autonomic failure due to idiopathic central and peripheral neurodegenerative diseases—the "synucleinopathies" Lewy body diseases Parkinson's disease Lewy body dementia Pure autonomic failure Multiple system atrophy (Shy-Drager syndrome) Secondary autonomic failure due to autonomic peripheral neuropathies Diabetes Hereditary amyloidosis (familial amyloid polyneuropathy) Primary amyloidosis (AL amyloidosis; immunoglobulin light chain associated) Hereditary sensory and autonomic neuropathies (HSAN) (especially type III—familial dysautonomia) Idiopathic immune-mediated autonomic neuropathy Autoimmune autonomic ganglionopathy Sjögren’s syndrome Paraneoplastic autonomic neuropathy HIV neuropathy Postprandial hypotension Iatrogenic (drug-induced) Volume depletion C. Cardiac Syncope Arrhythmias Sinus node dysfunction Atrioventricular dysfunction Supraventricular tachycardias Ventricular tachycardias Inherited channelopathies Cardiac structural disease Valvular disease Myocardial ischemia Obstructive and other cardiomyopathies Atrial myxoma Pericardial effusions and tamponade aHyperventilation for ~1 min, followed by sudden chest compression. bHyperventilation (~20 breaths) in a squatting position, rapid rise to standing, then Valsalva maneuver.

Hyperventilation, leading to hypocarbia and cerebral vasoconstriction, and raised intrathoracic pressure that impairs venous return to the heart play a central role in many of the situational reflex syncopes. The affer ent pathway of the reflex arc differs among these disorders, but the efferent response via the vagus and sympathetic pathways is similar. Alternately, neurally mediated syncope may be subdivided based on the predominant efferent pathway. Vasodepressor syncope describes syncope predominantly due to efferent, sympathetic, vasoconstrictor failure; cardioinhibitory syncope describes syncope predominantly associated with bradycardia or asystole due to increased vagal outflow; and mixed response syncope describes syncope in which there are both vagal and sympathetic reflex changes. Features of Neurally Mediated Syncope In addition to symp toms of orthostatic intolerance such as dizziness, lightheadedness, and fatigue, premonitory features of autonomic activation may be present in patients with neurally mediated syncope. These include diaphoresis, pallor, palpitations, nausea, hyperventilation, and yawning. During the syncopal event, proximal and distal myoclonus (typically arrhythmic and multifocal) may occur, raising the possibility of a seizure. The eyes typically remain open and usually deviate upward. Pupils are usually dilated. Roving eye movements may occur. Grunting, moaning, snort ing, and stertorous breathing may be present. Urinary incontinence may occur. Fecal incontinence is very rare, however. Postictal confu sion is also rare, although visual and auditory hallucinations and neardeath and out-of-body experiences are sometimes reported. Although some predisposing factors and provocative stimuli are well established (for example, motionless upright posture, warm ambi ent temperature, intravascular volume depletion, alcohol ingestion, hypoxemia, anemia, pain, the sight of blood, venipuncture, and intense emotion), the underlying basis for the widely different thresholds for syncope among individuals exposed to the same provocative stimulus is not known. A genetic basis for neurally mediated syncope may exist. Several studies have reported an increased incidence of syncope in first-degree relatives of fainters, and some candidate genes have been identified with sex-specific associations. These have not been repro duced in other large cohorts. It is likely that environmental, social, and cultural factors play a large role. TREATMENT Neurally Mediated Syncope Reassurance, education, avoidance of provocative stimuli, and plasma volume expansion with fluid and salt are the cornerstones of the management of neurally mediated syncope. Isometric coun terpressure maneuvers of the limbs (tensing of the abdominal and leg muscles, handgrip and arm tensing, and leg crossing) may raise blood pressure by increasing central blood volume and cardiac output. Of these, abdominal and leg muscle tensing is the most effective. By maintaining pressure in the autoregulatory zone, these maneuvers, which may be particularly helpful in patients with a long prodrome, avoid or delay the onset of syncope. A randomized controlled trial supports this intervention. Fludrocortisone, vasoconstricting agents, and β-adrenoreceptor antagonists are widely used by experts to treat refractory patients. Of these, only midodrine has been shown to be effective in interna tional, multicenter randomized controlled trials. Because vasodila tion, decreased central blood volume, decreased stroke volume, and cardiac output are the dominant pathophysiologic syncopal mecha nisms in most patients, use of a cardiac pacemaker is rarely beneficial. In patients with a cardioinhibitory syncope response during tilt-table testing, however, recent sham-controlled randomized clinical trial data have shown that a dual-chamber pacemaker with a closed-loop stimulation algorithm can decrease syncope recurrence. These stud ies restricted enrollment to older patients (>40 years) with frequent recurrence of syncope and a cardioinhibitory response on tilt-table test. In these patients, dual-chamber pacing may be helpful, although this continues to be an area of uncertainty.

■ ■ORTHOSTATIC HYPOTENSION Orthostatic hypotension, defined as a reduction in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg after 3 min of standing or head-up tilt on a tilt table, is a manifestation of sympathetic vasoconstrictor (autonomic) fail ure (Fig. 23-3). In many (but not all) cases, there is no compensatory increase in heart rate despite hypotension; with partial autonomic fail ure, heart rate may increase to some degree but is insufficient to main tain cardiac output. A variant of orthostatic hypotension is “delayed” orthostatic hypotension, which occurs beyond 3 min of standing; this may reflect a mild or early form of sympathetic adrenergic dysfunc tion. In some cases, orthostatic hypotension can occur within 15 s of standing with full resolution within 45 s (so-called initial orthostatic hypotension), a finding that may reflect a transient mismatch between cardiac output and peripheral vascular resistance and does not repre sent autonomic failure. Characteristic symptoms of orthostatic hypotension include lightheadedness, dizziness, and presyncope (near-faintness) occurring in response to sudden postural change. However, symptoms may be absent or nonspecific such as generalized weakness, fatigue, cognitive slowing, leg buckling, or headache. Visual blurring may occur, likely due to retinal or occipital lobe ischemia. Neck pain, typically in the suboccipital, posterior cervical, and shoulder region (the “coat-hanger headache”), most likely due to neck muscle ischemia, may be the only symptom. Patients may report orthostatic dyspnea (thought to reflect ventilation-perfusion mismatch due to inadequate perfusion of ventilated lung apices) or angina (attributed to impaired myocardial perfusion even with normal coronary arteries). Symptoms may be exacerbated by exertion, prolonged standing, increased ambient tem perature, or meals. Syncope is usually preceded by warning symptoms, but may occur suddenly, suggesting the possibility of a seizure or car diac cause. Some patients have profound decreases in blood pressure, sometimes without symptoms but placing them at risk for falls and injuries if the autoregulatory threshold is crossed with ensuing cerebral hypoperfusion. Supine hypertension is common in patients with orthostatic hypo tension due to autonomic failure, affecting >50% of patients in some series. Orthostatic hypotension may present after initiation of therapy for hypertension, and supine hypertension may follow treatment of orthostatic hypotension. However, in other cases, the association of the

HR (bpm)

BP (mm Hg)

A B Time (s) FIGURE 23-3 A. The gradual fall in blood pressure without a compensatory heart rate increase that is characteristic of orthostatic hypotension due to autonomic failure. Blood pressure and heart rate are shown >5 min (from 60 to 360 s) of an upright tilt on a tilt table. B. The same tracing expanded to show 40 s of the episode (from 180 to 220 s). BP, blood pressure; bpm, beats per minute; HR, heart rate.

two conditions is unrelated to therapy; it may in part be explained by baroreflex dysfunction in the presence of residual sympathetic outflow, particularly in patients with central autonomic degeneration.

Causes of Neurogenic Orthostatic Hypotension Causes of neurogenic orthostatic hypotension include central and peripheral autonomic nervous system dysfunction (Chap. 451). Autonomic dysfunction of other organ systems (including the bladder, bowels, sexual organs, and sudomotor system) of varying severity frequently accompanies orthostatic hypotension in these disorders (Table 23-2). The primary autonomic degenerative disorders are multiple sys tem atrophy (Shy-Drager syndrome; Chap. 451), Parkinson’s disease (Chap. 446), dementia with Lewy bodies (Chap. 445), and pure autonomic failure (Chap. 451). These are often grouped together as “synucleinopathies” due to the presence of α-synuclein, a protein that aggregates predominantly in the cytoplasm of neurons in the Lewy body disorders (Parkinson’s disease, dementia with Lewy bodies, and pure autonomic failure) and in the glia in multiple system atrophy. Syncope CHAPTER 23 Peripheral autonomic dysfunction may also accompany small-fiber peripheral neuropathies such as those associated with diabetes melli tus, acquired and hereditary amyloidosis, immune-mediated neuropa thies, and hereditary sensory and autonomic neuropathies (HSAN; particularly HSAN type III, familial dysautonomia) (Chaps. 457 and 458). Less frequently, orthostatic hypotension is associated with the peripheral neuropathies that accompany vitamin B12 deficiency, neuro toxin exposure, HIV and other infections, and porphyria. Patients with autonomic failure and the elderly are susceptible to falls in blood pressure associated with meals. The magnitude of the blood pressure fall is exacerbated by large meals, meals high in carbo hydrate, and alcohol intake. The mechanism of postprandial hypoten sion, and resultant syncope, is not fully elucidated. Orthostatic hypotension is often iatrogenic. Drugs from several classes may lower peripheral resistance (e.g., α-adrenoreceptor antago nists used to treat hypertension and prostatic hypertrophy; diuretics, nitrates and other venodilators and vasodilators; other antihyperten sive agents of several classes; tricyclic agents and phenothiazines). Iatrogenic volume depletion due to diuresis and volume depletion due to medical causes (hemorrhage, vomiting, diarrhea, or decreased fluid intake) may also result in decreased effective circulatory volume, orthostatic hypotension, and syncope.

HR (bpm)

BP (mm Hg)

Time (s)

TREATMENT Orthostatic Hypotension The first step is to remove reversible causes—usually vasoactive medications (see Table 451-6). Next, nonpharmacologic inter ventions should be introduced. These include patient education regarding staged moves from supine to upright;

warnings about the hypotensive effects of large meals; instructions about the isometric counterpressure maneuvers that increase intravascular pressure (see above); and raising the head of the bed to reduce supine hypertension and nocturnal diuresis. Intravascular volume should be expanded by increasing dietary fluid and salt. The rapid ingestion of 500 mL of plain water can often effect a short-term pressor response in these patients. If these nonpharmacologic measures fail, pharmacologic intervention with fludrocortisone acetate and vasoconstricting agents such as midodrine or l-dihy droxyphenylserine (droxidopa) should be introduced. Some patients with intractable symptoms require additional therapy with supplementary agents that include pyridostigmine, atomox etine, yohimbine, octreotide, desmopressin acetate (DDAVP), and erythropoietin (Chap. 451). PART 2 Cardinal Manifestations and Presentation of Diseases ■ ■CARDIAC SYNCOPE Cardiac (or cardiovascular) syncope is caused by arrhythmias and structural heart disease. These may occur in combination because structural disease renders the heart more vulnerable to abnormal elec trical activity. Arrhythmias Bradyarrhythmias that cause syncope include those due to severe sinus node dysfunction (e.g., sinus arrest or sinoatrial block) and atrioventricular (AV) block (e.g., Mobitz type II, highgrade, and complete AV block). The bradyarrhythmias due to sinus node dysfunction are often associated with an atrial tachyarrhythmia, a disorder known as the tachycardia-bradycardia syndrome. A pro longed pause following the termination of a tachycardic episode is a frequent cause of syncope in patients with the tachycardia-bradycardia syndrome. Medications of several classes may also cause bradyarrhyth mias of sufficient severity to cause syncope. Syncope due to bradycar dia or asystole has been referred to as a Stokes-Adams attack. Ventricular tachyarrhythmias frequently cause syncope. The likeli hood of syncope with ventricular tachycardia is in part dependent on the ventricular rate (rates <200 beats/min are less likely to cause syncope) and ventricular function (a patient with poor ventricular function is more likely to have syncope at a given ventricular rate). The compromised hemodynamic function during ventricular tachycardia is caused by ineffective ventricular contraction, reduced diastolic filling due to abbreviated filling periods, loss of AV synchrony, and concur rent myocardial ischemia. Several disorders associated with cardiac electrophysiologic instabil ity and arrhythmogenesis are due to mutations in ion channel subunit genes. These include the long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia. The long QT syndrome is a genetically heterogeneous disorder associated with prolonged cardiac repolarization and a predisposition to ventricular arrhythmias. Syncope and sudden death in patients with long QT syndrome result from a unique polymorphic ventricular tachycardia called torsades des pointes that may degenerate into ventricular fibril lation. The long QT syndrome has been linked to genes encoding K^+ channel α-subunits, K^+ channel β-subunits, voltage-gated Na^+ channel, and a scaffolding protein, ankyrin B (ANK2). Brugada syndrome is characterized by syncope, polymorphic ventricular tachycardia, and idiopathic ventricular fibrillation in association with right ventricu lar electrocardiogram (ECG) abnormalities without structural heart disease. This disorder is also genetically heterogeneous, although it is most frequently linked to mutations in the Na^+ channel α-subunit, SCN5A. Catecholaminergic polymorphic tachycardia is an inherited, genetically heterogeneous disorder often involving cardiac calcium handling that is associated with exercise- or stress-induced ventricular

arrhythmias, syncope, or sudden death. Acquired QT interval prolon gation, most commonly due to drugs, may also result in ventricular arrhythmias and syncope. These disorders are discussed in detail in Chap. 262. Structural Disease Structural heart disease (e.g., valvular disease, myocardial ischemia, hypertrophic and other cardiomyopathies, car diac masses such as atrial myxoma, and pericardial effusions) may lead to syncope by compromising cardiac output. Structural disease may also contribute to other pathophysiologic mechanisms of syncope. For example, cardiac structural disease may predispose to arrhythmogen esis; aggressive treatment of cardiac failure with diuretics and/or vaso dilators may lead to orthostatic hypotension; and inappropriate reflex vasodilation may occur with structural disorders such as aortic stenosis and hypertrophic cardiomyopathy, possibly provoked by increased ventricular contractility. TREATMENT Cardiac Syncope Treatment of cardiac disease depends on the underlying disorder. Therapies for arrhythmias consist of cardiac pacing for brady cardia, including sinus node disease and AV block, and ablation, antiarrhythmic drugs, and cardioverter-defibrillators for atrial and ventricular tachyarrhythmias. These disorders are best managed by physicians with specialized skills in this area. APPROACH TO THE PATIENT Syncope DIFFERENTIAL DIAGNOSIS Syncope is easily diagnosed when the characteristic features are present; however, several disorders with real or apparent transient loss of consciousness may create diagnostic confusion. Generalized and partial seizures (Chap. 436) may be confused with syncope; however, there are a number of differentiating fea tures. Whereas tonic-clonic movements are the hallmark of a gen eralized seizure, myoclonic and other movements also may occur in up to 90% of syncopal episodes. Myoclonic jerks associated with syncope may be multifocal or generalized. They are typically arrhythmic and of short duration (<30 s). Mild flexor and extensor posturing also may occur. Partial or partial-complex seizures with secondary generalization are usually preceded by an aura, com monly an unpleasant smell; fear; anxiety; abdominal discomfort; or other visceral sensations. These phenomena should be differenti ated from the premonitory features of syncope. Autonomic manifestations of seizures (autonomic epilepsy) may provide a more difficult diagnostic challenge. Autonomic sei zures have cardiovascular, gastrointestinal, pulmonary, urogenital, pupillary, and cutaneous manifestations that are similar to the premonitory features of syncope. Furthermore, the cardiovascular manifestations of autonomic epilepsy include clinically significant tachycardias and bradycardias that may be of sufficient magnitude to cause loss of consciousness. The presence of accompanying non autonomic auras may help differentiate these episodes from syncope. Loss of consciousness associated with a seizure usually lasts

> 5 min and is associated with prolonged postictal drowsiness and disorientation, whereas reorientation occurs almost immediately after a syncopal event. Muscle aches may occur after both syncope and seizures, although they tend to last longer and be more severe following a seizure. Seizures, unlike syncope, are rarely provoked by emotions or pain. Incontinence of urine may occur with both seizures and syncope; however, fecal incontinence occurs only very rarely with syncope. Hypoglycemia may cause transient loss of consciousness, typi cally in individuals with type 1 or type 2 diabetes (Chap. 415) treated with insulin. The clinical features associated with impending

or actual hypoglycemia include tremor, palpitations, anxiety, dia phoresis, hunger, and paresthesias. These symptoms are due to autonomic activation to counter the falling blood glucose. Hunger, in particular, is not a typical premonitory feature of syncope. Hypo glycemia also impairs neuronal function, leading to fatigue, weak ness, dizziness, and cognitive and behavioral symptoms. Diagnostic difficulties may occur in individuals in strict glycemic control; repeated hypoglycemia impairs the counterregulatory response and leads to a loss of the characteristic warning symptoms that are the hallmark of hypoglycemia. Patients with cataplexy (Chap. 33) experience an abrupt partial or complete loss of muscular tone triggered by strong emotions, typically anger or laughter. Unlike syncope, consciousness is main tained throughout the attacks, which typically last between 30 s and 2 min. There are no premonitory symptoms. Cataplexy occurs in 60–75% of patients with narcolepsy. The clinical interview and interrogation of eyewitnesses (and ancillary cellphone video of the spell, when available) usually allow differentiation of syncope from falls due to vestibular dysfunction, cerebellar disease, extrapyramidal system dysfunction, and other gait disorders. A diagnosis of syncope can be particularly challeng ing in patients with dementia who experience repeated falls and are unable to provide a clear history of the episodes. If the fall is accompanied by head trauma, a postconcussive syndrome, amnesia for the precipitating events, and/or a loss or alteration of conscious ness, this may also contribute to diagnostic difficulty. Apparent loss of consciousness can be a manifestation of psychi atric disorders such as generalized anxiety, panic disorders, major depression, and somatization disorder. These possibilities should be considered in individuals who faint frequently without prodromal symptoms. Such patients are rarely injured despite numerous falls. There are no clinically significant hemodynamic changes concur rent with these episodes. In contrast, transient loss of consciousness due to vasovagal syncope precipitated by fear, stress, anxiety, and emotional distress is accompanied by hypotension and sometimes bradycardia. INITIAL EVALUATION The goals of the initial evaluation are to determine whether the transient loss of consciousness was due to syncope; to identify the cause; and to assess risk for future episodes and serious harm (Table 23-1). The initial evaluation should include a detailed history, thorough questioning of eyewitnesses, and a complete physical and neurologic examination. Blood pressure and heart rate should be measured in the supine position and after 3 min of standing to determine whether orthostatic hypotension is present. High-risk features on history include the new onset of chest discomfort, abdominal pain, shortness of breath, or head ache; syncope during exertion or while supine; sudden onset of palpitations followed by syncope; and severe coronary artery or structural heart disease. High-risk features on examination include an unexplained sys tolic blood pressure of <90 mmHg; suggestion of gastrointestinal hemorrhage; persistent bradycardia (<40 beats/min); and an undi agnosed systolic murmur. An ECG should be performed if there is suspicion of syncope due to an arrhythmia or underlying cardiac disease. Relevant electrocardiographic abnormalities include bradyarrhythmias or tachyarrhythmias, AV block, acute myocardial ischemia, old myo cardial infarction, long QT, and bundle branch block. This initial assessment will lead to the identification of a cause of syncope in ~50% of patients and also allows stratification of patients at risk for cardiac mortality. Laboratory Tests Baseline laboratory blood tests are rarely help ful in identifying the cause of syncope. Blood tests should be per formed when specific disorders, e.g., myocardial infarction, anemia, and secondary autonomic failure, are suspected (Table 23-2).

Autonomic Nervous System Testing (Chap. 451) Autonomic test ing, including tilt-table testing, can be performed in specialized centers. Autonomic testing is helpful to uncover objective evidence of autonomic failure and also to demonstrate a predisposition to neurally mediated syncope. Autonomic testing includes assess ments of parasympathetic autonomic nervous system function (e.g., heart rate variability to deep respiration and a Valsalva maneuver), sympathetic cholinergic function (e.g., thermoregula tory sweat response and quantitative sudomotor axon reflex test), and sympathetic adrenergic function (e.g., blood pressure response to a Valsalva maneuver and a tilt-table test with beat-to-beat blood pressure measurement). The hemodynamic abnormalities demon strated on the tilt-table test (Figs. 23-2 and 23-3) may be useful in distinguishing orthostatic hypotension due to autonomic failure from the hypotensive bradycardic response of neurally mediated syncope. Similarly, the tilt-table test may help identify patients with syncope due to immediate or delayed orthostatic hypotension. Syncope CHAPTER 23 Carotid sinus massage should be considered in patients with symptoms suggestive of carotid sinus syncope and in patients

> 40 years with recurrent syncope of unknown etiology. This test should ideally be carried out under continuous ECG and blood pressure monitoring and should be avoided in patients with carotid bruits, possible or known plaques, or stenosis. Cardiac Evaluation ECG monitoring is indicated for patients with a high pretest probability of arrhythmia causing syncope. Patients should be monitored in the hospital if the likelihood of a lifethreatening arrhythmia is high, e.g., patients with severe coronary artery or structural heart disease, nonsustained ventricular tachy cardia, supraventricular tachycardia, paroxysmal atrial fibrillation, trifascicular heart block, prolonged QT interval, Brugada syndrome ECG pattern, syncope during exertion, syncope while seated or supine, and family history of sudden cardiac death (Table 23-1). Continuous ambulatory electrocardiographic (Holter) monitoring is recommended for patients who experience frequent syncopal episodes (e.g., daily or almost daily), whereas loop recorders, which continually record and erase cardiac rhythm, are indicated for patients with suspected arrhythmias with low risk of sudden car diac death. Loop recorders may be external (e.g., for evaluation of episodes that occur at a frequency of >1 per month) or implantable (e.g., if syncope occurs less frequently). The monitoring duration should ideally be at least twice the interspell duration. Echocardiography should be performed in patients with a his tory of cardiac disease or if abnormalities are found on physical examination or the ECG. Echocardiographic diagnoses that may be responsible for syncope include aortic stenosis, hypertrophic cardiomyopathy, cardiac tumors, aortic dissection, and pericardial tamponade. Echocardiography also has a role in risk stratification for sudden cardiac death based on the left ventricular ejection fraction. Treadmill exercise testing with ECG and blood pressure moni toring should be performed in patients who have experienced syncope during or shortly after exercise. Treadmill testing may help identify exercise-induced arrhythmias (e.g., tachycardia-related AV block) and exercise-induced exaggerated vasodilation. Invasive electrophysiologic studies are indicated in patients with structural heart disease and ECG abnormalities in whom noninvasive investigations have failed to yield a diagnosis. Elec trophysiologic studies have low sensitivity and specificity and should only be performed when a high pretest probability exists. Currently, these tests are rarely performed to evaluate patients with syncope. Psychiatric Evaluation Screening for psychiatric disorders may be appropriate in patients with recurrent unexplained syncope episodes. Tilt-table testing, with demonstration of symptoms in the absence of hemodynamic change, may be useful in reproducing syncope in patients with suspected psychogenic syncope.

Revision #1
Created 2026-01-06 16:31:14 UTC by Omar Ayman
Updated 2026-01-06 16:31:14 UTC by Omar Ayman