Neurologically injured patients, regardless of the nature of the injury, frequently experience hypotension and shock. Neurogenic shock refers to a neurologically mediated form of circulatory system failure that can occur with acute brain, spinal cord, or even peripheral nerve injuries. In this chapter, we will explain the epidemiology, pathophysiology, clinical presentation, and management strategies for this special form of shock.

Contrary to common belief, neurogenic shock is not a single entity due to one single pathologic mechanism. The term is sometimes used in neuroscience intensive care units to explain hypotension occurring in any brain-injured patient, but neurogenic shock should be considered only after systemic causes of shock have been carefully ruled out. Just like other critically ill patients, neurologically ill patients are prone to developing systemic conditions, such as dehydration, congestive heart failure, acute blood loss, sepsis, pericardial tamponade, or massive pulmonary embolism.

### SUBTYPES OF NEUROGENIC SHOCK

Once other systemic reasons for shock have been ruled out, neurogenic shock should be considered. Three mechanisms can lead to neurogenic shock (Fig. 59.1):

- Vasodilatory (distributive) shock from autonomic disturbance with interruption of sympathetic pathways, with associated parasympathetic excitation, which causes profound vasodilatation and bradycardia, as seen in spinal cord injury or diseases of the peripheral nervous system (Guillain-Barré syndrome).
- Cardiogenic shock, as frequently seen in subarachnoid hemorrhage (SAH) with stunned myocardium after a cerebrospinal fluid or ischemic stroke, especially those involving the right insula.
- Hypopituitarism/adrenal insufficiency.

Although some subtypes of neurogenic shock occur more frequently with certain disease entities—for example, cardiogenic neurogenic shock after SAH, vasodilatory neurogenic shock with spinal cord injury—significant overlap exists between different disease entities (intracerebral hemorrhage [ICH], SAH, traumatic brain injury [TBI], ischemic stroke), and one cannot establish a firm rule by which neurogenic shock occurs. Interestingly, only some patients with neurologic injuries experience true neurogenic shock, and it remains difficult to predict in whom this will be seen.

### INCIDENCE OF NEUROGENIC SHOCK

Due to the small number of prospective epidemiologic studies, it is difficult to establish the natural incidence of neurogenic shock. In a retrospective review of cervical spinal cord injuries, Bilello et al. (1) reported a 31% incidence of neurogenic shock with hypotension and bradycardia after high cervical spinal cord injury (C1–C3) and 24% after low cervical spinal cord injury (C6–C7).

Cardiogenic neurogenic shock has been studied foremost in SAH and ischemic stroke. Banks et al. (2) prospectively studied the incidence of left ventricular (LV) dysfunction with transesophageal echocardiography (TTE) in the first 7-day period after SAH in 173 patients. Thirteen percent had a normal ejection fraction (EF) but had regional wall motion abnormalities that did not correlate with coronary artery territories, and 15% had an LVEF of less than 50%. Others report a 9% incidence of LV wall motion abnormalities, resulting in hypotension requiring vasopressor therapy, as well as pulmonary edema in most (80%) of these patients (3). The spectrum of injury can range from mild to severe systolic dysfunction—the latter defined as an EF less than 30%. Pollick et al. (4) observed LV abnormalities on TTE in 4 of 13 patients (31%) studied within 48 hours of SAH. Resolution of these neurologically mediated wall motion abnormalities is usually seen (2,3,5).

The third subtype of neurogenic shock, adrenal insufficiency, has been studied primarily in traumatic brain injury: in the largest study to date, adrenal insufficiency occurred in about 50% of patients and led to hypotension in 26% (6). Although it has been documented in other cases of acute brain injury, the exact incidence and relationship to outcome is not clear (7).

### PATHOPHYSIOLOGY OF NEUROGENIC SHOCK

#### Vasodilatory Neurogenic Shock

This variation of neurogenic shock is commonly seen with spinal cord injuries and Guillain-Barré syndrome (acute demyelinating peripheral neuropathy) but also with traumatic brain injuries, large hemispheric ischemic strokes, and intracerebral hemorrhages. The hallmark of vasodilatory neurogenic shock is the combination of bradycardia with fluctuating blood pressures and heart rate variability due to interruption of sympathetic output and excitation of parasympathetic fibers.

The sympathetic fibers originate in the hypothalamus, giving rise to neurons projecting to autonomic centers in the...
Shock States

Neurogenic shock consists of three pathomechanisms. CNS, central nervous system; CO, cardiac output; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury.

Vasodilatory Shock due to autonomic dysfunction with unopposed vagal tone
- Bradycardia, hypotension
- Seen in cervical and upper thoracic spinal cord injury

Neurogenic Shock due to pial or adrenergic dysfunction after CNS injury
- Hypotension poorly responsive to vasopressor therapy
- Seen in TBI, SAH, hypotalmic stroke

Neuroendocrine Shock due to pial or autonomic dysfunction after CNS injury
- Hypotension poorly responsive to vasopressor therapy
- Seen in TBI, SAH, hypotalmic stroke

Cardiogenic Shock due to stunned myocardium after catecholamine surge
- Tachycardia, hypertension
- Seen in SAH, ischemic stroke

FIGURE 59.1. Neurogenic shock consists of three pathomechanisms. CNS, central nervous system; CO, cardiac output; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury.

Brainstem—the periaqueductal gray matter in the midbrain, the parabrachial regions in the pons, and the intermediate reticular formation located in the ventrolateral medulla. From here, neurons project to nuclei in the spinal cord. The sympathetic preganglionic neurons originate in the intermediolateral column of the spinal cord gray matter between T1 and L2 and are therefore called the thoracolumbar branches. From here, they exit the spinal cord and project to 22 pairs of paravertebral sympathetic trunk ganglia next to the vertebral column. The main ganglia within the sympathetic trunk are the cervical and stellate ganglia. The adrenal medulla receives preganglionic fibers and thus is equivalent to a sympathetic ganglion.

Blood pressure control depends on tonic activation of the sympathetic preganglionic neurons by descending input from the supraspinal structures (8).

The parasympathetic nervous system consists of cranial and sacral aspects. The cranial subdivision originates from the parasympathetic brainstem nuclei of cranial nerves III, VII, IX, X, and XI. The cranial parasympathetic neurons travel along the cranial nerves until they synapse in the parasympathetic ganglia in close proximity to the target organ. The sacral subdivision originates in the sacral spinal cord (S2–S4), forming the lateral intermediate gray zone where preganglionic neurons synapse with parasympathetic ganglia within the target organs. The main ganglia receiving sympathetic preganglionic innervation are the cardiac ganglia. Cardiac ganglia receive preganglionic fibers from the sympathetic nervous system by ascending input from the brainstem—the periaqueductal gray matter in the midbrain, the parabrachial regions in the pons, and the intermediate reticular formation located in the ventrolateral medulla. From here, neurons project to nuclei in the spinal cord. The sympathetic preganglionic neurons originate in the intermediolateral column of the spinal cord gray matter between T1 and L2 and are therefore called the thoracolumbar branches. From here, they exit the spinal cord and project to 22 pairs of paravertebral sympathetic trunk ganglia next to the vertebral column. The main ganglia within the sympathetic trunk are the cervical and stellate ganglia. The adrenal medulla receives preganglionic fibers and thus is equivalent to a sympathetic ganglion.

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Injury to the brain can also lead to vasodilatory neurogenic shock. Certain cerebral structures, such as the insular cortex, amygdala, lateral hypothalamus, and medulla, have great influence on the autonomic nervous system. Cortical asymmetry is present and is reflected in a higher incidence of tachycardia, ventricular arrhythmias, and hypertension with lesions of the right insula—resulting in loss of parasympathetic input and thus sympathetic predominance—and a higher incidence of bradycardia and hypertension with injuries to the left insula—resulting in a loss of sympathetic input and subsequent parasympathetic predominance (16–18) (Fig. 59.2).

Cardiogenic Neurogenic Shock

This form of neurogenic shock is primarily encountered in SAH and TBI but is also seen in ischemic stroke and intracerebral hemorrhage. Cardiac dysfunction is a well-known complication of ischemic and hemorrhagic stroke, first described over 50 years ago (19). It is most often recognized on the electrocardiogram (ECG) as arrhythmias, QRS, ST-segment, and
FIGURE 59.2. Example of a right ischemic stroke resulting in ventricular arrhythmias and cardiogenic shock. A 61-year-old man presents with sudden onset of left hemiparesis affecting his face and arm, left-sided neglect, and a left hemianopia. He presented outside of any acute treatment window and did not undergo thrombolysis. He was admitted to the neurointensive care unit (NICU) for close monitoring of his cardiac and respiratory function. The noncontrast head CT shows a right middle cerebral artery stroke and incidental hemorrhagic conversion. Electrocardiogram on admission showed diffuse T-wave inversion in all leads. Telemetry monitoring revealed frequent premature ventricular complexes and intermittent nonsustained ventricular tachycardia of 4 to 8 beats for the first 72 hours after stroke onset. His systolic blood pressure on admission was elevated at 190 mm Hg but then dropped to 85 mm Hg several hours after admission to the NICU, requiring vasopressor support for 2 days. Troponin T levels were elevated in the emergency room and peaked at 12 hours after stroke onset. Echocardiogram showed global hypokinesis and no regional wall motion abnormalities. No other causes for shock were found, so that the stroke involving the right insula was the most likely cause. The shock slowly resolved over 72 hours, and vasopressor infusion was weaned off successfully. A repeat echocardiogram 2 weeks later showed resolution of the abnormalities.

T-wave abnormalities (20,21). Studies of SAH and cardiac injury have shown that the severity of SAH is an independent predictor of cardiac injury, supporting the hypothesis that cardiac neurogenic shock is a neurally mediated process (22). Based on the similarities observed between pheochromocytoma crisis and SAH, the cardiovascular changes have been linked to a catecholamine surge. The hypothesis has been confirmed by many studies. Patients with SAH can have a threefold increase in norepinephrine levels that are sustained for 10 days or longer after SAH but that normalize after the acute phase of injury (23). In an animal model, an increase in plasma catecholamines after experimental SAH causes specific lesions on electron microscopy within 4 hours of SAH (24). Selective myocardial cell necrosis, also known as contraction band necrosis, is the hallmark of catecholamine exposure (25–27). The same lesions can be found in patients with pheochromocytoma (28) and SAH (29), underlining the pathologic mechanism of cardiac injury in SAH or other neurologic injuries (Fig. 59.3). The cardiac dysfunction is not related to coronary atherosclerosis, as normal coronary arteries have been documented in these patients studied at autopsy or by coronary angiography (5,29–31). In fact, it appears that pre-existing heart disease, such as hypertensive heart disease, might even be protective of this form of neurogenic shock (32).

In a case series of 54 consecutive SAH deaths, 42 had myocardial lesions consisting of foci of necrotic muscle fibers, hemorrhages, and inflammatory cells, none of which were found in the control group. Patients with a wider range of heart rate and blood pressure fluctuations were more likely to have myocardial lesions. Pre-existing hypertensive heart disease led to significantly fewer myocardial lesions, possibly reflecting a decreased sensitivity of these patients to the catecholamine surge (32).

Pathologic studies link the central catecholamine release to the posterior hypothalamus. Postmortem studies have found microscopic hypothalamic lesions consisting of small hemorrhages and infarctions in those patients with typical myocardial lesions as noted above (29,32–34). However, it appears that raised intracranial pressure (ICP) is not responsible for these hypothalamic changes, as the control group with elevated ICP did not have any hypothalamic injury (32).

Overall, by the described pathomechanism, the catecholamine surge results in direct myocardial injury resulting in decreased inotropy, and in addition an increase in cardiac preload due to venous constriction and increased cardiac afterload by peripheral arterial constriction. As a consequence, stroke volume diminishes, which cannot be compensated for by reflex tachycardia, thus resulting in decreased cardiac output and shock. This transient LV dysfunction with loss of myocardial compliance (stunning of the myocardium) is reflected by a characteristic shape of the cardiac silhouette on a ventriculogram and on chest radiograph, which has given this disease...
entity its other name, Takotsubo cardiomyopathy, derived from the Japanese word for the Japanese octopus fishing pot, *takotsubo* (35–37) (Fig. 59.4).

Pulmonary edema with concomitant hypoxia is frequently encountered in this context and may result from cardiac congestion but can occur independently from the cardiac dysfunction as its own entity: neurogenic pulmonary edema. Massive increases in pulmonary capillary pressures lead to pulmonary edema and hypoxia, which in turn decreases the uptake of oxygen in a high demand state, contributing to hemodynamic instability. The Vietnam war era head injury series (38) reported the rapid onset of acute pulmonary edema after severe head injury. In addition, experimental models as well as multiple human case reports of TBI and SAH have shown massive
sympathetic discharges as the primary cause of neurogenic pulmonary edema (39–41). Figure 59.5 summarizes the pathophysiology of cardiogenic neurogenic shock.

Overall, cardiac neurogenic shock, with or without neurogenic pulmonary edema, is usually transient, with resolution within several days to 2 weeks (2–4). Prevention of secondary brain injury from hypoxia and decreased cerebral perfusion pressures should be the focus of care in the management of this neurally mediated complication.

**Neuroendocrine Neurogenic Shock**

Insufficiency of the hypothalamic-pituitary-adrenal axis has been recognized as an important cause for shock. Inappropriately reduced release of cortisol in stress situations can lead to decreased systemic vascular resistance, reduced cardiac contractility, hypovolemic shock, or hyperdynamic shock that can mimic septic shock. Secondary adrenal insufficiency due to injury to the hypothalamic-pituitary feedback loop can cause neuroendocrine neurogenic shock. Acute brain injury, particularly TBI and SAH, can commonly lead to injury of the hypothalamus, pituitary gland, or the connecting structures (42). Cohan et al. (6) revealed that adrenal insufficiency after traumatic brain injury occurred in about half of all patients and led to a significantly higher rate of hypotension in these patients. Most cases of adrenal insufficiency developed within 4 days of injury. Importantly, the authors defined adrenal insufficiency using a low random serum cortisol value and highlight the fact that an increase in the cortisol level after a stimulation test does not rule out the presence of adrenal insufficiency.

This issue is particularly relevant in TBI patients, in whom the hypothalamus and the pituitary gland are the likely affected organs, and the adrenal glands might well be expected to mount an appropriate response when stimulated. When recognized, primary and secondary adrenal insufficiency can easily be treated.

In septic shock, a low-dose vasopressin infusion has been shown to successfully restore blood pressure in hypotension refractory to standard catecholamine therapy (43,44). Recent studies in SAH have shown that endogenous vasopressin serum levels are elevated during the first 2 days after SAH but decrease to subnormal levels after 4 days (45–47). Arginine vasopressin supplementation in SAH at low dose (0.01–0.04 units/min) has been studied in only one single retrospective study (48). The role of vasopressin in the setting of neurogenic shock remains to be studied in a prospective manner, but the changes in endogenous vasopressin levels might indicate neuroendocrine changes in neurogenic shock and potential new treatment options in SAH.

**CLINICAL MANIFESTATIONS**

Figure 59.6 illustrates the clinical manifestations and symptoms seen in neurogenic shock. Acutely, vasodilatory neurogenic shock presents with a “warm and dry” hemodynamic profile. The patient is hypotensive and frequently bradycardic; however, the peripheral vessels are dilated, leading to warm limbs and a normal capillary refill time. Central venous pressure (CVP) is normal or low, and systemic venous resistance (SVR) is always low. Stroke volume and cardiac output are low due to the unopposed vagal tone. When a spinal cord injury is present, a difference in smooth muscle and vasculature tone can be observed between the body parts above and below the level of the injury. For example, in an injury at thoracic level 7 (T7), normal upper limb perfusion might be observed, while vasodilatation below T7 leads to warm and dry lower extremities. Orthostatic hypotension without reflex tachycardia on changing from a supine to an upright position—by standing...
or with reverse Trendelenburg position—is common. When treating this form of neurogenic shock with a vasopressor infusion (such as phenylephrine or other pressors), extreme caution should be applied, as vasopressor hypersensitivity can lead to severe rebound hypertension, which can be difficult to control.

Cardiogenic neurogenic shock manifests as hypotension and tachycardia, with bradycardia seen rarely. Peripheral vessels are often vasoconstricted, leading to a high SVR and cold and wet skin. Vascular filling, as measured by CVP, pulmonary capillary wedge pressure (PCWP), and end-diastolic volume index (EDVI), is normal or high, with low stroke volumes and cardiac output due to global myocardial dysfunction. Leaking of cardiac enzymes—troponin, creatine kinase (CK), CK-MB—may be seen, but frequently the peak levels are not as high as one would find in myocardial infarction. It is difficult to establish a cutoff value that differentiates stunned myocardium from myocardial infarction with atherosclerotic coronary artery disease. A retrospective study in SAH measuring troponin-I levels has reported an appropriate cutoff value to be 2.8 ng/mL (49), whereas CK-MB did not help differentiate between the two kinds of myocardial injury. Higher levels of troponin should raise the suspicion of true myocardial infarction, and ECG and echocardiography correlation is important.

Neuroendocrine neurogenic shock presents with hypotension that does not respond well to vasopressor infusion. Hemodynamic signs of this category of neurogenic shock are low CVP, SVR, stroke volume, and cardiac output. Low baseline cortisol levels are the hallmark. A cosyntropin stimulation test frequently leads to an appropriate increase in the cortisol level, which does not rule out the presence of neuroendocrine neurogenic shock, as the adrenal gland is usually not the primarily affected organ (6). For this reason, we do not find any clinical utility in this test when neuroendocrine neurogenic shock is suspected. Resolution of the hypotension with the use of hydrocortisone clinically confirms the presence of this shock form.

### DIAGNOSTIC CONSIDERATIONS

In any case of hypotension and shock in the neurointensive care unit, systemic causes for shock must be ruled out first. Especially in the paralyzed patient (for example, one with a high spinal cord injury), recognition of other life-threatening injuries can be quite difficult. Signs of hypovolemic shock may be absent, even in a patient with profound internal bleeding, because of the absence of sympathetic tone below the level of injury. The usual pallor from vasoconstriction and reflex tachycardia might also be absent. The patient may even be bradycardic while continuing to bleed. For the same reason, signs of peritoneal irritation may be absent in patients with abdominal injuries. The reported incidence of pulmonary embolism (PE) varies tremendously in the neurocritical care patient population—ranging from 0.5% to 20% in ischemic stroke (50,51), to 1% in intracranial hemorrhage (52), to 8.4% in brain tumors (53)—and there are only limited data during the acute phase of subarachnoid hemorrhage, traumatic brain injury, and spinal cord injury (31). Interestingly, according to the study by Skaf et al. (50) using the National Hospital Discharge Survey, the incidence of PE did not change in patients with ischemic and hemorrhagic stroke between 1979 and 2003. However, the death rate from PE in the subgroup with ischemic stroke decreased, likely due to an increased use of antithrombotic prophylaxis over the last 20 years (54). Additionally, over the last two decades, the methods of PE detection have improved immensely—for example, pulmonary CT-angiogram versus nucleotide scan—and autopsy studies report additional asymptomatic cases. In our opinion, the true incidence of PE is underestimated. Pulmonary embolism should always be considered in cases of refractory shock. If profound hypotension is present, or hypotension becomes progressive, reasons other than neurogenic shock should be suspected and thoroughly ruled out.
Every patient should undergo serial ECGs, serial cardiac enzyme measurements, and a chest radiograph. As previously mentioned, neurogenic shock, neuroendocrine, and neurocardiogenic injury may occur together or separately, making chest x-ray films important diagnostic tools. In particular, one should look for pulmonary vascular congestion and evaluate the size and shape of the cardiac silhouette. Hemodynamic monitoring with continuous blood pressure and central venous pressure (CVP) monitoring with an arterial line and central venous line (CVL) should be undertaken. Blood pressure measurements should be done continuously with an arterial line. Arteriolar vasoconstriction of the upper extremities is common and should be kept in mind either when there is a large discrepancy between right- and left-sided pressures or when the clinical appearance of the patient does not match the readings from the arterial line. Central venous access is key for determining CVP and for the administration of fluids and medications, especially vasopressors. The site of the placement of the central venous line (CVL) may play an important role in the management of shock in a neurologically injured patient. Subclavian vein catheters are the preferred site in patients with elevated intracranial pressure (ICP), as there is a theoretical risk of venous stasis within the internal jugular vein with venous congestion and higher risk for venous sinus thrombosis, which could result in increased ICP (53). In addition, trauma patients frequently have cervical spine injuries and require cervical collars, making the internal jugular vein accessible only with difficulty.

In patients with cardiogenic neurogenic shock, more extensive hemodynamic monitoring may be necessary with either noninvasive cardiac monitoring devices or a pulmonary artery catheter (PAC). Echocardiography is very important to understanding the etiology of shock. In most cases, a transthoracic echocardiogram is sufficient. The typical echocardiographic appearance is that of apical ballooning, which results from global hypokinesis sparing the apex (56). This part of the heart is devoid of sympathetic nerve terminals, supporting the hypothesis that cardiac injury in SAH is neurally mediated by a sympathetic storm. Segmental wall motion abnormalities not conforming to distinct coronary artery territories is another characteristic echocardiographic finding. However, myocardial infarction from ischemic coronary disease is frequently seen in brain-injured patients, just as in any critically ill patient, and should always be ruled out first as a cause of shock. In the setting of fever and shock, blood cultures must be obtained and the patient appropriately covered with antibiotics until the cultures yield results. However, older and immunosuppressed patients may not mount an appropriate febrile response, and thus sepsis should still be considered in these patients even when they are afebrile, especially in the setting of a rising white blood cell (WBC) count. Cerebral spinal fluid cultures are very important in the neurointensive care unit, with antibiotic coverage of potential central nervous system CNS infections, especially in patients after head trauma with skull fracture or sinus disease, after instrumentation of the head or spinal canal, or in immunocompromised patients. Placement of intracranial pressure measurement devices do not contribute to the diagnostic workup of shock, but they are important tools in the management of neurogenic shock, such as when the goal mean arterial pressure (MAP) is being titrated to the cerebral perfusion pressure. Finally, adrenal insufficiency should always be considered. Random serum cortisol levels should be obtained in the early stages of shock, keeping in mind that in some forms of brain injury, low random serum cortisol levels, and thus adrenal insufficiency, may be encountered for several days after injury (6).

Many neurologically injured patients, especially those with spinal cord injuries, receive steroids while in the neurointensive care unit. The doses administered may be high enough to alter the result of a random serum cortisol level, but often the dose is not enough to treat true adrenal insufficiency appropriately. In these cases, one could either empirically treat with higher doses of steroids that also treat adrenal insufficiency—hydrocortisone, with or without fludrocortisone—or, keeping the potential adverse effects of steroids in acute injury in mind, one could withhold the administration of steroids for 12 hours, then obtain a random cortisol level and resume steroid treatment right after the blood draw. However, hypotension is frequently severe enough that immediate treatment is warranted, and withholding steroids often is not an option. Dexamethasone, which is frequently used in the neurointensive care unit, is the steroid that interferes the least with the cortisol assay after a corticotropin stimulation test and therefore allows for such a test. In cases of high suspicion, a random cortisol level is often preferred because of its simplicity. The cortisol level should be drawn immediately before the steroid dose. However, given the lack of mineralocorticoid activity of dexamethasone, changing to hydrocortisone with or without fludrocortisone is recommended when adrenal insufficiency is suspected.

**Chapter 59: Neurogenic Shock**

**Management**

Two important reasons for early and proactive treatment of patients in neurogenic shock (57).

1. Prevention of secondary brain injury from hypoxia and hypotension

2. The fact that neurogenic shock, especially cardiogenic and neuroendocrine forms, is easily treatable and transient, with potentially good outcomes despite the moribund appearance of the patient in the acute phase.

Identifying patients at risk has been very difficult, but at least in SAH it appears that poor neurologic grade, age older than 30 years, and ventricular repolarization abnormalities are risk factors for neurogenic shock (57).

Once the diagnosis of neurogenic shock has been established and the pathophysiology (subtype) has been understood, treatment tailored to the specific subtype is initiated. In all cases, euvolemia is of utmost importance and must be achieved before any other treatment can be successful. In general, vasopressor treatment as a continuous infusion is initiated and titrated to a goal MAP and cerebral perfusion pressure (CPP). As an important management tool, an intracranial pressure measurement device is very helpful, allowing the indirect measurement of CPP. We recommend a goal CPP of greater than or equal to 65 mm Hg. The optimal CPP is not known. Data regarding the minimum tolerable CPP comes from TBI patients, in whom the ICP is often elevated. Several studies have suggested an improved outcome when CPP is maintained at greater than 70 mm Hg (58,59). Other studies using physiologic measurements, such as cerebral blood flow and brain tissue PO2 (PbO2), indicate that adverse changes do not occur unless the CPP is below 50 to 60 mm Hg (60,61).

Vasodilatory neurogenic shock can be difficult to treat. In general, vagal tone predominates; however, in this state,
patients frequently have peripheral α-adrenergic receptor hyperre- sponsiveness, limiting the use of norepinephrine, epinephrine, ephedrine, and phenylephrine. In fact, sympathomimetics should be avoided as they can lead to severe blood pressure fluctuations. Since arginine vasopressin (AVP) does not affect α- or β-adrenergic receptors, but acts on V1 receptors, AVP may have adverse effects on neurologically ill patients. This concern is based on animal studies indicating that vasopressin may promote the development of vasospasm in SAH, and indi- rect experimental studies showing a reduction in brain edema with vasopressin antagonists. No prospective human study has been undertaken to confirm or dismiss this concern, and the only retrospective study on the use of vasopressin in SAH did not show any of these potentially adverse effects (48). In addi- tion to vasopressors, a temporary demand pacemaker and/or atropine may be required in cases of refractory bradycardia and hypotension.

In neurogenic shock, some form of inotropic support may be necessary, either in the form of a dobutamine, milrinone, or norepinephrine infusion. Dopamine is generally avoided because of its proarrhythmic properties. Dobutamine and milrinone also have vasodilatory effects, frequently lead- ing to more hypotension, requiring additional therapy with an α-receptor agonist, such as norepinephrine or phenylephrine. Afterload increases in the former, and tachycardia in the latter, might be limiting factors and need careful monitoring. Cardiac output monitoring may be undertaken with the guidance of a PAC, and β-blockade is usually not recommended. In neuro- genic cardiogenic shock, coronary artery disease is typically not present, and compensatory tachycardia is necessary to main- tain cardiac output. Afterload reduction with cautious use of angiotensin-converting enzyme (ACE) inhibitors should be at- tempted, but further hypotension must be avoided to main- tain tenuous cerebral perfusion pressures. Short-acting agents should be used whenever possible. Repeating a echocar- diogram several days after the initial one is recommended to moni- tor the progression/resolution of cardiac dysfunction. The need for an intra-aortic balloon pump to mechanically reduce after- load and improve coronary perfusion pressure may be consid- ered, albeit rarely used.

Once diagnosed, neuroendocrine neurogenic shock from primary, or more often secondary, adrenal insufficiency is treated with steroid replacement therapy. We use the same dos- ing as in adrenal insufficiency in septic shock: hydrocortisone, 50 mg intravenously every 6 hours. As previously discussed, a cortisol stimulation test is usually not helpful, and empiric treatment after a random cortisol level should be initiated.

**SUMMARY**

Neurogenic shock is not a single entity, but rather is composed of three subtypes and pathophysiologies: vasodilatory, cardiac, and neuroendocrine. Other causes of hypotension should be ruled out first, prior to making the diagnosis of neurogenic shock. In most cases, neurogenic shock is transient and re- versible, making this entity very treatable. Diagnosis and treat- ment should be tailored to the subtype of neurogenic shock. Maintenance of cerebral perfusion pressures is the key prin- ciple of management to prevent secondary brain injury and improve outcome.

**References**

Anaphylaxis is severe, has a rapid onset, and is potentially fatal—a systemic allergic reaction that occurs after contact with an allergy-causing substance (1,2). Activation of mast cell and basophil populations by either IgE-dependent (i.e., anaphylactic reactions) or IgE-independent (i.e., anaphylactoid reactions) mechanisms results in the release of multiple mediators capable of altering vascular permeability and vascular and bronchial smooth muscle tone, as well as recruiting and activating inflammatory cell cascades. Because the clinical presentations and severities of anaphylactic and anaphylactoid reactions are indistinguishable, they will be referred to as anaphylaxis for the purposes of this chapter. Initial sequelae, which occur within minutes to an hour after exposure to an inciting stimulus, include generalized hives, tachycardia, flushing, pruritus, faintness, and a sensation of impending doom. Dermatologic (i.e., urticaria and angioedema), respiratory (i.e., dyspnea, wheeze, stridor, bronchoospasm, and hypoxemia), and gastrointestinal (i.e., abdominal distension, nausea, emesis, and diarrhea) manifestations are common. Involvement of the cardiovascular and respiratory systems may result in potentially life-threatening manifestations, such as cardiovascular collapse caused by vasodilation and capillary leak, myocardial depression, myocardial ischemia and infarction, and atrial fibrillation (3). Prompt recognition and effective intervention are essential to prevent the fatal manifestations of anaphylactic and anaphylactoid reactions.
The incidence of anaphylaxis is difficult to determine accurately due to underdiagnosis and underreporting. In the United States, fatal anaphylaxis causes 500 to 1,000 fatalities per year and accounts for 1% of emergency department visits (1,4,5). The anaphylaxis rate was found to be 21 per 100,000 person-years in a study of nonhospitalized individuals in Olmsted County, Minnesota, between 1983 and 1987 (6). A subsequent analysis of the General Practice database in the United Kingdom noted the incidence to be 8.4 per 100,000 person-years (7). An epidemiologic study involving 481,752 individuals suggested that hospitalized patients are at increased risk of anaphylaxis, but these reactions are rarely fatal (8).

**ETIOLOGY**

The most common causes of anaphylaxis include insect stings, foods, drugs, and physical factors/exercise. Idiopathic anaphylaxis (where no causative agent is identified) accounts for up to two thirds of patients referred to allergy/immunology specialty clinics (9,10). Foods such as shellfish, eggs, nuts, and milk account for one third of food-induced anaphylactic episodes (10–13) (Tables 60.1 and 60.2). There is a syndrome of food-dependent, exercise-induced anaphylaxis (FDEIA) that develops only if food is ingested prior to exercise or exertion (14). Seafood, nuts, celery, wheat, and grains have been implicated as allergens in this syndrome. It is important to note that these foods are tolerated by the patient in the absence of exertion (14,15). Anaphylactic reactions to stings or bites of various insects, such as members of the order Hymenoptera (yellow jackets, bees, wasps, hornets, and saw flies) are commonly reported. A positive venom skin test along with a systemic reaction to the insect sting predicts a 50% to 60% risk of reaction to future stings (16). Medications can cause anaphylactic (IgE-mediated) and anaphylactoid (non-IgE-mediated) reactions. Previous exposure to drugs is required for IgE production and anaphylactic reactions, but anaphylactoid reactions can occur upon first administration. Penicillin is one of the most common causes of anaphylaxis, with 1 to 3 per 10,000 courses with penicillin resulting in allergic reactions and 1 in 50,000 to 1 in 100,000 courses with a fatal outcome (17–19). Non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin are the second most common class of drugs implicated in anaphylactic (20). Some hypersensitivity reactions will occur with different NSAID agents, while others are specific to a single drug (21).

With widespread adoption of universal precautions against infections, latex allergy has become a significant problem. The development of latex-free gloves has been associated with reduction in occupational-contact urticaria caused by latex rubber gloves (22). Despite this, latex allergy is still a concern since latex is found in gloves, catheters, and tubing (23–25). Iodinated radiocontrast media can cause anaphylaxis, however, life-threatening reactions are rare (26). A history of a previous reaction to radiocontrast media, asthma or atopic disease, treatment with β-blockers, and cardiovascular disease are risk factors for developing anaphylaxis to radiocontrast media (27–29).

**INCIDENCE**

The clinical syndromes associated with systemic anaphylactic and anaphylactoid reactions represent medical emergencies, as they are associated with a rapid, critical destabilization of vital organ systems. These syndromes, which are, again, clinically indistinguishable, may become rapidly fatal if appropriate therapy is not instituted immediately. Initial symptoms can appear within seconds to minutes but may be delayed by as much as 1 (or rarely more) hour after exposure to an inciting agent (30), and are often nonspecific (31). These symptoms include tachycardia, faintness, cutaneous flushing, urticaria, diffuse or palmar pruritus, and a sensation of impending doom (32). Of these, generalized urticaria is the most common, occurring in approximately 90% of patients (Table 60.3) (33,34). Subsequent manifestations indicate involvement of the cutaneous, gastrointestinal, respiratory, and cardiovascular systems. Involvement of the cardiovascular and respiratory systems is responsible for the fatal outcome (35).

**TABLE 60.1**

**ETOLOGIC AGENTS FOR ANAPHYLAXIS (IGE-MEDIATED)**

<table>
<thead>
<tr>
<th>HAPTONS</th>
<th>VENOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Lactam antibiotics</td>
<td>Stinging insects, particularly Hymenoptera, bees, wasps, flies, jelly fish, kissing bugs (triatoma), and rafflesianes</td>
</tr>
<tr>
<td>Sulfonylides</td>
<td>Others</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>HORMONES</td>
</tr>
<tr>
<td>Demethylchlortetracycline</td>
<td>Adrenal corticosterone hormone</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Thyroid-stimulating hormone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SERUM PRODUCTS</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>γ-Globulin</td>
<td>ENZYMES</td>
</tr>
<tr>
<td>Immunotherapy for allergic diseases</td>
<td>Chymopapain</td>
</tr>
<tr>
<td>Heterologous serum</td>
<td>L-Asparaginase</td>
</tr>
<tr>
<td>MISCELLANEOUS</td>
<td>Other</td>
</tr>
<tr>
<td>Seminal fluid</td>
<td>Others</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FOODS</th>
<th>VENOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuts (peanuts, Brazil nuts, hazelnuts, cashews, pistachios, almonds, soy nuts)</td>
<td>Others</td>
</tr>
<tr>
<td>Shellfish</td>
<td>MISCELLANEOUS</td>
</tr>
<tr>
<td>Buckwheat</td>
<td>Seminal fluid</td>
</tr>
<tr>
<td>Egg white</td>
<td>Others</td>
</tr>
<tr>
<td>Cottonseed</td>
<td>HORMONES</td>
</tr>
<tr>
<td>Cows’ milk</td>
<td>Adrenocorticosterone hormone</td>
</tr>
<tr>
<td>Corn</td>
<td>Thyroid-stimulating hormone</td>
</tr>
<tr>
<td>Potato</td>
<td>Others</td>
</tr>
<tr>
<td>Rice</td>
<td>Others</td>
</tr>
<tr>
<td>Legumes</td>
<td>Others</td>
</tr>
<tr>
<td>Citrus fruits</td>
<td>Others</td>
</tr>
<tr>
<td>Chocolate</td>
<td>Others</td>
</tr>
</tbody>
</table>

Boldface: relatively common causes

Chapter 60: Anaphylactic Shock

TABLE 60.2
ETIOLOGIC AGENTS FOR ANAPHYLACTOID REACTIONS

<table>
<thead>
<tr>
<th>COMPLEMENT-MEDIATED REACTIONS</th>
<th>ARACHIDONIC ACID MODULATORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Serum</td>
<td>Tarrazine (possible)</td>
</tr>
<tr>
<td>Plasma</td>
<td></td>
</tr>
<tr>
<td>Plasman (but not albumin)</td>
<td></td>
</tr>
<tr>
<td>Immunoglobins</td>
<td></td>
</tr>
<tr>
<td>NONIMMUNOLOGIC MAST CELL ACTIVATORS</td>
<td>UNKNOWN</td>
</tr>
<tr>
<td>Opiates and narcotics</td>
<td>Sulfites</td>
</tr>
<tr>
<td>Radiocontrast media</td>
<td>Others</td>
</tr>
<tr>
<td>Neurontics</td>
<td>THERMOREGULATORY MECHANISM</td>
</tr>
<tr>
<td></td>
<td>Cold temperature, exercise</td>
</tr>
</tbody>
</table>

**Boldface**: Relatively common causes.

Adapted from Kaliner M. Anaphylaxis. NER Allergy Proc. 1984;5:324.

Complications of anaphylactic/anaphylactoid reactions. An unsettling sensation—including hoarseness, dysphonia, or dyspnea—may precede acute upper airway obstruction secondary to laryngeal edema. Other pulmonary manifestations include acute bronchospasm, intra-alveolar pulmonary hemorrhage, bronchoconstriction, and antracoidogenic, high permeability-type pulmonary edema (17,35). Tachycardia and syncope may precede the development of hypotension and frank cardiovascular collapse (36,37). Anaphylactic shock occurs as a consequence of diminished venous return secondary to systemic vasodilatation and intravascular volume contraction caused by capillary leak. Although transient increases in cardiac output may occur at the onset of anaphylaxis, hemodynamic parameters later reveal decreases in cardiac output, systemic vascular resistance, stroke volume, pulmonary artery occlusion, and central venous pressures (38–44). In addition, the acute onset of a lactic acidosis and diminished oxygen consumption have been noticed after an anaphylactoid reaction (45). Other potentially serious cardiovascular manifestations are myocardial ischemia and acute myocardial infarction, atrioventricular and intraventricular conduction abnormalities such as prolonged PR interval, transient left bundle branch block, and supraventricular arrhythmias such as atrial fibrillation. Severe, but reversible, myocardial depression also has been reported (37). Hematologic manifestations, such as disseminated intravascular coagulation and hemoconcentration secondary to volume contraction, also may complicate anaphylactic and anaphylactoid reactions (32). Gastrointestinal manifestations include nausea, bloating, abdominal cramps, and diarrhea.

In 1% to 20% of patients, there is a recurrence of symptoms after a period of recovery, termed biphasic anaphylaxis (46). In most cases, the symptoms recurred 3 to 8 hours after the initial

TABLE 60.3
CLINICAL MANIFESTATIONS OF ANAPHYLACTIC AND ANAPHYLACTOID REACTIONS

<table>
<thead>
<tr>
<th>System</th>
<th>Symptom</th>
<th>Frequency</th>
<th>Sign/clinical manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESPIRATORY</td>
<td></td>
<td>60%–80%</td>
<td>Upper airway obstruction caused by laryngeal edema and spasms; bronchospasm</td>
</tr>
<tr>
<td>Upper</td>
<td>Dyspnea, dysphonia, cough “lump in throat”</td>
<td>60%–80%</td>
<td>Upper airway obstruction caused by laryngeal edema and spasms; bronchospasm</td>
</tr>
<tr>
<td>Lower</td>
<td>Dyspnea, cyanosis</td>
<td>20%</td>
<td>Shock, tachycardia, capillary leak, syncope, supraventricular arrhythmias, conduction</td>
</tr>
<tr>
<td>CARDIOVASCULAR</td>
<td>Palpitations, faintness, weakness</td>
<td>20%</td>
<td>Shock, tachycardia, capillary leak, syncope, supraventricular arrhythmias, conduction</td>
</tr>
<tr>
<td>GASTROINTESTINAL</td>
<td>Abdominal pain, bloating, cramps, nausea</td>
<td>30%</td>
<td>Emsis, diarrhea, hepatosplenic congestion; rarely hematemesis and bloody diarrhea</td>
</tr>
<tr>
<td>NEUROLOGIC</td>
<td>Dizziness, disorientation, hallucinations, headache, feeling of impending doom</td>
<td>5%–10%</td>
<td>Syncope, lethargy, seizures</td>
</tr>
<tr>
<td>NASAL</td>
<td>Pruritus, sneezing</td>
<td>16%–20%</td>
<td>Rhinorrhea, nasal congestion</td>
</tr>
<tr>
<td>OCULAR</td>
<td>Conjunctival pruritus, periorbital edema</td>
<td>10%–15%</td>
<td>Conjunctival suffusion, lacrimation</td>
</tr>
<tr>
<td>HEMATOLOGIC</td>
<td></td>
<td></td>
<td>Hemoconcentration, DIC</td>
</tr>
</tbody>
</table>

DIC, disseminated intravascular coagulation.
presentation, although there have been reports of recurrence up to 72 hours later. There were no features of the primary response that predicted the occurrence of a secondary response (47).

**DIAGNOSIS**

The diagnosis of anaphylaxis is established on the basis of clinical grounds alone because expedient institution of appropriate therapy is mandatory. These diagnoses should be considered when typical multisystem manifestations occur in a direct temporal relationship with exposure to an inciting agent. Recently, the National Institute of Allergy and Infectious Diseases (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) proposed clinical criteria for the diagnosis of anaphylaxis (Fig. 60.1) (1). Because of the multisystem nature of anaphylactic and anaphylactoid reactions, the list of differential diagnoses that must be considered is extensive. Diagnostic possibilities include cardiac dysrhythmias, myocardial infarction, distributive or hypovolemic shock, vasovagal syncope, asthma, pulmonary embolism, upper airway obstruction secondary to ingestion of a foreign body, hypoglycemia, and the carcinoid syndrome (Table 60.4).

Demonstration of acute elevations of markers specific to mast cell activation such as histamine and tryptase have been proposed to help confirm the diagnosis of anaphylaxis (48,49). However, in a series of 97 patients presenting to an emergency department and given the diagnosis of anaphylaxis, only 42% were found to have elevated plasma histamine levels, and 24% had increased plasma tryptase levels (50). Skin testing or serum antibody tests can help demonstrate the presence of IgE against a specific allergen. Skin testing should be delayed for up to 4 weeks to allow the dermal mast cells to replenish intracellular mediators (51).

**PATHOPHYSIOLOGY**

The systemic manifestations of anaphylactic and anaphylactoid reactions represent sequelae that result from the release of inflammatory mediators by mast cells and basophils. The classic anaphylactic response occurs through the allergen-induced crosslinking of IgE tightly bound to the high-affinity FceR1a receptor constitutively expressed by mast cells (52). Release of histamine from preformed mast cell granules seems to be the primary pathophysiologic mediator, resulting in systemic vasodilation, increased vascular permeability, bronchoconstriction, pruritus, and increased mucus production. However, a number of other preformed mediators are included heparin, serotonin, and mast cell proteases such as chymase and tryptase (53). In addition, other important mediators of anaphylaxis are generated by the metabolism of membrane phospholipids. Activation of the 5-lipoxygenase pathway results in synthesis of leukotrienes, including leukotrienes C4, D4, and E4 (termed the slow-reacting substance of anaphylaxis), and leukotrienes C4, D4, and E4, along with the intermediary products 5-hydroxyeicosatetraenoic acid and 5-hydroperoxyeicosatetraenoic acid, elicit increases in vascular permeability and bronchoconstriction, whereas leukotriene B4 possesses eosinophil and neutrophil chemotactic properties. Activation of the cyclooxygenase pathway leads to the production of prostaglandin D2, which produces bronchoconstriction. Platelet-activating factor is also newly synthesized by activated mast cells and can result in bronchoconstriction, increased vascular permeability, platelet aggregation, and neutrophil chemotaxis. It also leads to further production of platelet-activating factor through stimulation of nuclear factor (NF)-κB, a positive feed-back mechanism involving the cytokines interleukin-1 (IL-1) and tumor necrosis factor (TNF-α), and contributes to a biphasic pattern seen in some patients (54). Combined, these primary mediators then facilitate the production of a diverse number of secondary mediators by platelets, neutrophils, eosinophils, and other cells, resulting in activation of the complement, coagulation, and fibrinolytic pathways (55).

Many of these mediators have complicated effects, and their relative roles in mediating anaphylaxis in vivo have been difficult to evaluate. Mouse models of anaphylaxis using strains with targeted deletions of specific mediators have been useful in elucidating the importance of different effector molecules, such as the leukotrienes (56–58), and in identifying regulatory
Chapter 60: Anaphylactic Shock

TABLE 60.4
DIFFERENTIAL DIAGNOSIS OF ANAPHYLAXIS

<table>
<thead>
<tr>
<th>FLUSH SYNDROME</th>
<th>POSTPRANDIAL COLLAPSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td>Airway foreign body</td>
</tr>
<tr>
<td>Plexochromacytoma</td>
<td>Monosodium glutamate ingestion</td>
</tr>
<tr>
<td>Peri-menopausal hot flushes</td>
<td>Sulfite</td>
</tr>
<tr>
<td>Medullary carcinoma of thyroid</td>
<td>Scombroid fish poisoning</td>
</tr>
<tr>
<td>Red man syndrome (vasomotor)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HYPOTENSION</th>
<th>MISCELLANEOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis shock</td>
<td>Panic attacks</td>
</tr>
<tr>
<td>Hemorrhagic shock</td>
<td>Systemic mastocytosis</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>Basophilic leukemia</td>
</tr>
<tr>
<td>Hypovolemic shock</td>
<td>Hereditary angioedema</td>
</tr>
<tr>
<td>Vasovagal reaction</td>
<td>Hyper-IgE syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RESPIRATORY DISTRESS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Status asthmatics</td>
<td></td>
</tr>
<tr>
<td>Airway foreign body</td>
<td></td>
</tr>
<tr>
<td>Epiglottitis</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>Asthma and COPD exacerbiation</td>
<td></td>
</tr>
<tr>
<td>Vocal cord dysfunction</td>
<td></td>
</tr>
</tbody>
</table>

IgE, immunoglobulin E; COPD, chronic obstructive pulmonary disorder.

pathways, such as IL-10 (59), but have also provided some surprises that may lead to clinically useful information. For example, mice with targeted deletions of either the high-affinity Fc\(\epsilon\)R1 receptor or IgE, not surprisingly, had a markedly decreased susceptibility to IgE-mediated anaphylaxis (53,60). This pathway can also be blocked with targeted deletion of histamine receptor 1 and, to a lesser extent, platelet-activating factor (52,53). However, such mice also revealed the presence of an alternate IgE-independent pathway of anaphylaxis (61). This pathway was mediated largely through platelet-activating factor, which was triggered by the binding of IgG to Fc\(\gamma\)RIII receptors present on macrophages (52,62). Like the classic IgE-mediated pathway, this alternative pathway required prior exposure to antigen, but differed in that much higher concentrations of antigen were required. The importance of this pathway in humans is as yet unclear (52). However, the administration of biologic agents, such as the anti-TNF antibody infliximab, has been reported to cause an IgE-independent anaphylactic response (63), and may be an example of this alternative pathway. The use of these biologic agents is expected to continue to increase.

MANAGEMENT

The clinician must have a high index of suspicion for anaphylactic and anaphylactoid reactions because they require a prompt clinical diagnosis and a rapid therapeutic response. Because anaphylactic and anaphylactoid reactions both represent sequelae of mast cell and basophil degranulation, the therapeutic approaches to these disorders are identical. Initial attention should be given to assessment and stabilization of the pulmonary and cardiovascular manifestations of anaphylaxis, because these are the major causes of death.

Epinephrine is the mainstay of initial management and should be administered immediately. It decreases mediator synthesis and release by increasing intracellular concentrations of cyclic adenosine monophosphate (cAMP) and antagonizes many of the adverse actions of the mediators of anaphylaxis (41). Aqueous epinephrine, 0.01 mg/kg (maximum dose 0.5 mg) administered intramuscularly every 5 to 15 minutes as necessary to control symptoms and maintain blood pressure, is recommended (41,64). The participants of the NIAID/FAAN symposium concluded that the intramuscular administration of epinephrine in the anterior lateral thigh is preferred over subcutaneous injection (1,2). In cases of severe laryngospasm or frank cardiovascular collapse, or when there is an inadequate response to subcutaneous epinephrine administration and fluid resuscitation, intravenous epinephrine is an option. There is no established dosage regimen for intravenous epinephrine in anaphylaxis, but suggested dosages are 5 to 10 \(\mu\)g bolus (0.2 \(\mu\)g/kg) for hypotension and 0.1 to 0.5 mg in the setting of cardiovascular collapse (1,2,65). When epinephrine is administered IV, the clinician should be aware of the potential adverse consequences of severe tachycardia, myocardial ischemia, hypertension, severe vasoospasm, and gangrene—the latter when infused by peripheral venous access (66).

Blood pressure measurements should be obtained frequently, and an indwelling arterial catheter should be inserted in cases of moderate to severe anaphylaxis. High-flow oxygen given via endotracheal tube or a nonrebreather mask should be administered to patients experiencing hypoxemia, respiratory distress, or hemodynamic instability (1,2). Orotracheal intubation may be attempted if the airway obstruction compromises effective ventilation despite pharmacologic intervention; however, attempts may be unsuccessful if laryngeal edema is severe. If endotracheal intubation is unsuccessful, then either needle-catheter cricothyroid ventilation, cricothyrotomy,
Consider aggressive fluid resuscitation antagonists (1,2,67). Patients should be placed in the recumbent position, with lower extremities elevated to increase fluid return centrally, thereby increasing cardiac output (68). Airway protection should be ensured in the event of vomiting.

Antihistamines (H₁ and H₂ antagonists) are considered second-line treatment for anaphylaxis (1,2). They are useful in the treatment of symptomatic urticaria-angioedema and pruritus. Recent studies suggest that treatment with a combination of H₁ and H₂ antagonists is more effective in attenuating the cutaneous manifestations of anaphylaxis than H₂ antagonists alone (10,69). Diphenhydramine hydrochloride (25 to 50 mg IV or IM for adults and 1 mg/kg, up to 50 mg, for children) and ranitidine (50 mg IV over 5 minutes) are commonly used in this setting. If hypotension persists despite administration of epinephrine and H₁ and H₂ blockers, aggressive volume resuscitation should be instituted. Up to 35% of the blood volume may be extravasated in the first 10 minutes of a severe reaction, with subsequent reduction in blood volume due to vasodilatation, causing distributive shock (70). Persistent hypotension may require multiple fluid boluses (10 to 20 mL/kg under pressure) as well as colloid and crystalloid infusions (1,2). Vasopressors such as norepinephrine, vasopressin, Neo-Synephrine, or even metaraminol may be useful in persistent hypotension (31).

There have been no placebo-controlled trials evaluating the efficacy of corticosteroids in anaphylaxis, but their contribution in other allergic diseases has led to their inclusion in anaphylactic management. Due to their slow onset of action, they are not useful in acute management. However, it has been suggested that they may prevent protracted or biphasic reactions (67,71). The usual dose is 100 to 250 mg of hydrocortisone IV every 6 hours (39).

The management of anaphylaxis in a patient receiving β₁-antagonist medications, such as β blockers, represents a special circumstance in which the manifestations of anaphylaxis may be exceptionally severe (72). β Blockade increases mediator synthesis and release, as well as end-organ sensitivity. In addition, β blockade antagonizes the beneficial β-mediated effects of epinephrine therapy, thereby resulting in unopposed α-adrenergic and reflex vagotonic effects: vasoconstriction, bronchoconstriction, and bradycardia. Therapy of anaphylaxis occurring in patients receiving β-antagonist drugs, however, is similar to that of other patients. In addition, atropine may be useful for heart block and refractory bronchospasm, whereas glucagon—which increase CAMP levels through a β-receptor-independent mechanism—have been reported to reverse the cardiovascular manifestations of anaphylaxis in patients receiving β-antagonists (72). Glucagon can be administered as a 1- to 5-mg (20–100 μg/kg with maximum dose of 1 mg in children) intravenous infusion over 5 minutes, followed by an infusion of 5 to 15 μg/minute titrated to a clinical response (1,2). Furthermore, these patients may require extended periods of observation because of the long duration of action of many β-antagonist medications.

An emergent evaluation for the inciting etiologic agent must accompany initial therapeutic interventions. After the etiologic agent is identified, the clinician should attempt to prevent further access to the circulation or limit further absorption. Infusions of possible etiologic agents should be stopped and the contents saved for analysis. If a Hymenoptera sting is responsible, the stinger should be removed. Small amounts of local epinephrine—0.1 to 0.2 mL of a 1:1,000 solution—should be injected next to a subcutaneous or intramuscular injection site that is dispersing the inciting agent. A tourniquet also should be placed proximal to the injection site and pressure applied to occlude venous return. After successful pharmacologic therapy, the tourniquet may be cautiously removed and the patient carefully observed for recurrent adverse sequelae. In cases where the offending agent was ingested, consideration may be given to insertion of a nasogastric tube to perform gastric lavage and gastric instillation of activated charcoal.

**Therapeutic Pearls**

1. Rapidly assess and maintain the airway, breathing, and circulation. If airway obstruction is imminent, perform endotracheal intubation; if unsuccessful, consider needle-catheter cricothyroid ventilation, cricothyrotomy, or tracheostomy. Patients in anaphylactic shock should be placed in a recumbent position with the lower extremities elevated, unless precluded by shortness of breath or vomiting.

2. Remove the inciting agent (i.e., remove Hymenoptera stinger) and follow with an intramuscular epinephrine injection in the anterior lateral thigh. Consider gastric lavage and administration of activated charcoal if the inciting agent was ingested.

3. Administer aqueous epinephrine, 0.01 mg/kg (maximum dose, 0.5 mg) intramuscularly every 5 to 15 minutes as necessary for controlling symptoms and maintaining blood pressure.

4. Establish intravenous access for hydration and provide supplemental oxygen.

5. Administer histamine antagonists to block vasodilation, capillary leak, and shock (H₁ blockade, 25–50 mg of diphenhydramine IV or IM for adults, and 1 mg/kg—up to 50 mg—for children; H₂ blockade, 50 mg of ranitidine IV).

6. Administer vasopressors for persistent hypotension and titrate to a mean arterial pressure of 60 mm Hg.

7. Consider aggressive fluid resuscitation with multiple fluid boluses (30–20 mL/kg under pressure), including colloid as well as crystalloid, in patients who remain hypotensive despite epinephrine.

8. Administer unhaled β₂-agonists such as albuterol for bronchospasm refractory to epinephrine (73).

9. Consider corticosteroid therapy for protracted anaphylaxis or to prevent biphasic anaphylaxis (1.0–2.0 mg/kg methylprednisolone IV every 6 hours). Oral prednisone at 1.0 mg/kg, up to 50 mg, may be used for milder attacks. Corticosteroids are not effective therapy for the acute manifestations of anaphylaxis.

10. Consider glucagon administration (1–5 mg IV over 1 minute, then 1–5 mg/hour in a continuous infusion) in the setting of prior β-blockade because of its positive inotropic and chronotropic effects mediated by a β-receptor–independent mechanism.
11. Prevent recurrent episodes by avoiding the inciting agent, desensitization, or premedication with corticosteroids and H1 and H2 blockade.

12. Admission to the intensive care unit is warranted for invasive monitoring with arterial and pulmonary artery catheters, echocardiography, pulse oximetry, and frequent arterial blood gas measurements.

**OBSERVATION**

An observation period should be considered for all patients following treatment of an anaphylactic reaction. On the basis of clinical data available to date, the NIAID/FAAN symposium recommends that observation periods be individualized on the basis of severity of initial reaction, reliability of the patient, and access to care. A reasonable time would be 4 to 6 hours for most patients, with prolonged observation or hospital admission for severe or refractory symptoms and patients with reactive airway disease (1,2).

**FOLLOW-UP, MANAGEMENT, AND PREVENTION**

The ideal method for managing severe systemic anaphylactic and anaphylactoid reactions is by preventing their occurrence. Persons with a known sensitivity should avoid re-exposure to the inciting etiologic agents. Patients who have experienced respiratory or cardiovascular symptoms of anaphylaxis should receive self-injectable epinephrine for use if anaphylaxis develops. These patients should also have an emergency action plan detailing its use and follow-up management (1,2). If a precipitating allergen is known or identified, patients should receive information about avoiding it in the future, prior to their discharge from the emergency facility. They should be encouraged to obtain prompt follow-up with their primary care physician as well as an allergist (1,2).

**IMPLICATIONATIONS AND OUTCOME**

Anaphylaxis/anaphylactoid reactions represent important, potentially reversible, acute respiratory and cardiovascular emergencies. Although the optimal management method is that of prevention, prompt diagnosis and institution of therapy are crucial after these reactions have been initiated in order to prevent the fatal cardiovascular and pulmonary manifestations. Factors associated with improved survival include the sensitivity of the person to the inciting agent, the duration between the exposure and the onset of symptoms (short latency periods are associated with more severe manifestations), the route and dose of the offending agent (larger doses and parenteral administration are associated with more severe manifestations), and the interval between onset of symptoms and subsequent diagnosis and institution of appropriate therapy (74). Optimal management of acute systemic reactions includes appropriate pharmacologic intervention, support of pulmonary and cardiovascular function, and removal of the offending agent. Expedient institution of these measures helps to reduce the morbidity and mortality associated with these potentially life-threatening syndromes.

**Chapter 60: Anaphylactic Shock**

939

**SUMMARY**

1. Anaphylactic reactions represent type I immune responses mediated by IgE bound to mast cells or basophils. Common inciting agents include β-lactam antibiotics and Hypo- menoptera stings. Other common causes include foods, local anesthetics, and serum products.

2. Anaphylactoid reactions represent IgE-independent activation of mast cells or basophils, with resultant degranulation and mediator release. Common inciting agents include inhaled radiocontrast media, neuromuscular depolarizing agents, and opiates, all of which induce direct mast cell activation; nonsteroidal anti-inflammatory agents acting through cyclooxygenase inhibition; and blood products acting through complement activation.

3. A history of a previous reaction to radiocontrast media, asthma or atopic disease, treatment with β-blockers, and cardiovascular disease are risk factors for developing anaphylaxis to radiocontrast media (27–29).

4. The differential diagnosis of anaphylactic and anaphylactoid reactions includes cardiac arrhythmias, myocardial infarction and cardiogenic shock, distributive or hypovolemic shock, vasovagal syncope, asthma, pulmonary embolism, upper airway obstruction secondary to a foreign body, vocal chord dysfunction, hypoglycemia, carcinoid syndrome, systemic mastocytosis, hereditary angioedema, and leukemia with excess histamine production.

5. Epinephrine is the initial drug of choice for the management of anaphylactic or anaphylactoid reactions. H1 and H2-blocking agents also should be administered. Corticosteroids are not effective for the acute management of anaphylactic or anaphylactoid reactions, but may prevent biphasic anaphylaxis or attenuate prolonged reactions. Glucagon may be used for persistent hypotension in patients taking β-blockers.

**References**


